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## Introduction to Classical Molecular Dynamics

Alessandro Grottesi a.grottesi@cineca.it HPC department, CINECA

## MD ingredients



## Equation of motion

The equations that describe the temporal evolution of a physical system is called equation of motion. There are different equations of motions, which characterize the motion with different levels of approximation:

- Time-dependent Schrödinger's Equation
- for quantum-mechanical system
- Newton's Equation
- for classical-mechanical system
- Langevin's Equation
> for stochastic system


## Newton's Equation of motion

Molecules are quantum-mechanical systems whose motion should be described by Schrödinger's Equation. However, technical difficulties make solving Schrödinger's Equation for large systems impractical.

Therefore the motion of a molecule is usually approximated by the laws of classical mechanics and by Newton's equation of Motion. In its most simplistic form Newton's second law of motion states:

$$
\mathbf{f}_{\mathrm{i}}=\mathrm{m}_{\mathrm{i}} \cdot \mathbf{a}_{\mathrm{i}}
$$

where $m_{i}$ is the mass of particle $i, a_{i}$ is its acceleration. The force $f_{i}$ is given as the derivative of the potential energy function $V$ :

$$
\mathbf{f}_{\mathrm{i}}=-\frac{\partial V}{\partial \mathbf{r}_{i}}
$$

where $r_{i}$ is the position of particle $i$

## Potential energy function

$$
\begin{aligned}
& V\left(\mathbf{r}_{1}, \mathbf{r}_{2}, \ldots, \mathbf{r}_{n}\right)=\sum_{\text {bond }} \frac{1}{2} k_{b_{n}}\left(b_{n}-b_{0_{n}}\right)^{2}+\sum_{\text {angle }} \frac{1}{2} k_{\theta_{n}}\left(\theta_{n}-\theta_{0_{n}}\right)^{2}+ \\
& +\sum_{\text {improper }} \frac{1}{2} k_{\xi_{n}}\left(\xi_{n}-\xi_{0_{n}}\right)^{2}+\sum_{\text {diheedral }} k_{\phi_{n}}\left[1+\cos \left(m_{n} \phi_{n}-\delta_{n}\right)\right]+ \\
& \text { dihedral } \\
& +\sum_{\substack{\text { nonbonded } \\
\text { pairs } i j}}\left(\left(\frac{C_{i j}^{(12)}}{r_{i j}^{12}}-\frac{C_{i j}^{(6)}}{r_{i j}^{6}}\right)+\frac{1}{4 \pi \varepsilon_{0}} \frac{q_{i} q_{j}}{\varepsilon_{r} r_{i j}}\right) \\
& \text { bonded interactions }
\end{aligned}
$$

non bonded interactions

| Model | Degree of freedom | Example of predicted properties |  |
| :---: | :---: | :---: | :---: |
|  | Considered | Removed |  |
| Quantum mechanic | Nucleus, electrons | Nucleons | Chemistry reaction |
| Polarizable atoms | Atoms, dipoles | Electrons | Binding of charged substrates |
| Non polarizable atoms | Solute atoms, solvent atoms | Dipoles | Conformational transitions |
|  |  |  | Hydration |
| mplicit solvent | Solute atoms | Solvent atoms | Folding topology of macromolecules |

## Classical Molecular Dynamics

## A Brief History

## Year

System
1964 Liquid Argon (Rahman Phys Rev)
1974 Water (Rahman J. Chem Phys.)
1977 Small protein in vacuo
(Mc Cammon Karplus Nature)
1988 First Protein in explicit water (Levitt PNAS )

From 1995 Protein-DNA Complexes - Membrane Proteins- Complex Systems

## Bond Stretching Energy

$$
=\sum_{\text {bond }} \frac{1}{2} k_{b_{n}}\left(b_{n}-b_{0_{n}}\right)^{2}+. .
$$

Unique $\mathrm{k}_{\mathrm{b}}$ and $\mathrm{b}_{0}$
$\mathrm{k}_{\mathrm{b}}$ is the spring constant of the bond $\mathrm{b}_{0}$ is the bond length at equilibrium assigned for each bond pair, i.e. C-C, O-H


Principle of bond stretching (left), and the bond stretching potential (right).

