Biomolecular modeling III

Marcus Elstner and Tomáš Kubař

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Non-bonded interactions

speeding up the number-crunching

Non-bonded interactions – why care?

$$E^{\mathrm{el}}(r) = \frac{1}{4\pi\varepsilon_0} \cdot \frac{q_1 \cdot q_2}{r}$$

$$E^{\mathrm{LJ}}(r) = 4E_0 \left(\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6} \right)$$

- key to understand biomolecular structure and function
  - binding of a ligand
  - efficiency of a reaction
  - color of a chromophore
- two-body potentials $\rightarrow$ computational effort of $\mathcal{O}(N^2)$
  - good target of optimization

Cut-off – simple idea

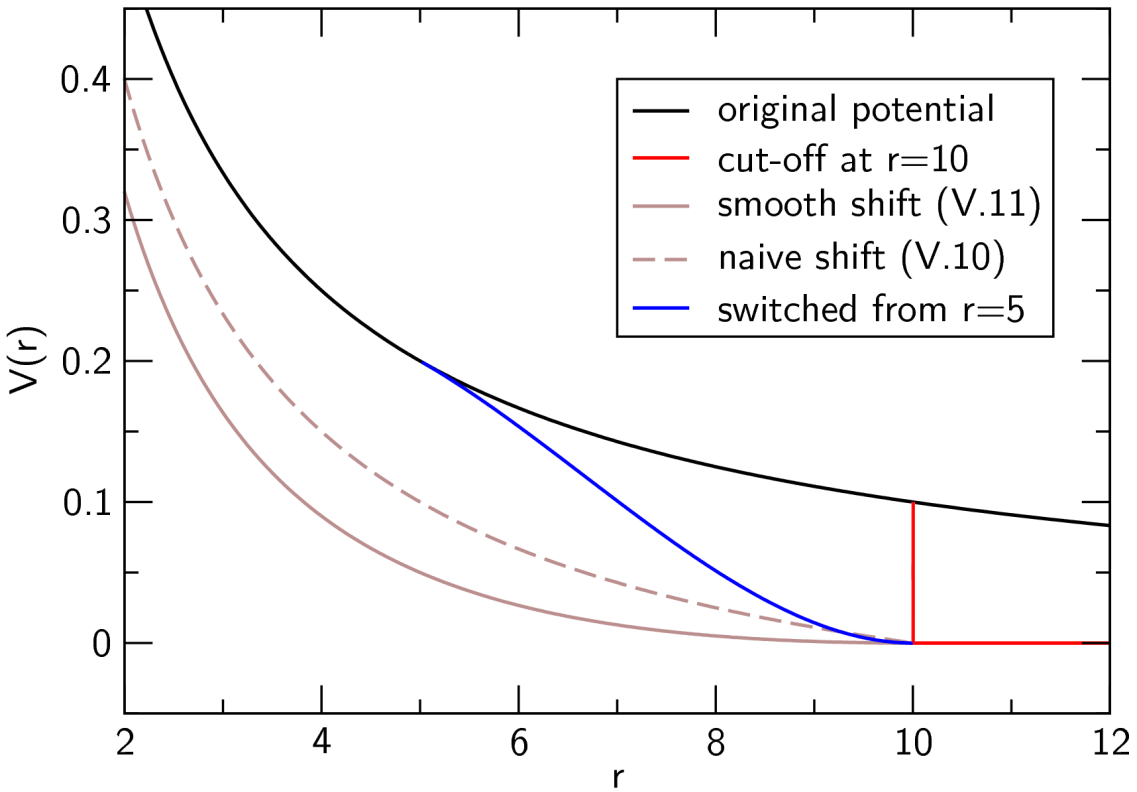
with PBC – infinite number of interaction pairs in principle,
but the interaction gets weaker with distance

simplest and crudest approach to limit the number of calculations
neglect interaction of atoms further apart than r_c – cut-off

very good for rapidly decaying LJ interaction $(1/r^6)$ ($r_c = 10$ Å)

not so good for slowly decaying electrostatics $(1/r)$
– sudden jump (discontinuity) of potential energy,
disaster for forces at the cut-off distance

Cut-off – better alternatives



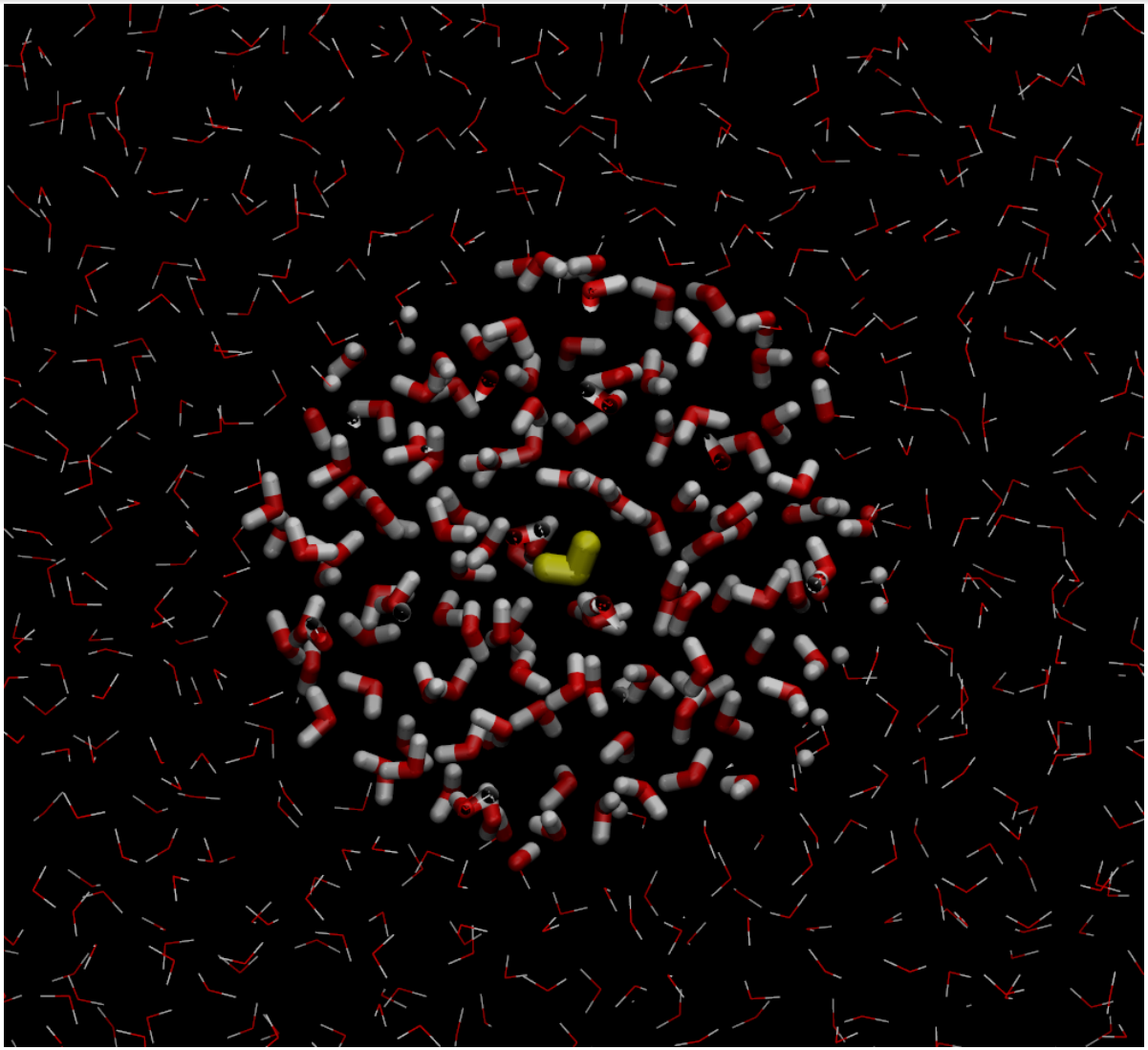
Neighbor lists

cut-off – we still have to calculate the distance for every two atoms
(to compare it with the cut-off distance)
$\rightarrow$ we do not win much yet – there are still $\mathcal{O}(N^2)$ distances

observation: pick an atom A.
the atoms that are within cut-off distance r_c around A,
remain within r_c for several consecutive steps of dynamics,
while no other atoms approach A that close

idea: maybe it is only necessary to calculate the interactions
between A and these close atoms – neighbors

Neighbor lists



Neighbor lists

what will we do?

calculate the distances for every pair of atoms

less frequently, i.e. every 10 or 20 steps of dynamics, and

record the atoms within cut-off distance in a neighbor list

atom	how many?	list of neigboring atoms											
1	378	2191	408	1114	1802	262	872	649	805	1896	2683	114	189
2	403	1788	1624	1048	1745	2546	506	203	288	2618	1445	880	133
3	385	779	2869	800	2246	1252	570	454	1615	1656	1912	2395	152
4	399	367	2143	1392	1448	1460	1411	2921	2725	429	845	2601	181
5	406	1385	425	1178	2112	1689	1897	1650	1747	1028	1366	605	176
6	388	1748	130	2244	631	1677	1748	2566	303	552	562	1142	255
7	379	20	15	1322	196	1590	655	552	1401	2177	411	2904	236
8	395	888	1074	786	2132	1703	218	1846	337	1683	1917	2005	94
9	396	2433	934	1055	1518	2750	2534	1697	2006	769	2407	1478	123
10	381	2461	1910	459	2628	2523	1709	2069	1151	1710	2107	1909	13
11	400	1029	756	670	1592	612	676	1473	2859	392	986	155	265

then – calculate the interaction for each atom

only with for the atoms in the neighbor list – formally $\mathcal{O}(N)$

Accounting of all of the replicas

cut-off – often bad, e.g. with highly charged systems
(DNA, some proteins)

switching function – deforms the forces (slightly)
$\rightarrow$ e.g. artificial accumulation of ions around cut-off

only way – abandon the minimum image convention and cut-off
– sum up the long-range Coulomb interaction
between all the replicas of the simulation cell

Accounting of all of the replicas

the infinite system is periodic – a trick may be applied:

Ewald summation method $\mathcal{O}(N^{\frac{3}{2}})$ or even
particle–mesh Ewald method PME, $\mathcal{O}(N \cdot \log N)$

2 main contributions:

- 'real-space' – similar to the usual Coulomb law,
  but decreasing much quicker with distance
- 'reciprocal-space' – here are the tricks concentrated
  - atom charges artificially smeared (Gaussian densities)
  - Fourier transformation can sum up the interaction
    of all of the periodic images!

