# Various topics

## Coarse graining; hard bodies; Monte Carlo techniques

Marcus Elstner and Tomáš Kubař

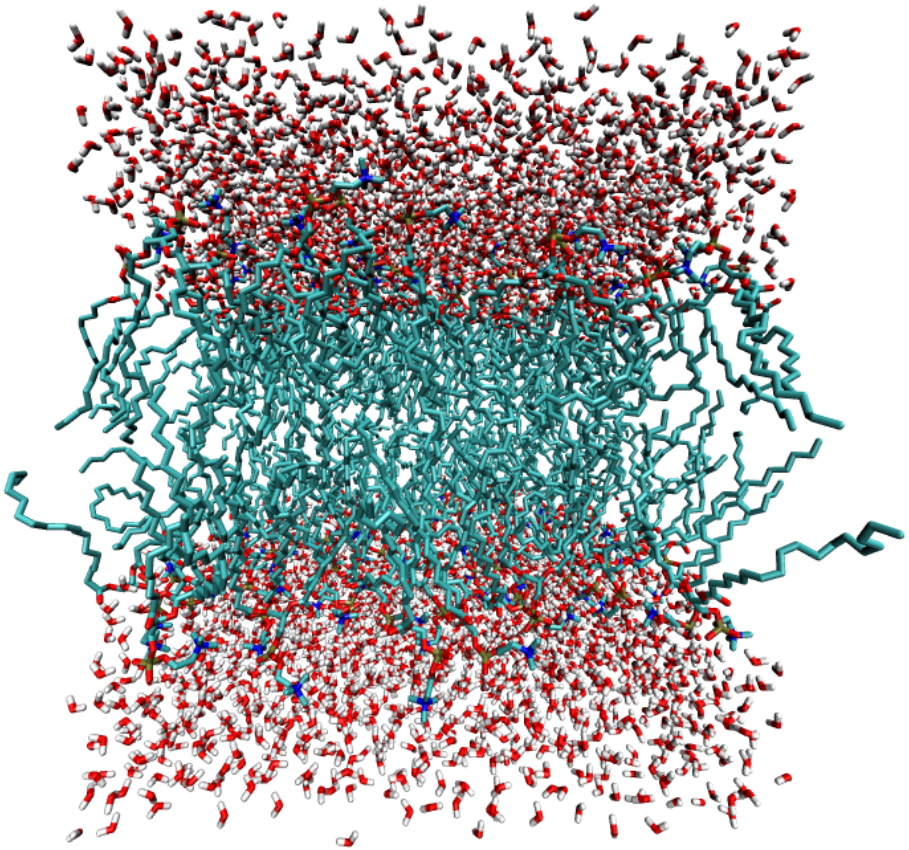
2019, July 25

# United-atom force fields

- early biomolecular FF (e.g. Weiner84), popular in the 1990's
- hydrogen atoms considered as condensed to the heavy atom
- mass and charge represent such a group of atoms as a whole
- number of atoms reduced considerably relative to all-atom FF
- good for non-polar C–H bonds – so $CH_3$ is one united atom
- polar O–H group by a single 'atom' – too crude
  $\rightarrow$ only non-polar hydrogens usually condensed with heavy

# United-atom force fields

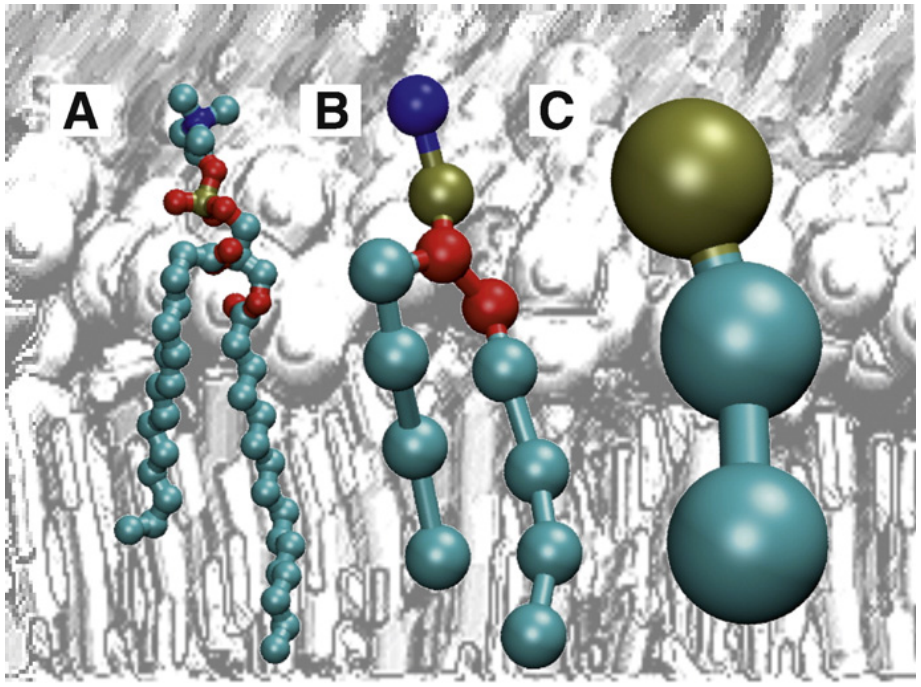
still sometimes used e.g. for lipids – each $CH_2$ is a united atom