## Bond Stretching Force

$$
\begin{array}{r}
\mathbf{f}_{i}=-\frac{\partial V^{\text {bond }}}{\partial \mathbf{r}_{i}}=-\frac{\partial V^{\text {bond }}}{\partial r_{i j}} \frac{\partial r_{i j}}{\partial \mathbf{r}_{i}}=k_{b}\left(r_{i j}-b_{0} \frac{\mathbf{r}_{i j}}{r_{i j}}\right. \\
\mathbf{f}_{j}=-\mathbf{f}_{i}
\end{array}
$$

If atom $i$ and $j$ are closer than $b_{0}$, the bond force separates them


$i$


If atom $i$ and $j$ are farther than $b_{0}$, the bond force draws them nearer

## Bending Energy

$$
+\sum_{\text {angle }} \frac{1}{2} k_{\theta_{n}}\left(\theta_{n}-\theta_{0 n}\right)^{2}+
$$

$k_{\theta}$ is the spring constant of the bending $\theta_{0}$ is the angle bending at equilibrium


Principle of angle vibration (left) and the bond angle potential (right).

> Unique parameters for angle bending are assigned to each bonded triplet of atoms based on their types (e.g. C-C-C, C-O-C, C-CH, etc.)

## Torsional o Dihedral Energy



$$
+\sum_{\text {dihededrall }} k_{\phi_{l}}\left[1+\cos \left(m_{n} \phi_{n}-\delta_{n}\right)\right]+
$$

$\phi=$ angle
$\delta=$ phase
$m=$ number of peaks in a full rotation



## Improper Dihedral Energy

The energy required to deform a group of atoms from its equilibrium angle, $x_{0}$. Used for tetrahedral or planar groups


$$
+\sum_{\substack{\text { inppropere } \\ \text { aliearal }}} \frac{1}{2} k_{\xi_{n}}\left(\xi_{n}-\xi_{0 n}\right)^{2}+
$$

Again this system can be modeled by a spring, and the energy is given by the Hookean potential with respect to the planar angle

## The "Hookean" potential

$$
\mathrm{k}_{\theta}\left(\theta-\theta_{\mathrm{o}}\right)^{2} \text { or } \mathrm{k}_{\mathrm{b}}\left(\mathrm{r}-\mathrm{r}_{\mathrm{o}}\right)^{2}
$$


$k_{b}$ and $k_{0}$ broaden or steepen the slope of the parabola. The larger the value of $k$, the more energy is required to deform an angle (or bond) from its equilibrium value

## PINECA $+888$ <br> $S \subset A_{\text {Lennard Jones (Van der Waals) interactions }}$




Johannes Diderik Van der Waals

$$
+\sum_{\substack{\text { nonbonded } \\
\text { pairstij }}}\left(\begin{array}{l}
\text { LJ interactions } \\
\left.\left(\frac{C_{i j}^{(12)}}{r_{i j}^{12}}-\frac{C_{i j}^{(6)}}{r_{i j}^{6}}\right)+\frac{1}{4 \pi \varepsilon_{0}} \frac{q_{i} q_{j}}{\varepsilon_{r} r_{i j}}\right)
\end{array}\right.
$$

non bonded interactions

## Electrostatic interactions

$q_{i}$ and $q_{j}$ are the partial atomic charges for atoms $i$ and $j$, separated by a distance $\mathrm{r}_{\mathrm{ij}}$ and $\varepsilon_{\mathrm{r}}$ is the relative dielectric constant:


## Electrostatic

non bonded interactions

The Coulomb interaction (for particles with equal signed charge)