Ewald – realistic simulations of highly charged systems possible

Preparing an MD simulation

the procedures – briefly

Work plan

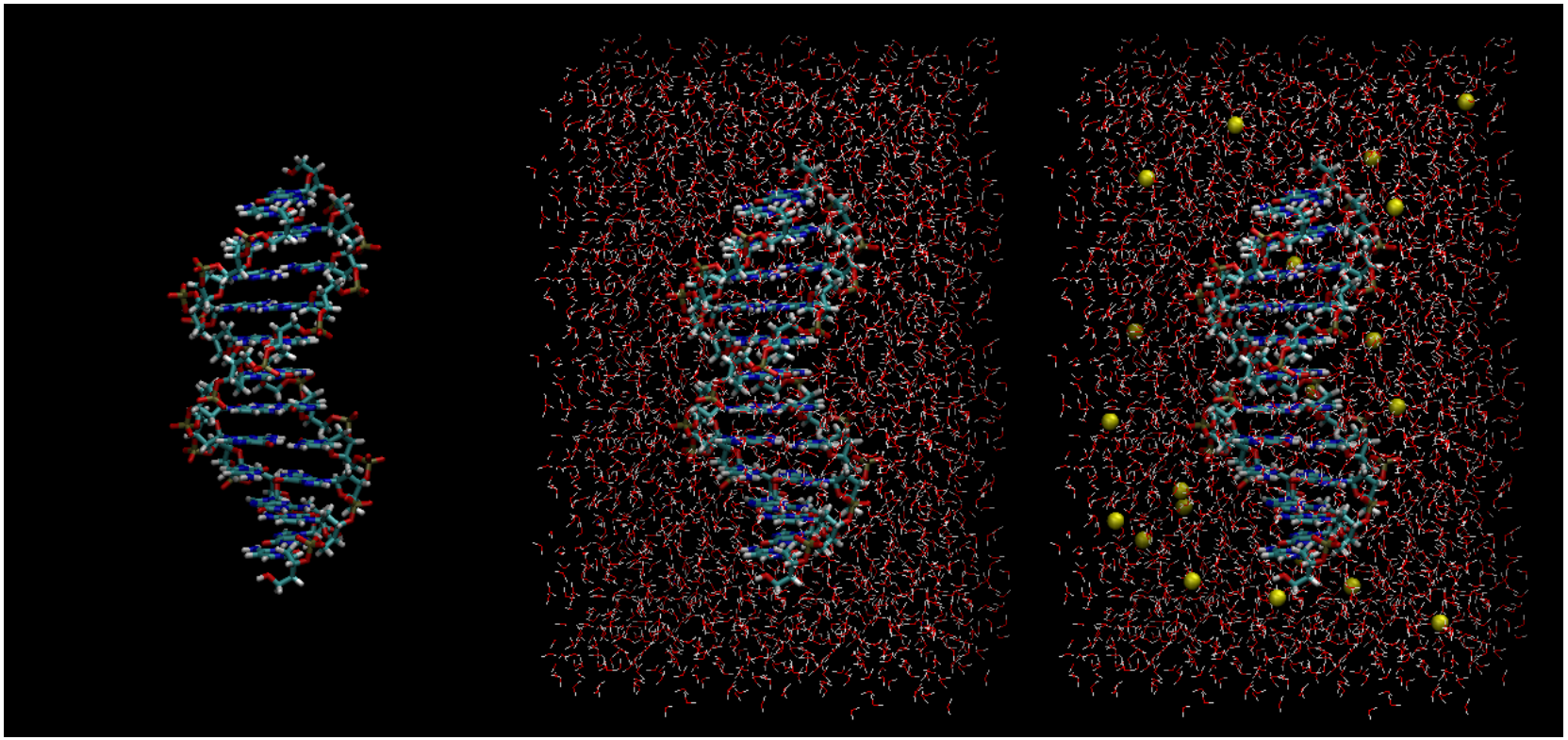
1. build the initial structure
2. bring the system into equilibrium
3. do the productive simulation
4. analyze the trajectory

Tools to build the structure

- do it yourself
- specific programs within simulation packages
- 'universal' visualization programs – VMD, Molden, Pymol
- databases of biomolecular systems – PDB, NDB
- specialized web services – Make-NA
- tools to create periodic box and hydrate system

Tools to build the structure

build the solute, solvate it and add counterions



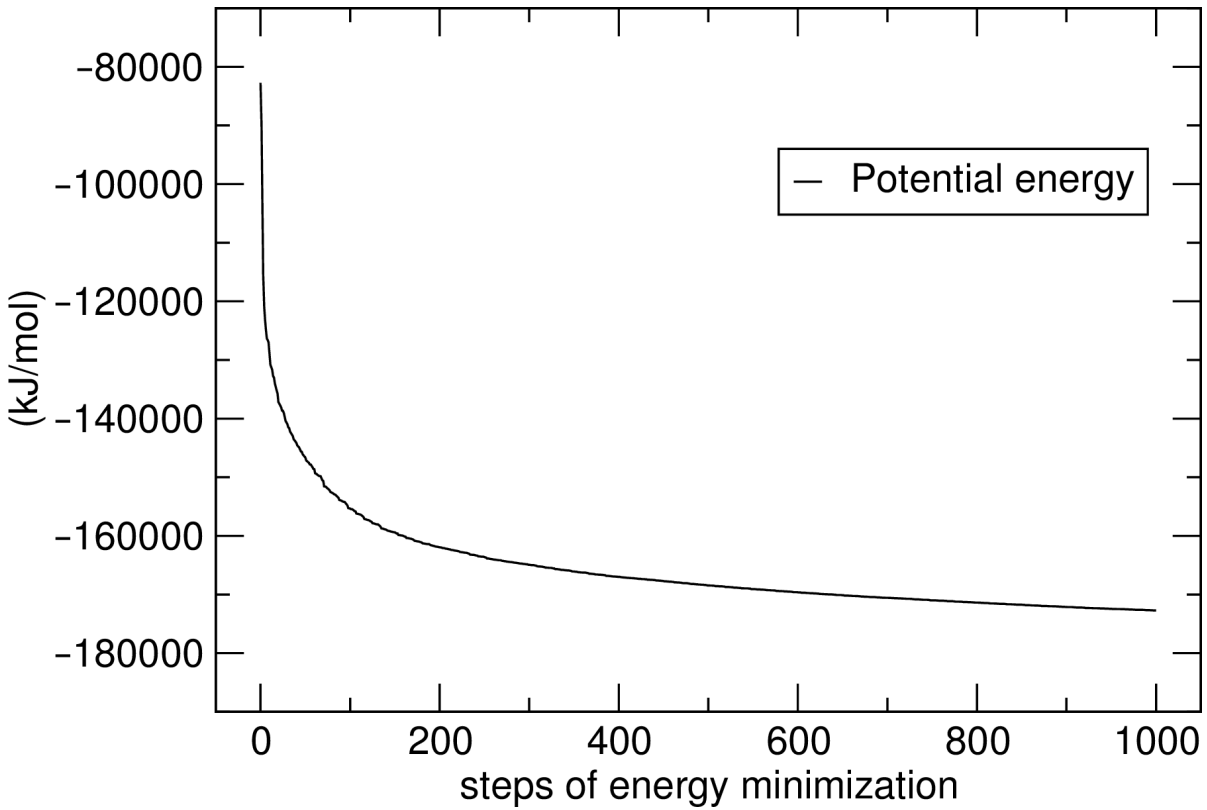
Why equilibrate?

- the initial structure may have high potential energy
  – dangerous – remove 'close contacts'
- often, static structure available – velocities missing
- often, structure resolved at different conditions (xtal)
- structure of solvent artificially regular – entropy wrong