(simulation of a DOPC bilayer in water – Berger FF for the lipid)

from the website of Rainer Böckmann

# United-atom and coarse-grained force fields




(A) united-atom, (B) specific and (C) generic coarse-grained

from Marrink et al., Biochim. Biophys. Acta 2009

# Coarse-grained models

Coarse graining – an advanced and sophisticated approach
to reduce the computational expense of simulations

The same idea – reduction of the number of particles
Considered are particles composed of several atoms – beads
Fewer inter-particle interactions $\rightarrow$ reduced computational expense

The necessary parameters – often obtained
by fitting to all-atom force fields

# Coarse-grained models

Every bead usually represents several atoms,
and a molecule is composed of several beads
Solvent – e.g. a 'water bead' composed of 4 $H_2O$ molecules

Some of the transferability of all-atom FF is lost:

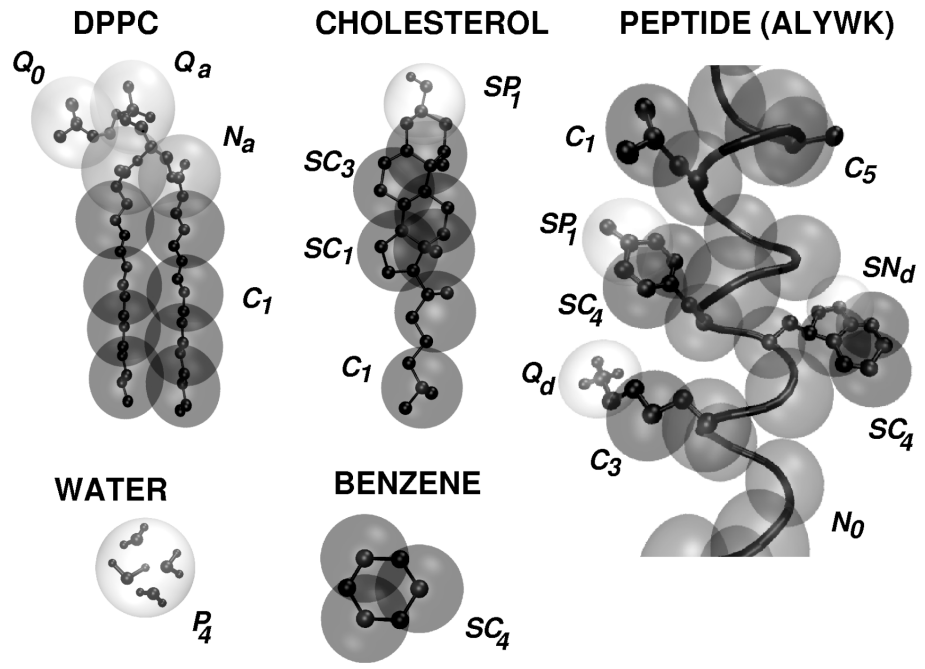
- secondary structure of proteins is fixed with Martini FF
- hydrogen bonding cannot be described with beads explicitly (solution – compensation with Lennard-Jones contributions)