## Electrostatic interactions: Particle Mesh Ewald (PME)

- Short range in the real space
- Long range in the Fourier space

The cut-off radius method for electrostatic interactions is particularly inaccurate for charged molecules such as DNA of for dipolar groups such as alpha helices

PME corrects these errors and it helps maintaining short the cut-off in the real space: i.e. the number of atom pairs is reduced
electrostatic potential

$$
V=\frac{1}{2} \sum_{i, j=1}^{N} \sum_{\mathbf{n} \in \mathbb{Z}^{3}}^{\prime} \frac{q_{i} q_{j}}{\left|\mathbf{r}_{i j}+\mathbf{n} L\right|}
$$

straightforward summation impracticable


- Trick 1: Split problem into 2 parts with help of:

$$
\frac{1}{r}=\underbrace{\frac{f(r)}{r}}_{\text {short range }}+\underbrace{\frac{1-f(r)}{r}}_{\text {long range }}
$$



- $V=$


Darden et al., Particle mesh Ewald-an NlogN method for Ewald sums in large systems. J. Chem. Phys, 98 (1993), 10089

Charge groups and atom types
SuperComputing Applications and Innovation
Fig. 4.2.70 Molecular topology building block definition

Solute building block:
Name:
Benzoic acid (neutral)
BA


A charge group is a neutral charge group composed by several partially charged atoms of a chemical group. Electrostatics can be calculated between charge groups instead that atom pairs

Charge groups were first introduced to reduce artifacts in the electrostatics calculation but they can also speed up the calculations; given a pair of water molecules for instance, we only need to determine one atom distance instead of nine (or sixteen for a four-site water model)
Note that an atom type is not a physical feature. O8 is defined with a different atom type than O9. In fact, their bond constants with C7 and atomic charges are different

SuperComputing Applications and Innovation

## Periodic boundary conditions and cut-off radius

To simulate our finite system in liquid conditions, we apply the pbc: i.e. the system box is virtually surrounded in all directions by copy of itself.


An atom close to a box border interacts with the atoms in another pbc image. The non-bonded interactions are only calculated between atom pairs closer than a spherical cut-off

## BOX dimension

The edge of cubic box must be large enough to avoid interactions of the solute with itself. Its minimal dimension therefore depends by the chosen cut-off for the non bonded interactions


Edge of the box $=3.2 \mathrm{~nm}$
( 2.4 nm of water plus the solute size)

Force field

$$
\begin{aligned}
& V\left(\mathbf{r}_{1}, \mathbf{r}_{2}, \ldots, \mathbf{r}_{n}\right)=\sum_{\text {bond }} \frac{1}{2} k_{b_{n}}\left(b_{n}-b_{0 n}\right)^{2}+\sum_{\text {angle }} \frac{1}{2} k_{\theta_{n}}\left(\theta_{n}-\theta_{0 n}\right)^{2}+ \\
& +\sum_{\begin{array}{c}
\text { improper } \\
\text { dihedral }
\end{array}} \frac{1}{2} k_{\xi_{n}}\left(\xi_{n}-\xi_{0 n}\right)^{2}+\sum_{\text {dihedral }} k_{\phi_{n}}\left[1+\cos \left(m_{n} \phi_{n}-\delta_{n}\right)\right]+ \\
& +\sum_{\begin{array}{c}
\text { nonbonded } \\
\text { pairs }(i j)
\end{array}} \frac{C_{i j}^{(12)}}{r_{i j}^{12}}-\frac{C_{i j}^{(6)}}{r_{i j}^{6}}+\frac{1}{4 \pi \varepsilon_{0}} \frac{q_{i} q_{j}}{\varepsilon_{r} r_{i j}}
\end{aligned}
$$

The potential energy function, together with the parameters required to describe the behavior of different kinds of atoms and bonds $\left(\mathrm{k}_{\mathrm{b}}, \mathrm{k}_{\theta}, \mathrm{k}_{\xi}, \mathrm{C}_{\mathrm{i}}, \ldots\right)$, is called: force field.