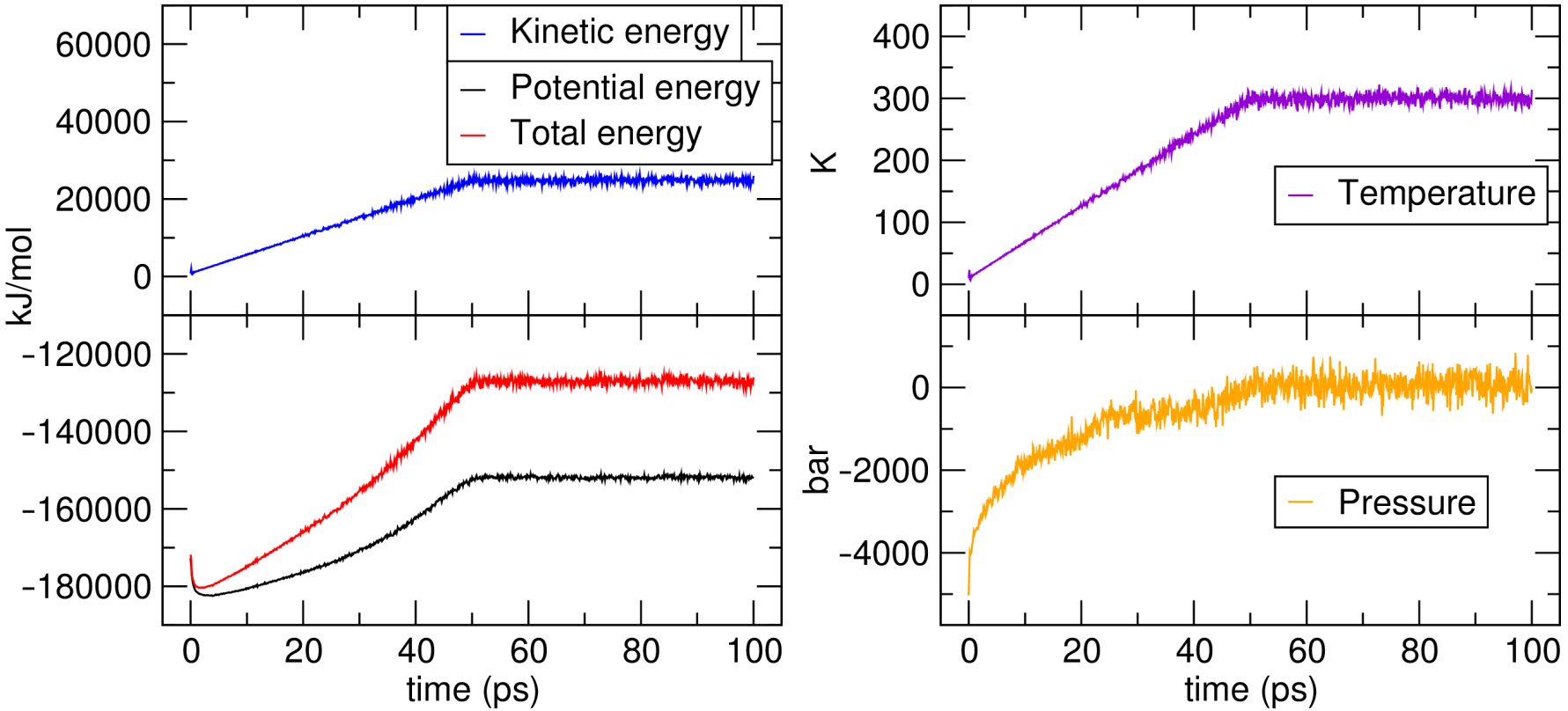
How to equilibrate

1. short optimization of structure – remove 'bad contacts'
2. assignment of velocities – randomly, at some (low) T
3. thermalization – heating the system up to the desired T, possibly gradually, with a thermostat – NVT simulation
4. simulation with the same setup as the production – probably NPT, with correct thermostat and barostat

Short optimization

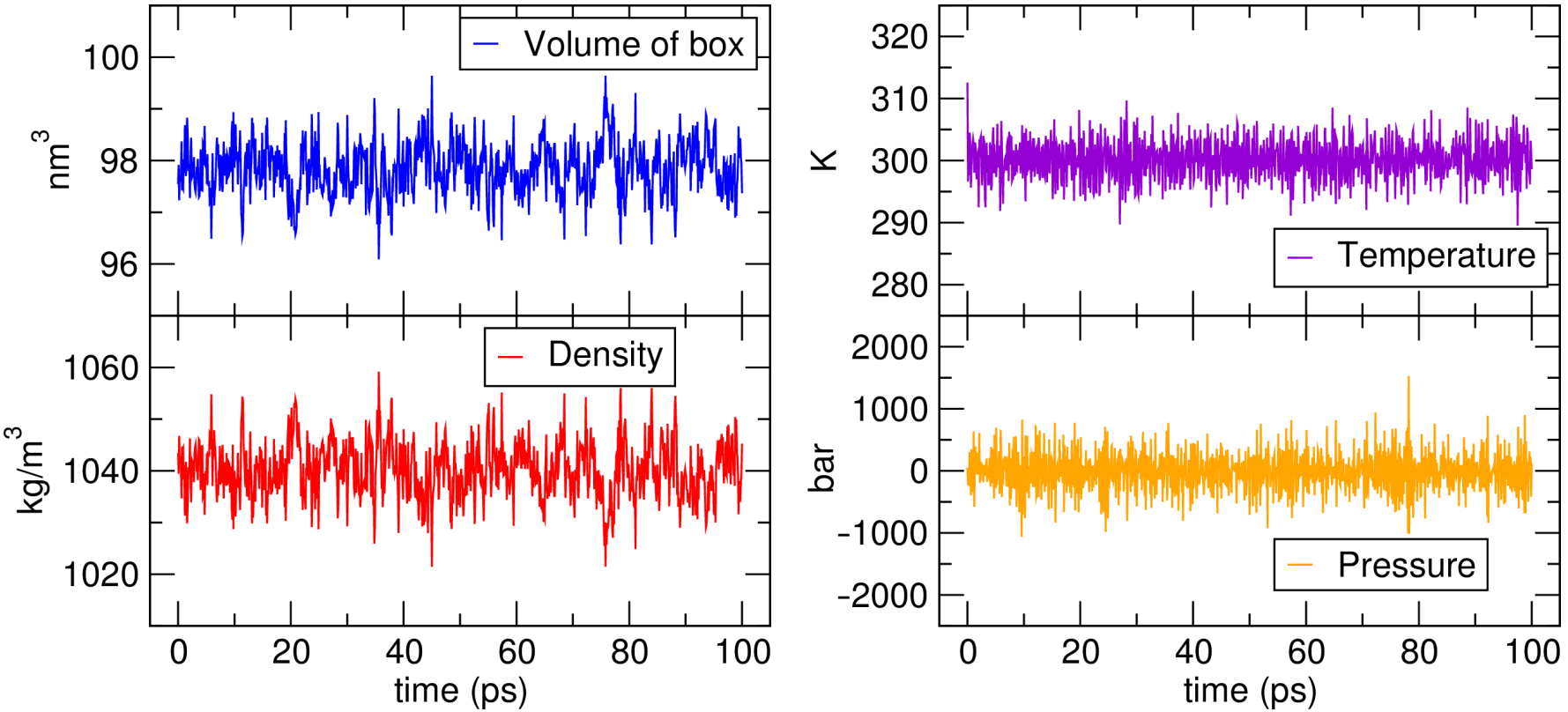


Thermalization



last 40 ps: $T = 300 \pm 7$ K, $p = 64 \pm 266$ bar

Equilibration



last 40 ps: $T = 300 \pm 3$ K, $p = -11 \pm 331$ bar

What comes then?

Productive simulation

– easy ☺

Analysis of the trajectory

– let us see. . .

Analysis of the simulation

Thermodynamic properties

- time averages of thermodynamic quantities
  – correspond to ensemble averages (ergodic theorem)
- some quantities – evaluated directly

$$U = \langle E \rangle_t$$

- fluctuations – may determine interesting properties:
  isochoric heat capacity:

$$C_V = \left(\frac{\partial U}{\partial T} \right)_V = \frac{\sigma_E^2}{k_B T^2} = \frac{\langle E^2 \rangle - \langle E \rangle^2}{k_B T^2}$$

  – elegant way to get heat capacity from a single simulation

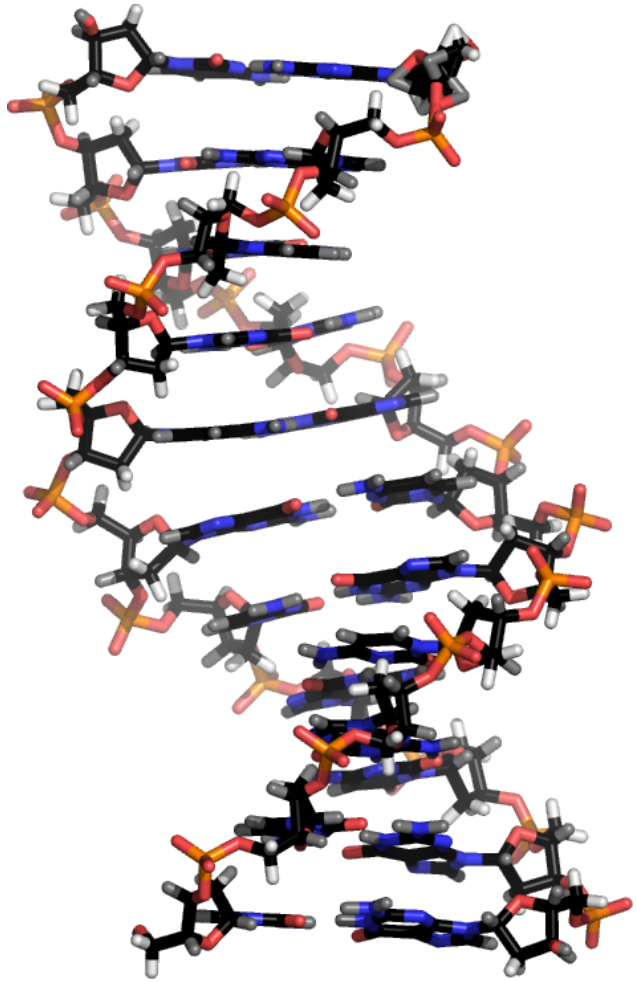
Structure – single molecule in solvent

concentrating on the dissolved molecule
- protein, DNA,...

average structure
- arithmetic mean of coordinates from snapshots along MD trajectory

$$\vec{r}_i = \frac{1}{N} \sum_{n=1}^{N} \vec{r}_i^{(n)}$$

- clear, simple, often reasonable



Average structure

Possible problems:

- freely rotatable single bonds – CH_3
  - all 3 hydrogens collapse to a single point
  - no problem – ignore hydrogens
- rotation of the entire molecule – no big issue
  - RMSD fitting of every snapshot to the starting structure

    what is RMSD? see on the next slide. . .
- molecule does not oscillate around a single structure
  - several available minima of free energy
  - possibly averaging over multiple sections of trajectory

Dynamic information

root mean square deviation (RMSD)
of structure in time t
from a suitable reference structure $\vec{r}^{\text{ref}}$