Application area – large-scale conformational transitions involving

- exceedingly large molecular systems
- excessive time scales
- or both

# Martini force field

mapping of beads onto molecular fragments with Martini FF

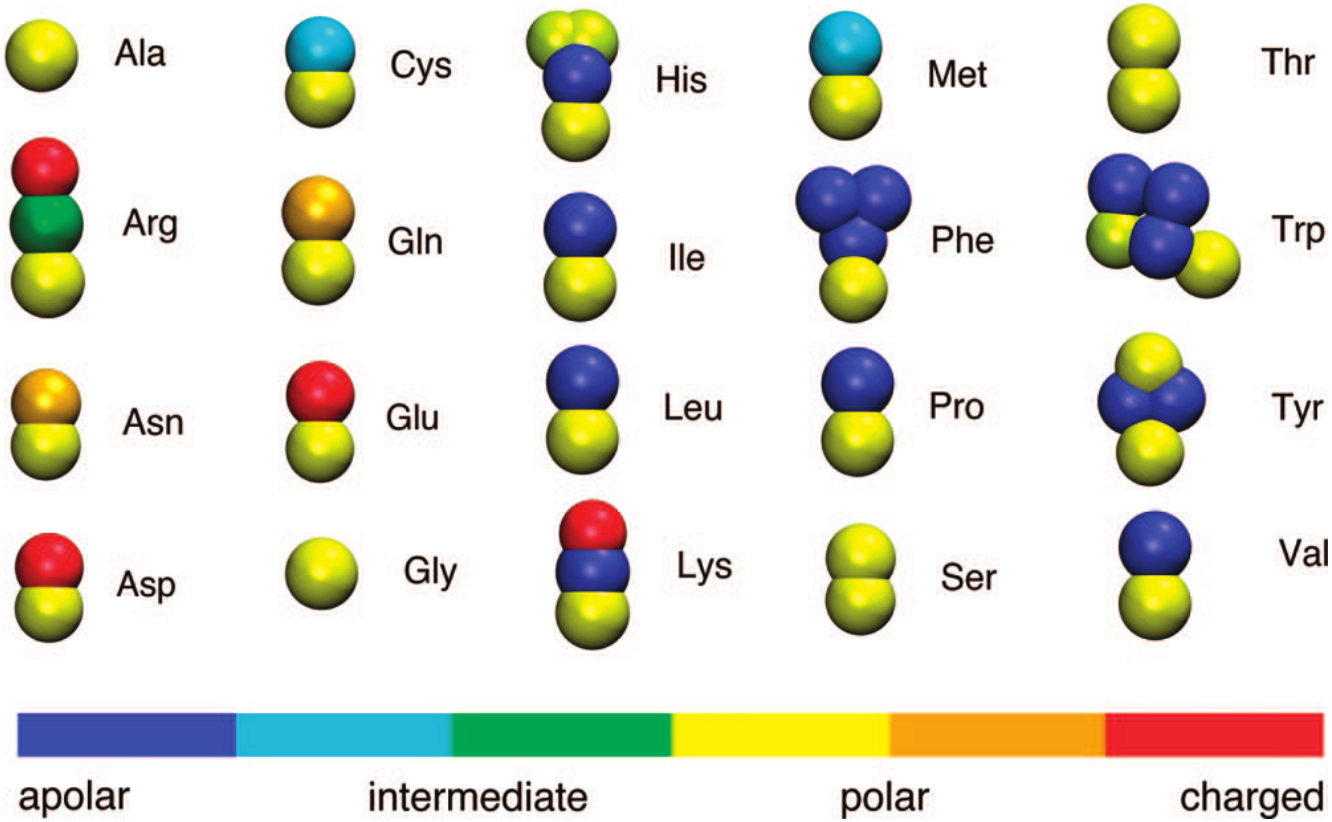



- 3 to 4 heavy atoms compose one bead ('4-to-1 mapping')
- mass of beads – 72 u (= 4 $H_2O$), or 45 u in ring structures

from the Martini website

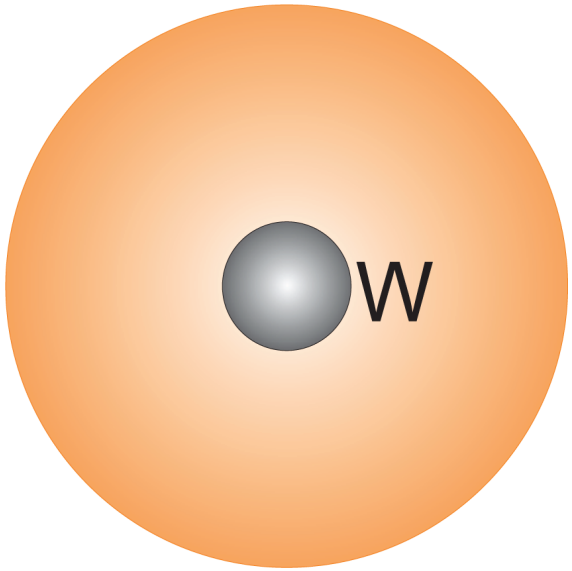
# Martini force field

the amino acids:




from Monticelli et al., J. Chem. Theory Comput. 2008

# Martini force field

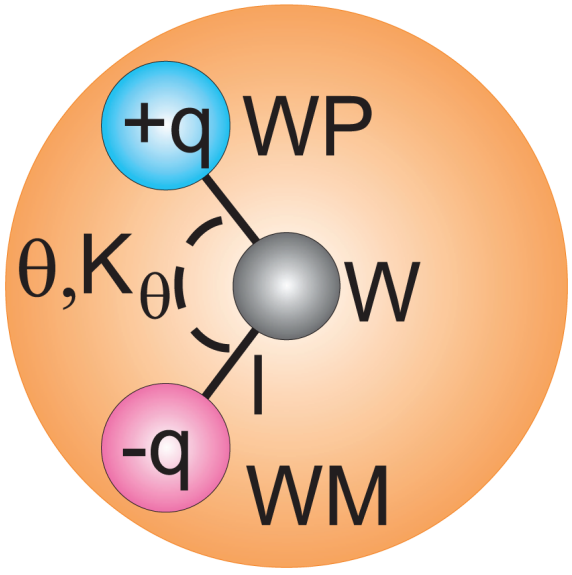



standard water
in the Martini FF

from Yesylevskyy, Schäfer et al.
PLOS Comput. Biol. 2010

- 1 bead represents 4 $H_2O$ molecules
- too high freezing temperature – solution:
  10 % of 'antifreeze' particles – W with large $\sigma$
- no charges $\rightarrow$ blind to electrostatic field and polarization
- Martini has implicit screening of electrostatic interactions,
  assuming a uniform relative dielectric constant
- problematic at phase interfaces and close to charged particles