Several force fields are currently used and the choice depends from the studied system. Some force field are better suited for nucleic acids, for example, while others for membrane proteins

1: AMBER03 protein, nucleic AMBER94 (Duan et al., J. Comp. Chem. 24, 1999-2012, 2003)
2: AMBER94 force field (Cornell et al., JACS 117, 5179-5197, 1995)
3: AMBER96 protein, nucleic AMBER94 (Kollman et al., Acc. Chem. Res. 29, 461-469, 1996)
4: AMBER99 protein, nucleic AMBER94 (Wang et al., J. Comp. Chem. 21, 1049-1074, 2000)
5: AMBER99SB protein, nucleic AMBER94 (Hornak et al., Proteins 65, 712-725, 2006)
6: AMBER99SB-ILDN protein, nucleic AMBER94 (Lindorff-Larsen et al., Proteins 78, 1950-58, 2010)
7: AMBERGS force field (Garcia \& Sanbonmatsu, PNAS 99, 2782-2787, 2002)
8: CHARMM27 all-atom force field (CHARM22 plus CMAP for proteins)
9: GROMOS96 43a1 force field
10: GROMOS96 43 a 2 force field (improved alkane dihedrals)
11: GROMOS96 45a3 force field (Schuler JCC 200122 1205)
12: GROMOS96 $53 a 5$ force field (JCC 2004 vol 25 pag 1656)
13: GROMOS96 53a6 force field (JCC 2004 vol 25 pag 1656)
14: GROMOS96 54a7 force field (Eur. Biophys. J. (2011), 40, 843-856
15: OPLS-AA/L all-atom force field (2001 aminoacid dihedrals)

## 

Numeric integration of Newton's equation of motion is typically done step by step using methods that are called Finite Difference methods.

These methods use the information available at time to predict the system's coordinates and velocities at a time $t+$ $\delta t$, where $\delta \mathrm{t}$ is a short time interval and are based on a

Taylor expansion of the position at time $t+\delta t$

$$
r(t+\delta t)=r(t)+v(t) \delta t+\frac{1}{2} a(t) \delta t^{2}+\ldots
$$

## 北路 CAl Integration of the equation of motion

$$
r(t+\delta t)=2 r(t)-r(t-\delta t)+a(t) \delta t^{2}
$$

－Varlet integrator


$$
r(t+\delta t)=r(t)-v\left(t+\frac{1}{2} \delta t\right) \delta t
$$

$$
v\left(t+\frac{1}{2} \delta t\right)=v\left(t-\frac{1}{2} \delta t\right)+a(t) \delta t
$$

＊Leap－frog integrator

$$
\begin{aligned}
& r(t+\delta t)=r(t)+v(t) \delta t+\frac{1}{2} a(t) \delta t^{2} \\
& v(t+\delta t)=v(t)+[a(t)+a(t+\delta t)] \frac{\delta t}{2}
\end{aligned}
$$

－Velocity Varlet

## Choice of the timestep

The length of the timestep must be small compared to the period of the highest frequency motions being simulated

Force characteristics Relaxation time (fs) Time step (fs)

High frequency motion: bond stretching vibrations
Medium frequency motion: angle bending, proper and improper dihedral angle deformation, LJ and short range Coulombian interactions
Low frequency motion: long range Coulombian interactions coulombian interactions

The bond stretching vibrations are generally of minimal interest in the study of biomolecular structure and function. Therefore this degree of freedom is usually kept frozen with constraint algorithms ( $2 \times 10^{-15} \mathrm{~s}$ )

Constraints


The application of geometrical constraints to maintain fixed all
the bond lengths, during a simulation, allows the use of a time step up to 2 fs

In SHAKE (the first constraints algorithm to be implemented in a MD code) changes a set of unconstrained coordinates to a set of coordinates that fulfill a list of distance constraints, solving a set of Lagrange multipliers in the constrained equations of motion (iterative)

Constraints

The SETTLE algorithm (developed in 1992) is an analytical solution of SHAKE, specifically for water (non-iterative)


Figure 3.9: The three position updates needed for one time step. The dashed line is the old bond of length $d$, the solid lines are the new bonds. $l=d \cos \theta$ and $p=\left(2 d^{2}-l^{2}\right)^{\frac{1}{2}}$.