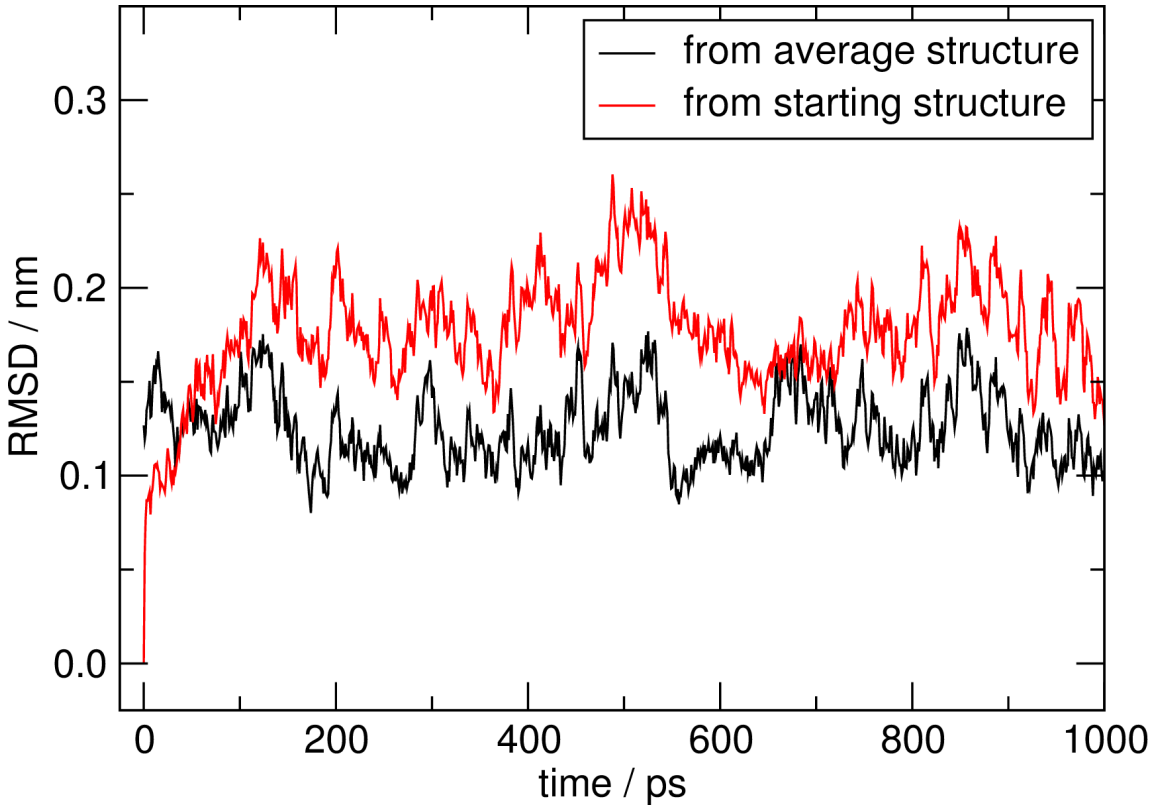
$$\text{RMSD}(t) = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left|\vec{r}_i(t) - \vec{r}_i^{\text{ref}}\right|^2}$$

- follows the development of structure in time
- reference structure – starting or average geometry
- also possible – comparison with another geometry of interest
  DNA: A- and B-like; proteins: α-helix and extended β

RMSD fitting – finding such a translation + rotation
that minimizes the RMSD from the reference structure

Root mean square deviation

RMSD of non-hydrogen atoms of a DNA oligonucleotide from given geometries



Root mean square deviation

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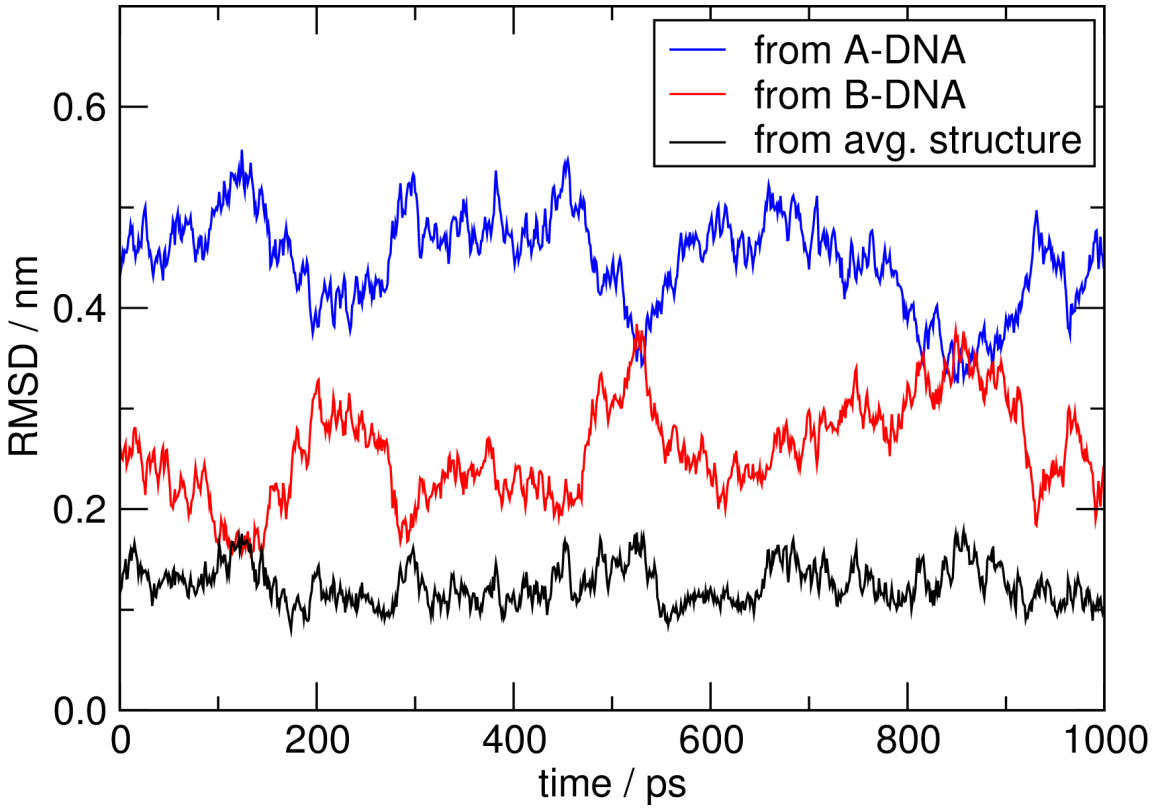
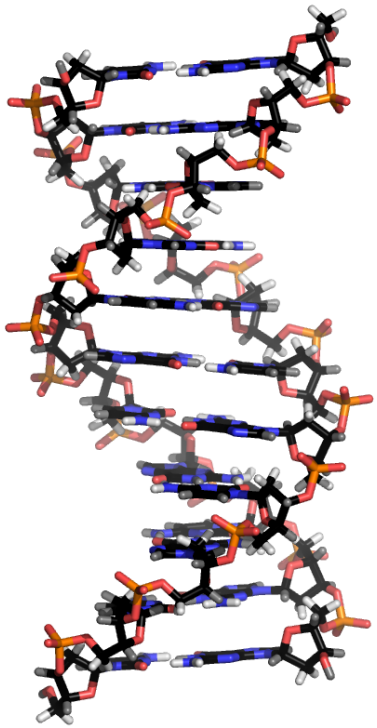
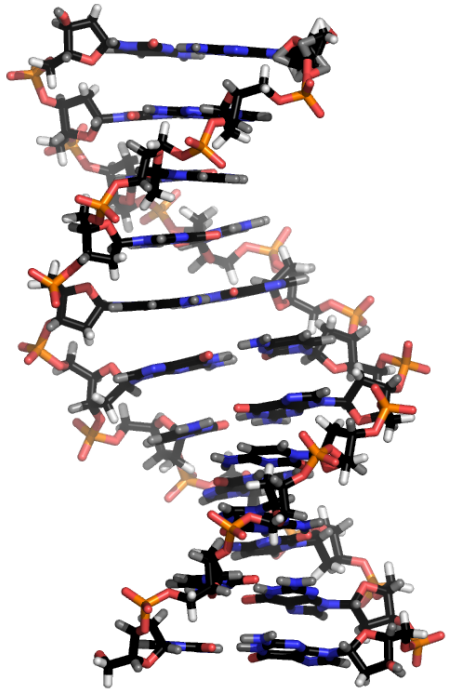


Root mean square deviation

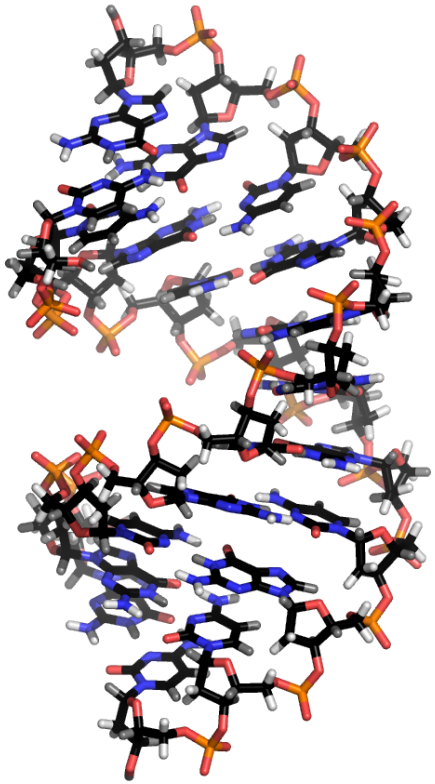
B-DNA



average structure



A-DNA



Magnitude of structural fluctuation

root mean square fluctuation (RMSF)
of position of every single atom
averaged along MD trajectory

$$\mathrm{RMSF}_i = \sqrt{\left\langle \left| \vec{r}_i - \langle \vec{r}_i \rangle \right|^2 \right\rangle}$$