# Martini force field



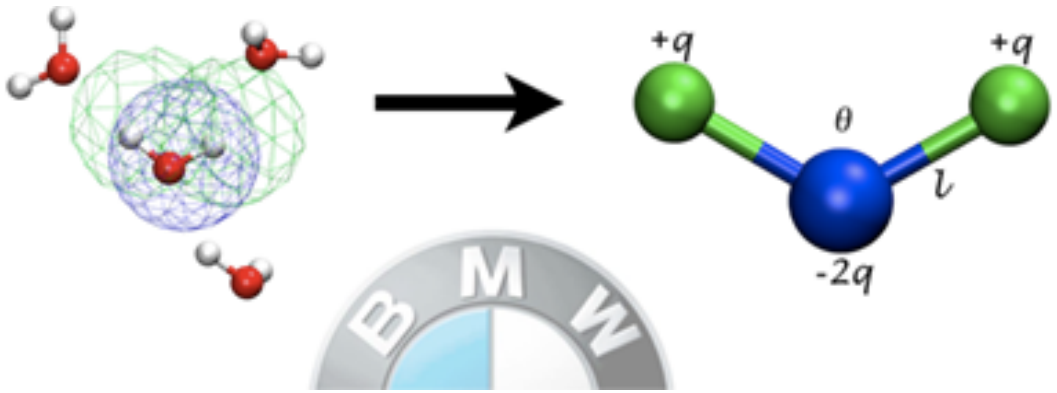

an alternative model
– polarizable water

from Yesylevskyy, Schäfer et al.
PLOS Comput. Biol. 2010

- expectation – more realistic description of processes
  involving interactions between charged and polar groups
  in a low-dielectric medium
- a new class of applications of Martini possible, e.g.:
  - translocation of ions through lipid bilayers
  - electroporation (octane slab, lipid bilayer)
- does not cure all problems, though...

# Martini force field

big multipole water – another polarizable model for Martini FF

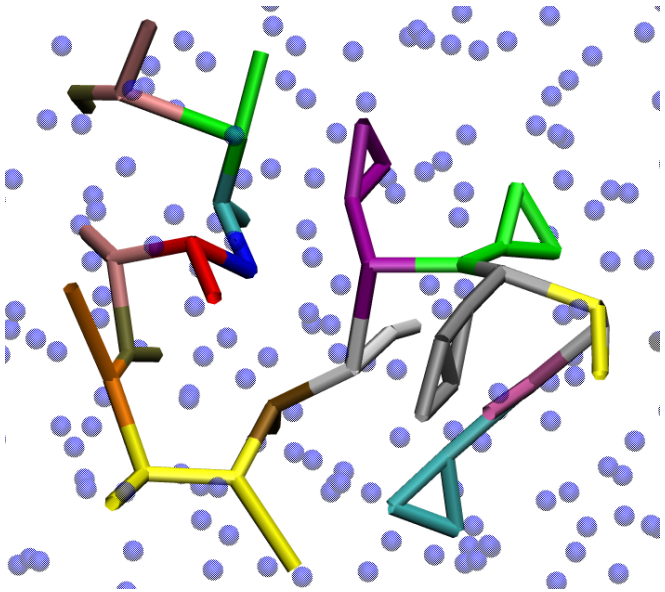



- parametrized by fitting of elstat. and van-der-Waals potentials of $(H_2O)_4$ clusters, generated with an atomistic model
- infer appropriate functional forms of non-bonded interactions (e.g., use a much softer potential than LJ for vdW)
- particularly suitable for cases difficult to original Martini – highly charged peptides + lipid bilayers, like antimicrobial, cell penetrating, membrane deforming pept.

Wu et al., J. Chem. Theory Comput. 2011

# Martini force field

a solvated peptide with Martini FF



# Martini force field

development continues. . .

# Acceleration of the simulation

Why does a coarse-grained simulation run faster?

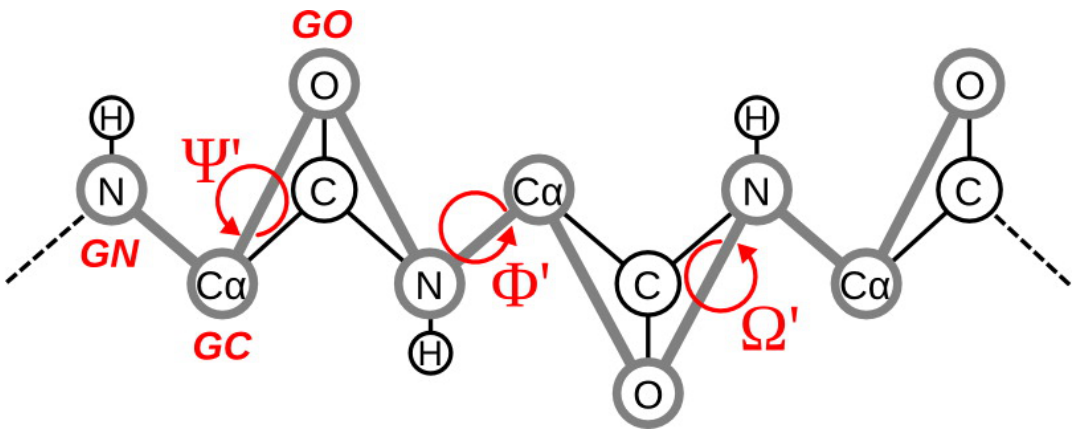
- smaller number of particles $\rightarrow$ fewer interactions to compute
- long integration time step due to large masses of beads
  – 25 fs with Martini (i.e. 100 fs effectively, see below)
- FF often constructed for use with faster simulation algorithms
  – e.g. cut-off for electrostatics with Martini
- smaller number of DOF $\rightarrow$ smoother free energy surfaces
  $\rightarrow$ fewer barriers $\rightarrow$ acceleration of all processes
  (by a factor of 3 to 8 for Martini, but not uniformly!
  – factor of 4 for acceleration of diffusion in water)

"... length and time scales that are 2 to 3 orders of magnitude larger compared to atomistic simulations, providing a bridge between the atomistic and the mesoscopic scale."