The LINCS algorithm (developed in 1997, twenty years after SHAKE) solves the bond length constraints, always in two steps
(non-iterative)

## Constraints

constraints:
none
No constraints except for those defined explicitly in the topology, i.e. bonds are represented by a harmonic (or other) potential or a Morse potential (depending on the setting of morse) and angles by a harmonic (or other) potential.

## h-bonds

Convert the bonds with H -atoms to constraints.

## all-bonds

Convert all bonds to constraints.
h-angles
Convert all bonds and additionally the angles that involve H -atoms to bond-constraints.
all-angles
Convert all bonds and angles to bond-constraints.

## Timescale

| Rotation of buried sidechains | s | Protein Folding milliseconds/seconds ( $10^{-3}-1 \mathrm{~s}$ ) |
| :---: | :---: | :---: |
| Local denaturations Allosteric transitions | ms | Ligand Binding micro/milliseconds ( $10^{-6}-10^{-3} \mathrm{~s}$ ) |
|  | $\mu \mathrm{s}$ | Enzyme catalysis micro/milliseconds ( $10^{-6}-10^{-3} \mathrm{~s}$ ) |
| Hinge bending | ns | - Conformational transitions pico/nanoseconds ( $10^{-12}-10^{-9} \mathrm{~s}$ ) |
| Rotation of surface sidechains |  | Collective vibrations - |
| Elastic vibrations $\{$ | ps | 1 picosecond ( $10^{-12} \mathrm{~s}$ ) |
|  |  | > Bond vibrations - |
| Molecular dynamics timestep $\rightarrow$ |  | 1 femtosecond ( $10^{-15} \mathrm{~s}$ ) |

## Topology

The topology file describes the atoms composing a molecule and their bond connections Es: flexspc.itp in gromacs

```
[ moleculetype ]
; molname nrexcl
SOL 2
```

[ atoms ]
; id at type res nr res name at name cg nr charge mass
1 OW_spc 1 SOL OW 1 -0.82 15.99940
2 HW_spc 1 SOL HW1 $1 \quad 0.41$ 1.00800
3 HW_spc $1 \quad$ SOL HW2 1
[ bonds ]
;i j funct length force.c.
$\begin{array}{lllllll}1 & 2 & 1 & 0.1 & 345000 & 0.1 & 345000\end{array}$
$\begin{array}{llllllll}1 & 3 & 1 & 0.1 & 345000 & 0.1 & 345000\end{array}$
[ angles ]
; i j $k$ funct angle force.c.
$\begin{array}{llllllll}2 & 1 & 3 & 1 & 109.47 & 383 & 109.47 & 383\end{array}$

## PPddd <br> SCAl <br> Constraints in Topology

Only in case of water, the constraint algorithm can be selected in the topology file

| $\left[\begin{array}{llll}\text { bonds ] } & & & \\ ; i & j & \text { funct } & \text { length }\end{array}\right.$ | force.c. |  |  |  |
| :--- | :---: | :---: | :---: | :---: |
| 1 | 2 | 1 | 0.1 | 345000 |
| 1 | 3 | 1 | 0.1 | 345000 |

flexspc.itp

$[$ angles ]

| i | $j$ | $k$ | funct | angle | force.c. |
| :--- | :--- | :--- | :--- | :--- | :--- |
| 2 | 1 | 3 | 1 | 109 | 383 |

[ settles]
: OW funct doh dhh spc.itp
$\begin{array}{llll}1 & 1 & 0.1 & 0.16333\end{array}$