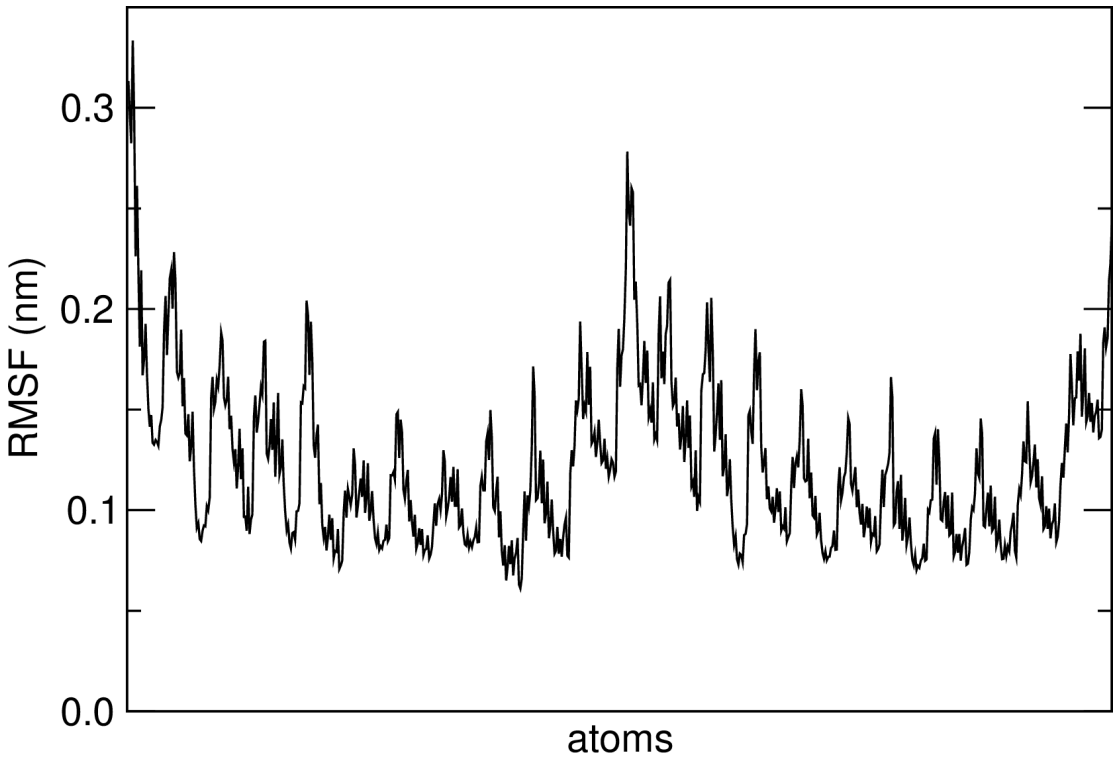
– may be converted to B-factor

$$B_i = \frac{8}{3}\pi^2 \cdot \mathrm{RMSF}_i^2$$

– observable in diffraction experiments (X-ray. . .)
– contained in structure files deposited in the PDB
– comparison of simulation with X-ray may be difficult

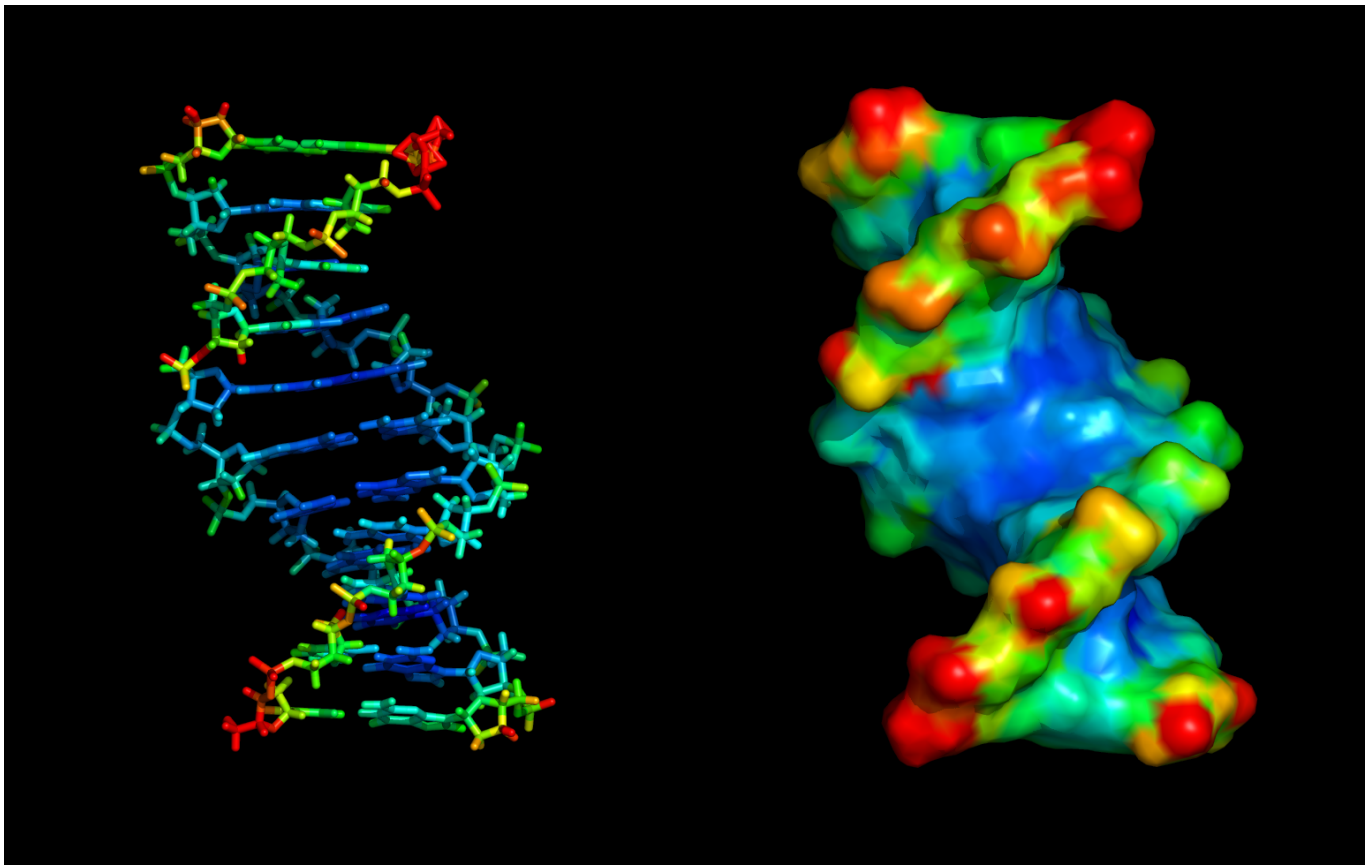
Root mean square fluctuation

RMSF of atomic positions in DNA oligonucleotide



Root mean square fluctuation

RMSF of atomic positions in DNA oligonucleotide

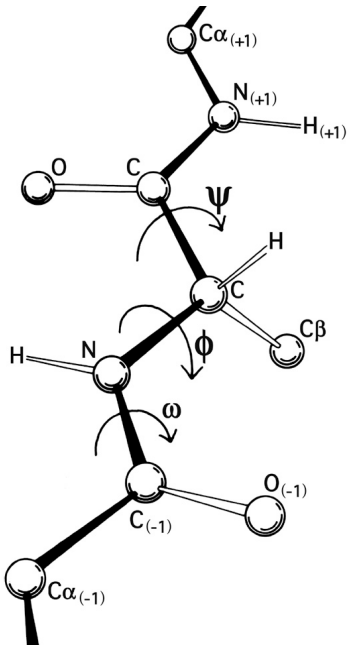


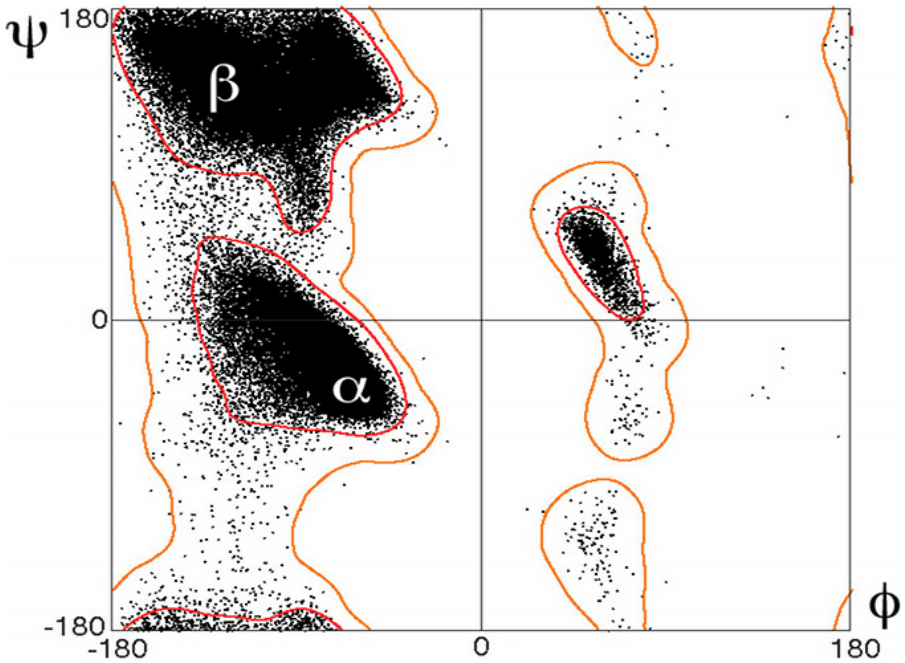
(blue $<$ green $<$ yellow $<$ red)

Structure of peptides and proteins

Ramachandran plot

- 2D histogram of dihedrals ϕ and ψ along the backbone
- different regions correspond to various second. structures
- may be generated easily in simulation software packages