# Coarse-grained models

SIRAH force field

- somewhat less coarse-grained, closer to united-atom
- representation of backbone dihedral angles retained

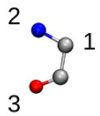
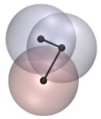
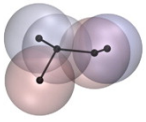
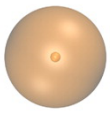


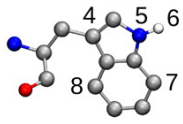
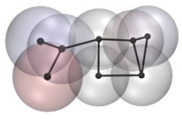
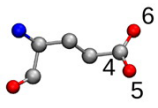
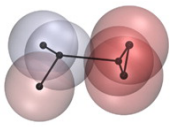
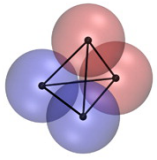

from Pantano et al., J. Chem. Theory. Comput. 2015

# Coarse-grained models

## SIRAH force field

- less coarse-grained → possibly improved transferability
- explicit solvent, long-range electrostatics (no cut-off)

| FG | CG | SIRAH name | q (e) | σ (nm) | ε (kJ/mol) |
|---|---|---|---|---|---|
| G  |  | 1: GC | 0,10 | 0,40 | 0,55 |
| | | 2: GN | 0,125 | 0,40 | 0,55 |
| | | 3: GO | -0,225 | 0,40 | 0,55 |
| S  |  | 4: BOG | -0,20 | 0,41 | 0,35 |
| | | 5: BPG | 0,20 | 0,40 | 0,01 |
| $Na^+$ and 6 water molecules |  | 1: NaW | 1,00 | 0,58 | 0,55 |

| FG | CG | SIRAH name | q (e) | σ (nm) | ε (kJ/mol) |
|---|---|---|---|---|---|
| W  |  | 4: BCG | 0 | 0,35 | 1,70 |
| | | 5: BNE | -0,10 | 0,35 | 0,10 |
| | | 6: BPE | 0,10 | 0,35 | 0,01 |
| | | 7: BCZ | 0 | 0,35 | 1,70 |
| | | 8: BCE | 0 | 0,35 | 1,70 |
| E  |  | 4: BCD | -0,30 | 0,40 | 0,35 |
| | | 5: BOE1 | -0,35 | 0,45 | 0,55 |
| | | 6: BOE2 | -0,35 | 0,45 | 0,55 |
| WT4 11 water molecules |  | 1: WN1 | -0,41 | 0,42 | 0,55 |
| | | 2: WN2 | -0,41 | 0,42 | 0,55 |
| | | 3: WP1 | 0,41 | 0,42 | 0,55 |
| | | 4: WP2 | 0,41 | 0,42 | 0,55 |

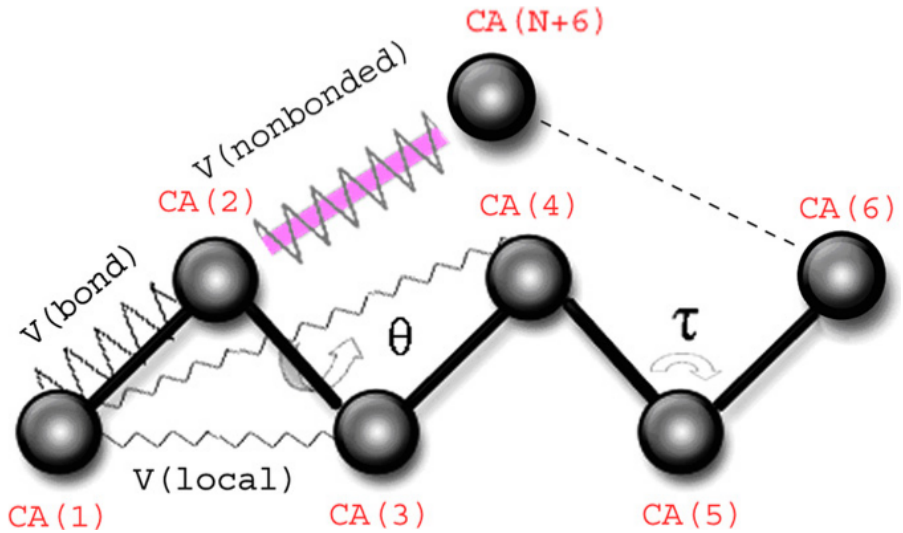
- illustration – different compromises may be made

from Pantano et al., J. Chem. Theory. Comput. 2015

# Coarse-grained models

VAMM force field for proteins

- every amino acid represented by a single bead at $C_\alpha$




- more coarse-grained than Martini

from Korkut & Hendrickson 2009

# MD simulation of hard bodies

first MD simulation of a system in the condensed phase

- used the model of hard spheres
  (Alder & Wainwright, J. Chem. Phys. 1957)
- first step from the ideal gas towards realistic molecules
- valuable tool in statistical thermodynamics
  $\rightarrow$ equations of state and virial expansions