## Topology

Solute building block: Benzoic acid (neutral)
Name:
a. Atoms


## Initial velocities

The initial velocity of each atom is random assigned through a Maxwell-Boltzmann distribution that is function of the temperature


## To recapitulate..



## THE GLOBAL MD ALGORITHM

## 1. Input initial conditions

Potential interaction $V$ as a function of atom positions
Positions $r$ of all atoms in the system
Velocities $v$ of all atoms in the system
$\Downarrow$
repeat $\mathbf{2 , 3 , 4}$ for the required number of steps:

## 2. Compute forces

The force on any atom

$$
\boldsymbol{F}_{i}=-\frac{\partial V}{\partial \boldsymbol{r}_{i}}
$$

is computed by calculating the force between non-bonded atom

$$
\stackrel{\text { pairs: }}{\boldsymbol{F}_{i} \stackrel{\sum_{j}}{=} \boldsymbol{F}_{i j}}
$$

plus the forces due to bonded interactions (which may depend on 1 ,
2,3 , or 4 atoms), plus restraining and/or external forces.
The potential and kinetic energies and the pressure tensor are computed.
$\Downarrow$

## 3. Update configuration

The movement of the atoms is simulated by numerically solving
Newton's equations of motion

$$
\begin{gathered}
\frac{\mathrm{d}^{2} \boldsymbol{r}_{i}}{\mathrm{~d} t^{2}}=\frac{\boldsymbol{F}_{i}}{m_{i}} \\
\frac{\mathrm{~d} \boldsymbol{r}_{i}}{\mathrm{~d} t}=\boldsymbol{v}_{i} ; \quad \frac{\mathrm{d} \boldsymbol{v}_{i}}{\mathrm{~d} t}=\frac{\boldsymbol{F}_{i}}{m_{i}} \\
\Downarrow
\end{gathered}
$$

4. if required: Output step
write positions, velocities, energies, temperature, pressure, etc.

## Molecular Dynamics ensembles

The method discussed above is appropriate for the microcanonical ensemble: constant N (number of particles), V (volume) and $E_{T}$ (total energy $=E+E_{\text {kin }}$ )

Note that if time step is short enough, the system loses/gains no net energy (potential + kinetic) when running MD in the NVE ensemble.

When simulating biological macromolecules, it might be more appropriate to simulate under constant Temperature (T) or constant Pressure (P):

## Canonical ensemble: NVT Isothermal-isobaric: NPT

## Simulating at constant T: the Berendsen scheme



Bath supplies or removes heat from the system as appropriate

$$
\frac{d T(t)}{d t}=\frac{T_{0}-T(t)}{\tau_{T}}
$$

where $\tau$ determines how strong the bath influences the system

Exponentially scale the velocities at each time step by the factor $\lambda$ :

$$
\lambda=\left[1+\frac{\Delta t}{\tau_{T}}\left(\frac{T_{0}}{T(t)}-1\right)\right]^{\frac{1}{2}}
$$

T: "kinetic" temperature

## Simulating at constant T: the Berendsen scheme



A small $\tau$, close to the timestep (strong thermostat), is useful in the equilibration phase, when the quick decreasing of the potential energy could increase too much the kinetic energy of the protein

A bigger $\tau$, e.g. equal to ten times the timestep (weak thermostat), is useful in the production phase, when we want to keep at minimum the perturbation to the conformational sampling

## Simulating at constant P: the Berendsen scheme

## system

## Pressure bath

Couple the system to a pressure bath: $\quad \frac{d P(t)}{d t}=\frac{P_{0}-P(t)}{\tau_{P}}$
A change in pressure $P$ is related to a change in volume $V$
To regulate pressure: exponentially scale the volume of the simulation box at each time step by a factor $\mu$
where $k_{T}$ : isothermal compressibility $\tau_{\mathrm{p}}$ : coupling constant

$$
\mu(t)=\left[1-k_{T} \frac{\Delta t}{\tau_{P}}\left(P_{o}-P(t)\right)\right]^{\frac{1}{3}}
$$