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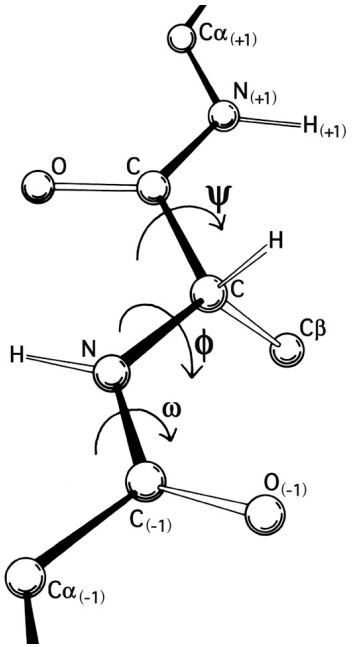
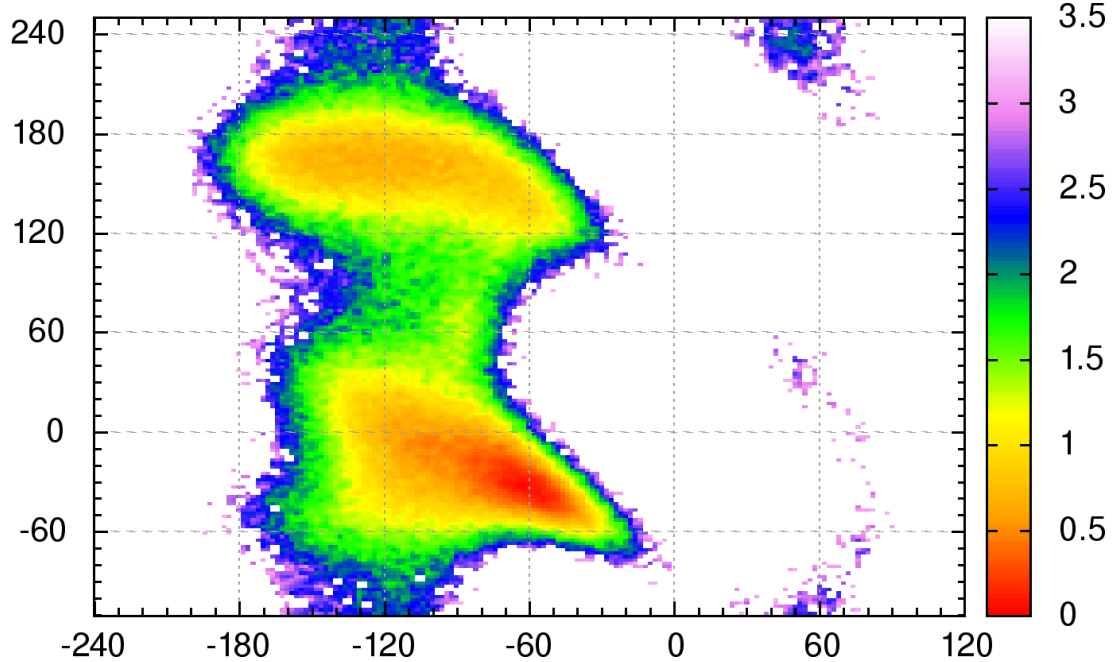
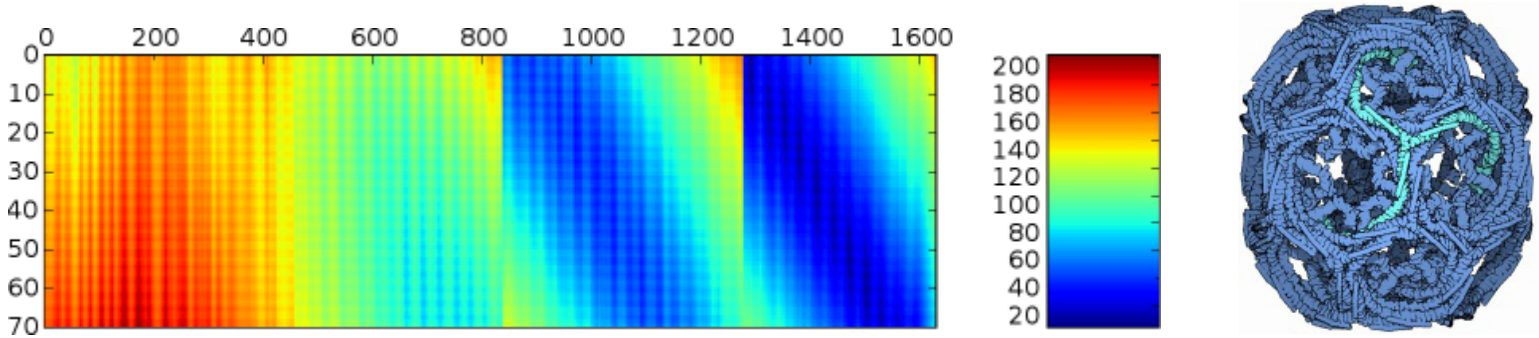




Structure of peptides and proteins

Distance matrix

- distances of amino-acid residues, represented e.g. by centers of mass or by C^{α} atoms
- either time-dependent or averaged over trajectory
- bioinformatics



distance matrix between two chains (horiz. and vertical axes) shows contacts between secondary structure elements

PDB ID 1XI4, clathrin cage lattice, April 2007 Molecule of the Month

http://www2.warwick.ac.uk/fac/sci/moac/people/students/peter_cock/python/protein_contact_map

Structure of fluids

example – pure argon or water – different situation
– many molecules, which are all equally important

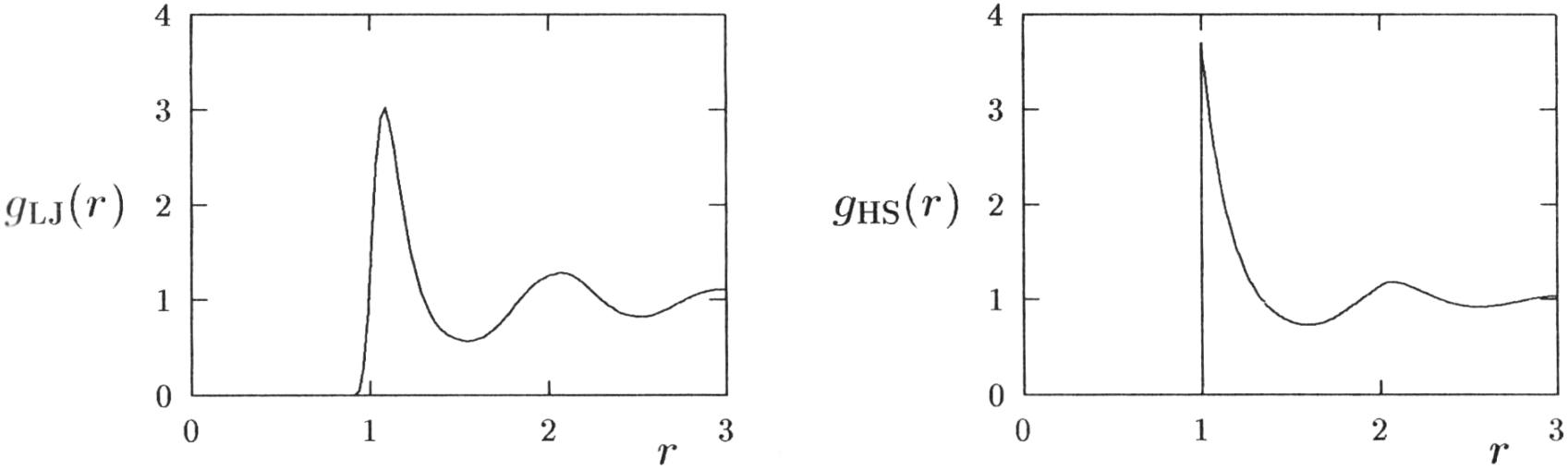
radial distribution functions

- describe how the molecular density varies
  as a function of the distance from one particular molecule
- spherical shell of thickness δr at a distance r: $\delta V \approx 4\pi r^2 \cdot \delta r$
- count the number of molecules in this shell: n
- divide by δV to obtain a 'local density' at distance r
- pair distribution function
  – probability to find a molecule in distance r from ref. mol.

$$g(r) = \frac{n/\delta V}{\rho} = \frac{n}{4\pi r^2 \cdot \delta r} \cdot \frac{1}{\rho}$$

Pair distribution function

Lennard-Jones fluid near the triple point and hard-sphere fluid – reprinted from Nezbeda, Kolafa and Kotrla 1998



- $g(r)$ vanishes on short distances – molecules cannot intersect
- high peak – van der Waals radius, closest-contact distance
  (even though hard spheres do not have any attraction!)
  – much more likely to find this distance in LJ or HS than in IG
- longer distances – a few shallow minima and maxima,
  converges to unity – uniform probability as in IG

Pair distribution function

Fourier transform of $g(r)$ – structure factor S

$$S(\vec{q}) = \frac{1}{N} \left\langle \sum_j \sum_k \exp\left[-i \cdot \vec{q} \cdot (\vec{r_j} - \vec{r_k})\right] \right\rangle$$

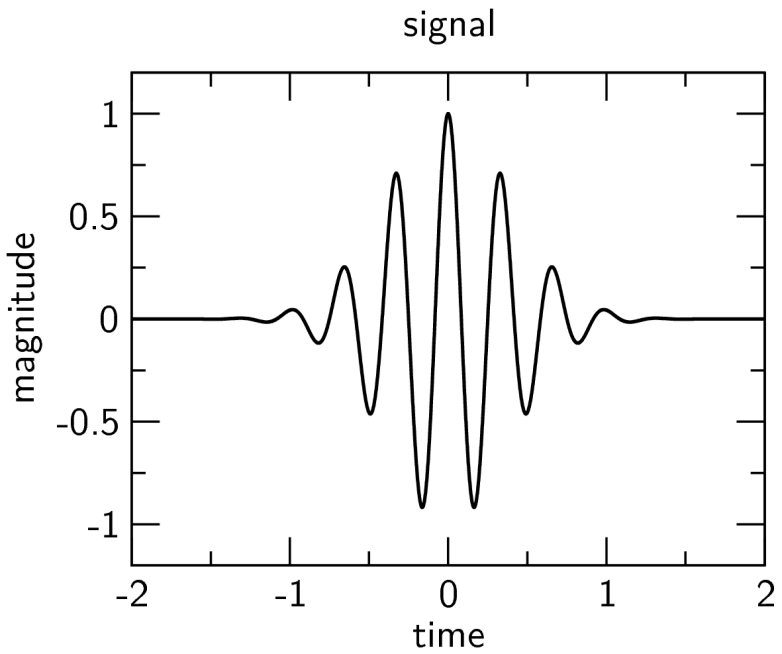
– quantifies the scattering of incoming radiation in the material
– measured in diffraction experiments (X-ray, neutron)