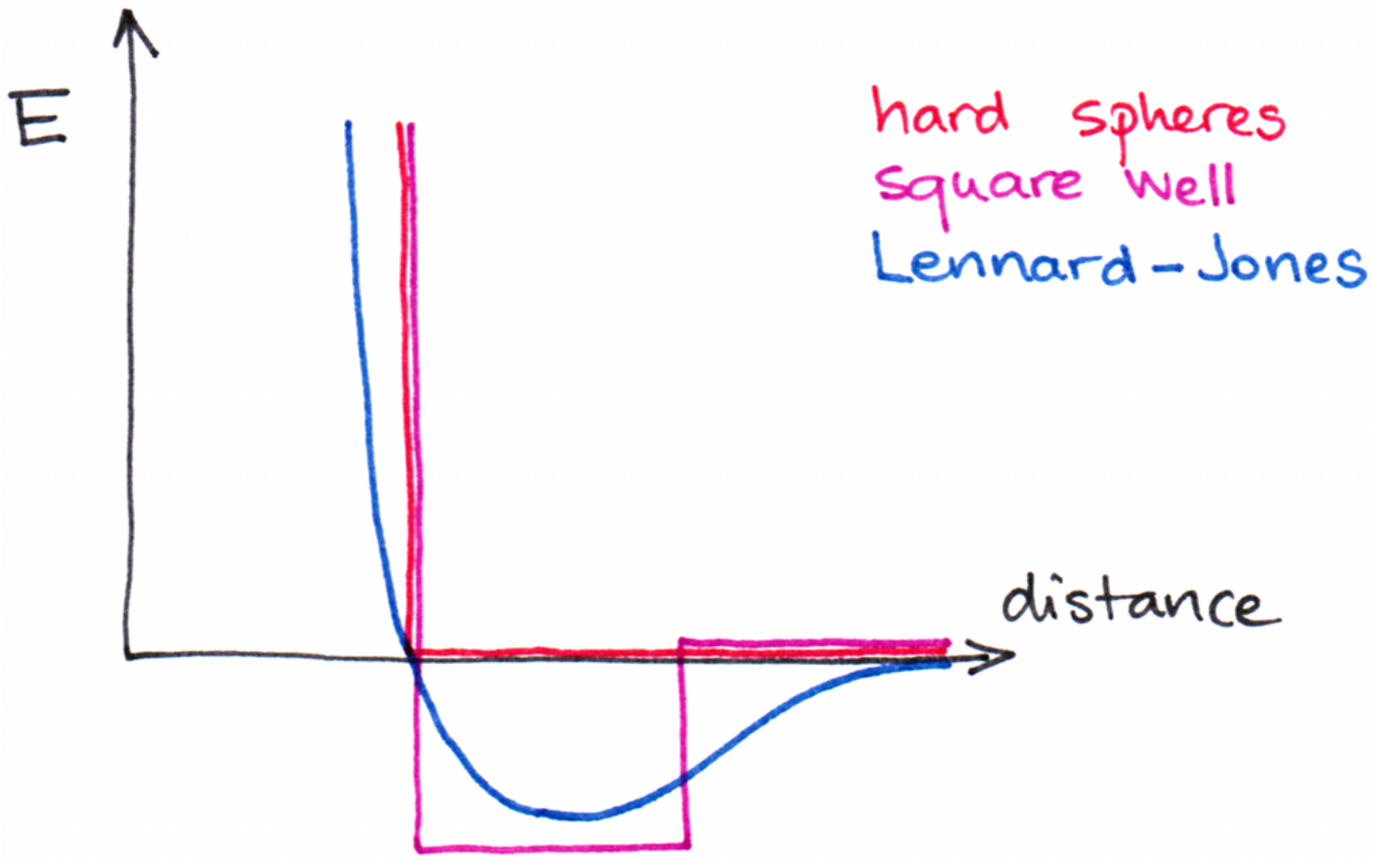
# The hard-sphere potential

- pairwise potential
- potential energy of a system of two hard spheres with radius $R$
  - is zero for distances larger than the diameter of the spheres
  - is infinity for shorter distances, when the spheres overlap:

$$V(r) = \begin{cases} 0 & \text{if } r > 2R \\ +\infty & \text{otherwise} \end{cases}$$

- is discontinuous $\rightarrow$ not differentiable
- different from potentials typically used in biomol. simulation

# The hard-sphere potential



# The square-well potential

a more realistic description preserving the simplicity of the model?