## Sample input file of gromacs

http://manual.gromacs.org/current/online/mdp.html

```
title
cpp
include
define
integrator
dt
nsteps
nstxout
nstvout
nstlog
nstenergy
nstxout-compressed
compressed-x-grps
energygrps
nstlist
ns-type
rlist
coulombtype
rcoulomb
rvdw
= Yo
= /lib/cpp
= -I../top
=
= md
= 0.002
= 500000
= 5000
= 5000
= 5000
= 250
= 250
= Protein
= Protein SOL
= 10
= grid
= 0.8
= cut-off
= 1.4
= 0.8
```


## Sample input file of gromacs

```
tcoupl
tc-grps
tau-t
ref-t
Pcoupl
tau-p
compressibility
ref-p
gen-vel
gen-temp
gen-seed
constraints
```

```
= Berendsen
```

= Berendsen
= Protein SOL
= Protein SOL
= 1.0
= 1.0

```
= 0.1 0.1
```

= 0.1 0.1
= 300 300
= 300 300
= Berendsen
= Berendsen
=4.5e-5
=4.5e-5
= 1.0
= 1.0
= yes
= yes
= 300
= 300
= 173529
= 173529
= all-bonds

```
= all-bonds
```


## Conformational sampling



## Energy minimization

The potential energy surface of a molecule is defined by only a global minumum and a great number of local minima: i.e. conformations where all the first derivative of the potential energy function with respect to the coordinates are zero and all second derivatives are non-negative


The energy minimization algorithms finds the nearest local minimum, i.e. the minimum that can be reached by systematically moving down the steepest local gradient

Usually they cannot found the global minumum

Two algorithms very used in MD codes are

- steepest descent
- conjugate gradient

Both of the first order: they use the first derivative of the energy potential function with respect to the coordinates

The steepest descent uses only the gradient of the potential energy function in the local position to calculate the coordinate movement

It is quicker in the single iteration but less precise in finding the local minumum. Therefore is useful in the first steps of minimizations

The conjugate gradient uses also the gradient of the potential energy function in the previous step

It is more accurate in finding the local minumum but it is slower than the steepest descent. Therefore is usually applied after some steps of steepest descent


Starting from A, the steepest descents goes through A-B-C (or A-D-F) While the conjugate gradient, weighting the $\mathrm{A}-\mathrm{B}$ and $\mathrm{B}-\mathrm{C}$ gradients, goes through A-B-O

## GROMACS USER MANUAL

## steep

A steepest descent algorithm for energy minimization. The maximum step size is emstep [ nm ], the tolerance is emtol $\left[\mathrm{kJ} \mathrm{mol}^{-1} \mathrm{~nm}^{-1}\right.$ ].
cg
A conjugate gradient algorithm for energy minimization, the tolerance is emtol $[\mathrm{kJ}$ $\left.\mathrm{mol}^{-1} \mathrm{~nm}^{-1}\right]$. CG is more efficient when a steepest descent step is done every once in a while, this is determined by nstcgsteep.
emtol: (100.0) [ $\left.\mathrm{kJ} \mathrm{mol}^{-1} \mathbf{n m}^{-1}\right]$
the minimization is converged when the maximum force is smaller than this value
emstep: (0.01) [nm]
initial step-size
nstcgsteep: (1000) [steps]
frequency of performing 1 steepest descent step while doing conjugate gradient energy minimization.

## 1-4 interactions



Figure 4.15: Atoms along an alkane chain.
Atoms covalently bound are defined as first neighbours second neighbours and so on....
LJ and electrostatic interactions are not calculated among first and second neighbours since they are considered in the stretching (first) or in the bending potential (second).
The standard non-bonding interactions are too strong for the third neighbours and are reduced (interactions 1-4; list 1-4).