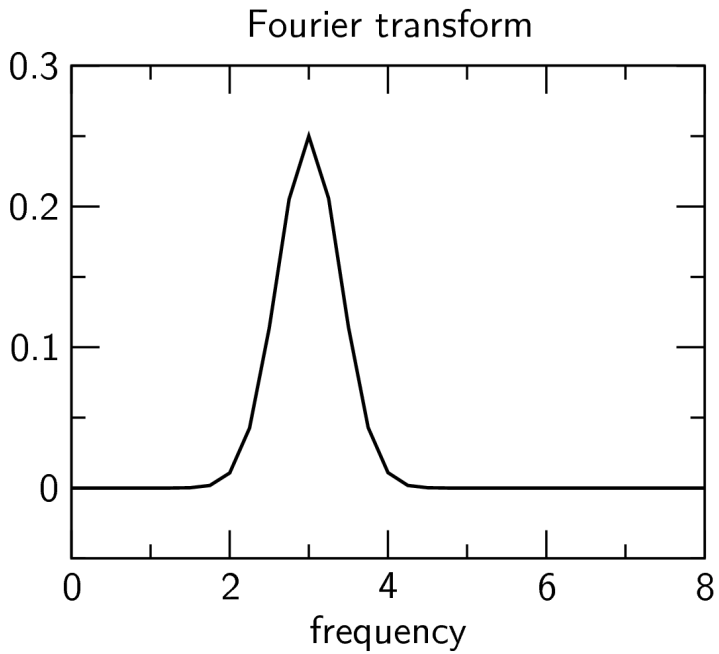
intermission: Fourier transformation

FT describes which frequencies are present in a function (of time)
– decomposes $f(t)$ into a 'sum' of periodic oscillatory functions

$$F(\omega) = \int_{-\infty}^{\infty} f(t) \cdot \exp\left[-\mathrm{i}\,\omega t\right] \,\mathrm{d}t$$

note that $\exp\left[-\mathrm{i}\,\omega t\right] = \cos\left[\omega t\right] - \mathrm{i}\sin\left[\omega t\right]$





Pair distribution function

Importance – not only information about the structure

calculation of thermodynamic properties possible

using potential energy $u(r)$ and force $f(r)$ of a molecule pair

corrections to the IG values of total energy and pressure (EOS!):

$$E - \frac{3}{2} N k_B T = 2\pi N \rho \int_0^\infty r^2 \cdot u(r) \cdot g(r)\, \mathrm{d}r$$

$$P - \rho\, k_B T = -\frac{2\pi}{3} \rho^2 \int_0^\infty r^3 \cdot f(r) \cdot g(r)\, \mathrm{d}r$$

(as long as pairwise additivity of forces can be assumed)

Correlation functions

two physical quantities x and y may exhibit correlation

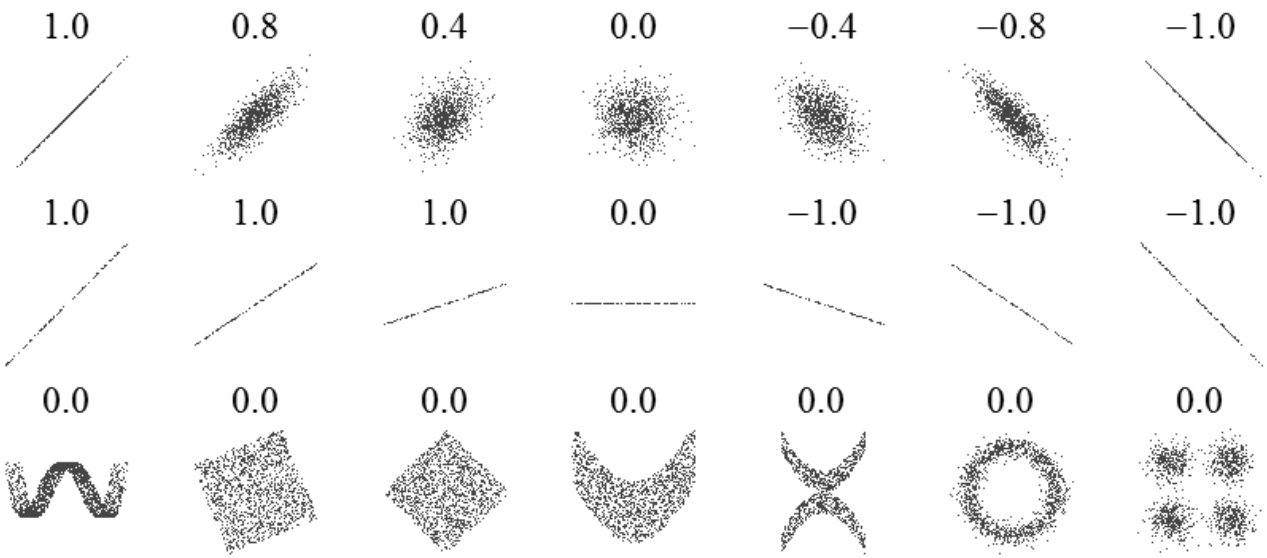
- indicates a relation of x and y, opposed to independence
- Pearson correlation coefficients
  - describe linear relationship between x and y
  - quantities fluctuate around mean values $\langle x \rangle$ and $\langle y \rangle$
  - consider only the fluctuating part
  - introduce correlation coefficient ρ_{xy}

$$\rho_{xy} = \frac{\langle (x - \langle x \rangle) \cdot (y - \langle y \rangle) \rangle}{\sqrt{\langle (x - \langle x \rangle)^2 \rangle \cdot \langle (y - \langle y \rangle)^2 \rangle}} = \frac{\mathrm{cov}(x, y)}{\sigma_x \cdot \sigma_y}$$

$\mathrm{cov}(x, y)$: covariance of x and y

Correlation functions

(not necessarily linear) correlation of two quantities and the corresponding correlation coefficients



Downloaded from Wikipedia

Correlation functions

MD – values of a quantity x as a function of time: $x = x(t)$
the value of x may be correlated

with the value of x at an earlier time point

– described by autocorrelation function (ACF)

$$c_x(t) = \frac{\langle x(t) \cdot x(0) \rangle}{\langle x(0) \cdot x(0) \rangle} = \frac{\int x(t')\, x(t'+t)\, \mathrm{d}t'}{\int x^2(t')\, \mathrm{d}t'}$$

– correlation of the same property x

at two time points separated by t,

averaged over all pairs of such time points,

normalized to take values between -1 and $+1$

Autocorrelation of velocity

autocorrelation function – quantifies 'memory' of the system, or how quickly the system 'forgets' its previous state

velocity autocorrelation function

– tells how closely the velocities of atoms at time t resemble those at time 0

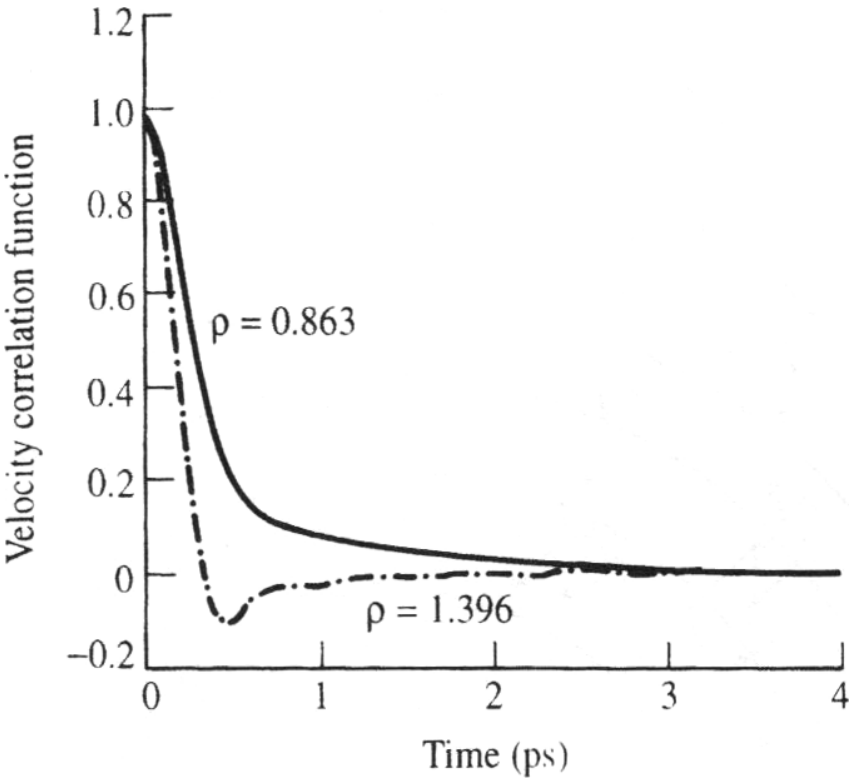
– usually averaged over all atoms i in the simulation

$$c_v(t) = \frac{1}{N} \sum_{i=1}^{N} \frac{\langle \vec{v}_i(t) \cdot \vec{v}_i(0) \rangle}{\langle \vec{v}_i(0) \cdot \vec{v}_i(0) \rangle}$$