square well model

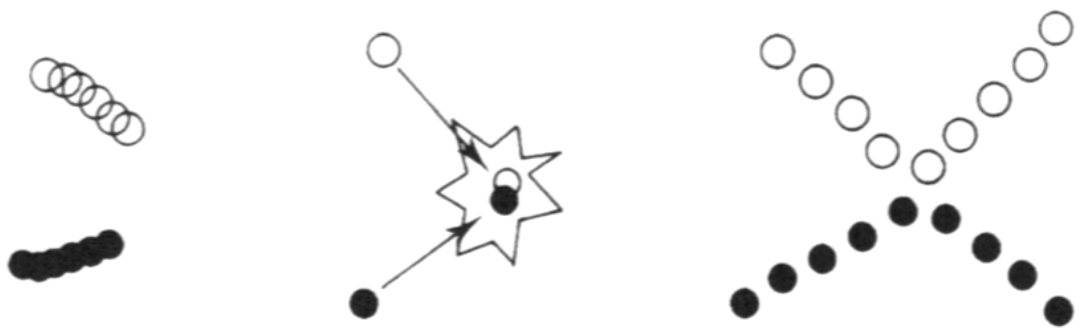
- region of negative potential energy (attractive interaction) starting at the contact distance $2R$
- goes in the direction of the Lennard-Jones potential, which describes nonpolar fluids very well

# Hard convex bodies

- another extension used in statistical thermodynamics
- potential energy function is discontinuous, still:
  zero if the bodies do not intersect; infinity if they do
- enhancement – the bodies are not spherical anymore,
  but rather ellipsoidal or polyhedral
- may describe e.g. diatomic molecules better than hard sphere

# Simulation protocol

propagation of Newton's EOM with e.g. Verlet integrator
– continuous and smooth potential required
otherwise – sudden 'jumps' in forces lead to unstable simulations,
or at least wrong sampling of the configuration space



reprinted from Leach, Molecular Modelling

# Simulation protocol

Hard spheres cannot be simulated with a usual integrator
– explosions caused by sudden clashes of atoms would occur
(similar to those in usual MD simulations with too large $\Delta t$)
However, with hard spheres, any arbitrarily short $\Delta t$ is 'too long'

What would a simulation of hard spheres with Verlet look like?
There are no forces in any initial configuration,
and so the spheres move with their initial velocities
until, all of a sudden, two spheres start to overlap.
The energy and forces are infinite, and the simulation crashes.

# Simulation protocol

The protocol has to be adjusted to the discontinous potential
– event-driven protocol

The spheres move along straight lines between collisions,
which are perfectly elastic and instantaneous

1. Identify the next pair of spheres to collide,
   and calculate when this collision will occur
2. Calculate the positions of all spheres at the collision time –
   conservation of linear momentum and of kinetic energy
3. Determine the new velocities of the two spheres after collision
4. Repeat from start

# Simulation protocol

No further approximations are involved in this protocol
→ simulation will be exact within the model of hard spheres

Note: With continuous potentials, we had to make approximations, like a stepwise integration of the eqns of motion

Potential energy – constant (zero) throughout the simulation
Conservation of total energy → conservation of kinetic energy
→ temperature is constant in any hard-spheres simulation

# Monte Carlo simulation

The main objective of molecular dynamics –
mostly not to study how the molecular system evolves in time,
rather to generate configurations of the system
(sampling $\rightarrow$ calculation of thermodynamic quantites)
MD is not the only possibility to do this ...

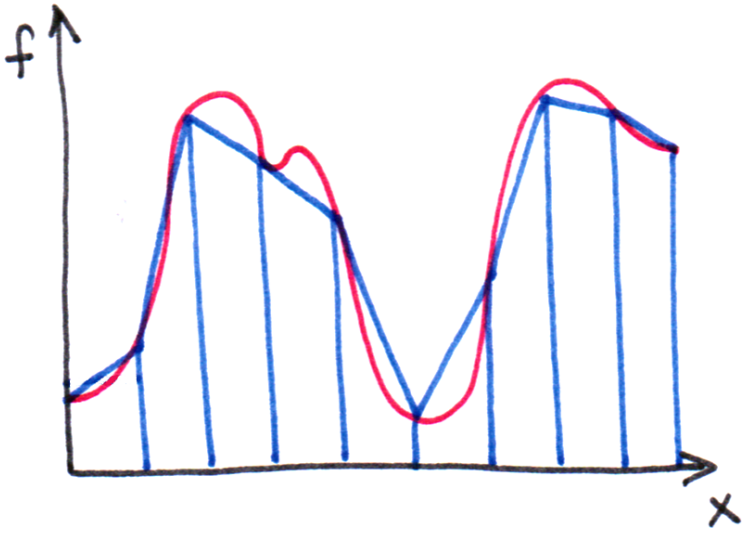
Another possibility – Monte Carlo methods (MC),
which involve random number generators

Actually, first computer simulations of molecular systems were MC
(Metropolis et al., J. Chem. Phys. 1953)

# Monte Carlo integration

Major goal of molecular simulation – calculation of thermodynamic properties – integration (formally)

Can we use a method based on randomness for integration?