– typical ACF starts at 1 in $t = 0$ and decreases afterwards

Autocorrelation of velocity

ACF of velocity in simulations of liquid argon (densities in g·cm^{-3})



Reprinted from Leach: Molecular Modelling

lower ρ – gradual decay to 0
higher ρ – ACF comes faster to 0
– even becomes negative briefly
– 'cage' structure of the liquid
– one of the most interesting achievements of early simulations

Autocorrelation of velocity

time needed to lose the autocorrelation whatsoever
– correlation time or relaxation time:

$$\tau_v = \int_0^\infty c_v(t)\,\mathrm{d}t$$

may help to resolve certain statistical issues:
when averaging over time the properties of system,
it is necessary to take uncorrelated values
if the property is dynamical (related to v),
we can take values of the property separated by τ_v

Autocorrelation of velocity

connection between velocity ACF and transport properties

- Green–Kubo relation for self-diffusion coefficient D:

$$D = \frac{1}{3} \int_0^\infty \langle \vec{v}_i(t) \cdot \vec{v}_i(0) \rangle_i \, \mathrm{d}t$$

- interesting observable quantities
- important to be able to calculate them from MD
- another way: Einstein relation for D

$$D = \frac{1}{6} \lim_{t \to \infty} \frac{\left\langle |\vec{r}_i(t) - \vec{r}_i(0)|^2 \right\rangle_i}{t}$$

NB: Fick's laws of diffusion $J = -D \frac{\partial \phi}{\partial x}$, $\frac{\partial \phi}{\partial t} = D \frac{\partial^2 \phi}{\partial x^2}$

Autocorrelation of dipole moment

velocity – property of a single atom; contrary to that –

– some quantities need to be evaluated for whole system

total dipole moment:

$$\vec{\mu}_{\text{tot}}(t) = \sum_{i=1}^{N} \vec{\mu}_i(t)$$

ACF of total dipole moment:

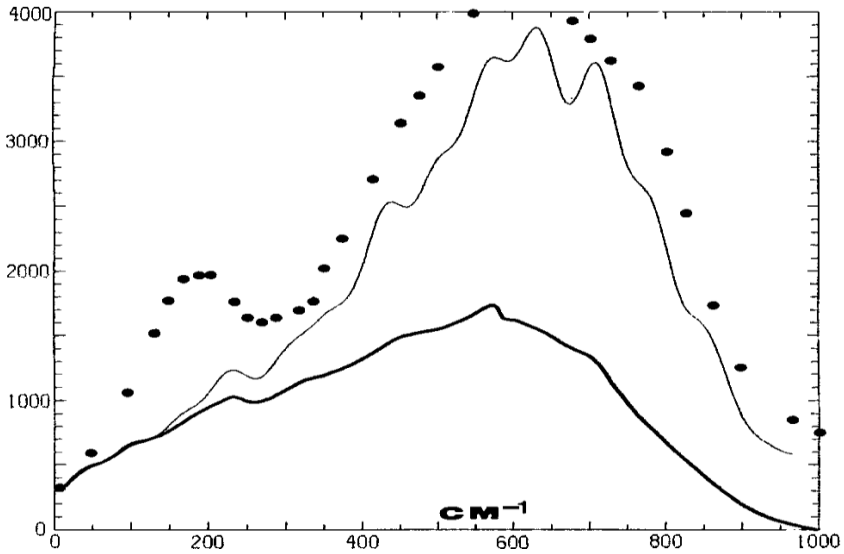
$$c_\mu(t) = \frac{\langle \vec{\mu}_{\text{tot}}(t) \cdot \vec{\mu}_{\text{tot}}(0) \rangle}{\langle \vec{\mu}_{\text{tot}}(0) \cdot \vec{\mu}_{\text{tot}}(0) \rangle}$$

– related to the vibrational spectrum of the sample

– IR spectrum to be obtained as Fourier transform of dipolar ACF

Autocorrelation of dipole moment

IR spectra for liquid water from simulations



thick – classical MD,
thin – quantum correction,
black dots – experiment

B. Guillot, J. Phys. Chem. 1991

no sharp peaks at well-defined frequencies (as in gas phase)

rather – continuous bands – liquid absorbs frequencies in a broad interval

frequencies – equivalent to the rate of change of total dipole moment

Principal component analysis

covariance analysis on the atomic coordinates along MD trajectory
= principal component analysis (PCA), or essential dynamics

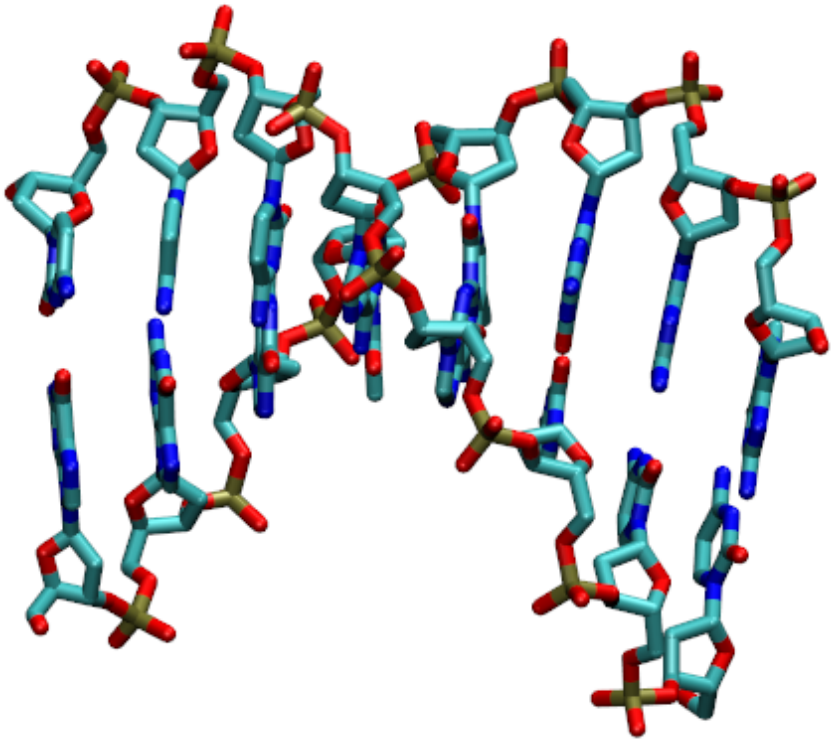
$3N$-dim. covariance matrix C of atomic coordinates $r_i \in \{x_i, y_i, z_i\}$

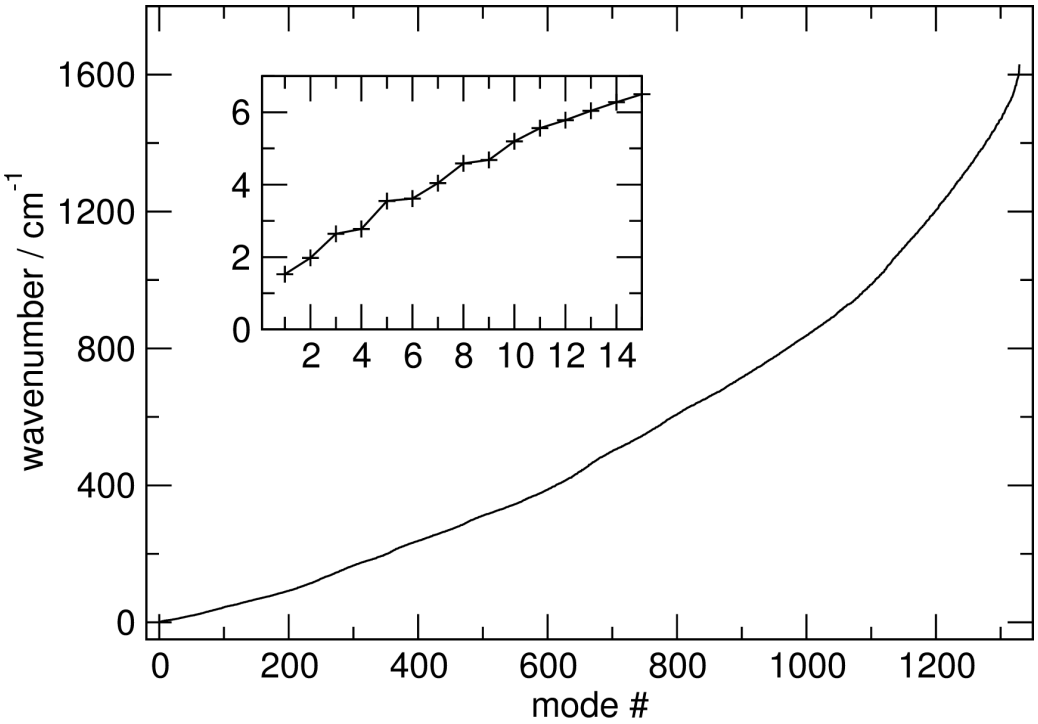
$$C_{ij} = \langle (r_i - \langle r_i \rangle) \cdot (r_j - \langle r_j \rangle) \rangle_t \quad \text{or}$$
$$C_{ij} = \left\langle \sqrt{m_i}(r_i - \langle r_i \rangle) \cdot \sqrt{m_j}(r_j - \langle r_j \rangle) \right\rangle_t$$

diagonalization $\rightarrow$
- eigenvalues – may be expressed as vibrational frequencies
- eigenvectors – principal or essential modes of motion
  - – analogy of normal modes of vibration
  - – first few – global, collective motions, many atoms involved

Principal component analysis

example – PCA of a double-stranded DNA octanucleotide, frequencies and 3 lowest eigenvectors





Principal component analysis

DNA – the modes are the same as expected for a flexible rod
- 2 bending modes around axes perpendicular to the principal axis of the DNA, and a twisting mode

PCA – gives an idea of what the modes of motion look like
- additionally – basis for thermodynamic calculations
  - vibrational frequencies may lead to configurational entropy