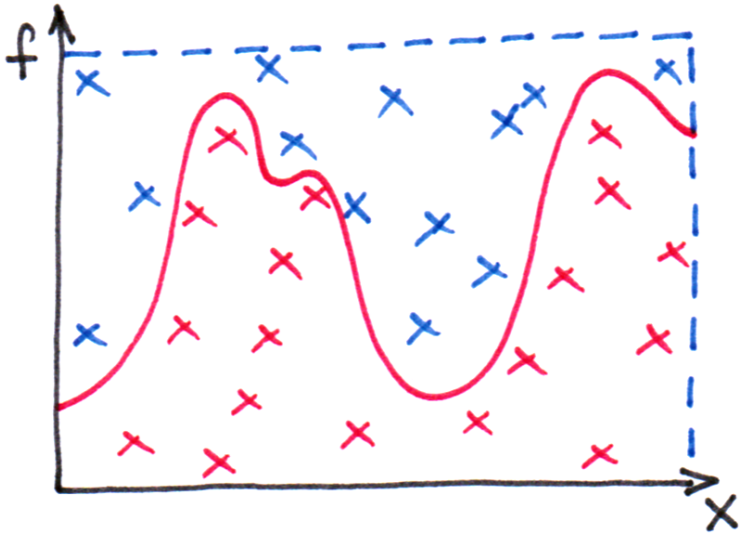

Possibility – trapezium rule

- comes intro trouble for functions of many variables
- we always have many variables in molecular systems

# Monte Carlo integration

Major goal of molecular simulation – calculation of thermodynamic properties – integration (formally)

Can we use a method based on randomness for integration?




Alternatively

- generate $N$ points randomly
- count points ($n$) under curve
- area under the curve relative to the rectangle $\approx n/N$

Apply the Monte Carlo idea to calculate $\pi$ as follows:

Generate pairs of random number between 0 and 1 $(x, y)$.
Count the pairs for which $x^2 + y^2 < 1$, i.e. the point $(x, y)$ lies within the circle centered at (0,0) with a radius of 1.
The ratio of this number to the total number of pairs approaches $\pi/4$.

# Monte Carlo integration

Importantly:
Extension of this ansatz to many dimensions is straightforward
– useful for studies of molecular systems

Groundbreaking idea (Metropolis):
Generate the configurations with the right probability,
creating the correct thermodynamic (e.g. canonical) ensemble

Such importance sampling will make it trivial to average
thermodynamics quantities over the generated configurations

# Metropolis' method

Typical MC simulation of a molecular system:

- a sequence of configurations is generated in an iterative way
- in every iteration, one configuration is produced.

Usually:

1. A trial configuration is constructed from the current one
   by randomly shifting one randomly chosen particle (atom).
2. It is tested if this configuration shall be accepted or not.
   For this, potential energy of the entire system is calculated.
   (possible optimization – only small part of the system changes,
   $\rightarrow$ only a small fraction of the interactions changes)

# Metropolis' method

1. trial coordinates are calculated with random $\xi_{x,y,z} \in (0,1)$:

$$x_{\text{trial}} = x + (2\xi_x - 1) \cdot \delta r$$
$$y_{\text{trial}} = y + (2\xi_y - 1) \cdot \delta r$$
$$z_{\text{trial}} = z + (2\xi_z - 1) \cdot \delta r$$

$\delta r$ – maximum allowed displacement

2. acceptance probability of the trial configuration is obtained from potential energy – current $U$, of trial config $U_{\text{trial}}$:

$$\mathcal{P} = \begin{cases} 1 & \text{if } U_{\text{trial}} < U \\ \exp\left[-\frac{U_{\text{trial}} - U}{k_B T}\right] & \text{otherwise} \end{cases}$$

The trial configuration is accepted if $\mathcal{P} >$ random $\zeta \in (0,1)$ otherwise it is discarded and another trial is generated

# Acceptance ratio

The percentage of accepted configurations (among all generated) governed by max. allowed displacement $\delta r$ – adjustable parameter

- usually chosen so that $\frac{1}{3}$ to $\frac{1}{2}$ of all configs are accepted
- this was shown to lead to the most efficient sampling

$\delta r$ too small $\rightarrow$ most configurations are accepted though,
but the configurations are very similar $\rightarrow$ slow sampling
$\delta r$ too large $\rightarrow$ too many trial configurations are rejected

Often – $\delta r$ adjusted in the course of the simulation
in order to reach a certain target acceptance ratio

# Properties of MC

- generates a correct thermodynamic ensemble (canonical)
- involves temperature naturally
  - no additional thermostat necessary
  - difference from MD
- no kinetic information (velocities, $E_{\text{kin}}$)

# MC protocol – variations

Possible modifications to the algorithm:

- move the atoms sequentially, in a preset order,
  instead of selecting one randomly
  – one fewer random number needed
- move several atoms at once,
  instead of a single atom
  – very efficient sampling of config space
  (with appropriate $\delta r$)

# Generators of pseudorandom numbers

Several random numbers in every iteration have to be obtained
and a large number of iterations is needed
→ reliable and efficient source of random numbers needed.

Most convenient – 'calculate' random numbers in some way
paradoxical requirement (computers are deterministic)

There are ways to generate sequences of pseudorandom numbers
not actually random, but still independent enough of each other,
with right statistical properties → useful for MC

# Linear congruential generators

- most commonly used generators
- produce sequences of pseudorandom numbers
- a following number in the sequence $\xi_{i+1}$ is obtained
  1. from the previous number $\xi_i$
  2. multiplying by a constant $a$
  3. adding another constant $b$
  4. and taking the remainder when dividing by a constant $m$
- initial value (seed) has to be chosen (often – system time)

$$\begin{aligned} \xi_0 &= \text{seed} \\ \xi_{i+1} &= (a \cdot \xi_i + b) \bmod m \end{aligned}$$

- value $\in (0, 1)$ is obtained by dividing $\xi_{i+1}$ by the modulus $m$

# Linear congruential generators

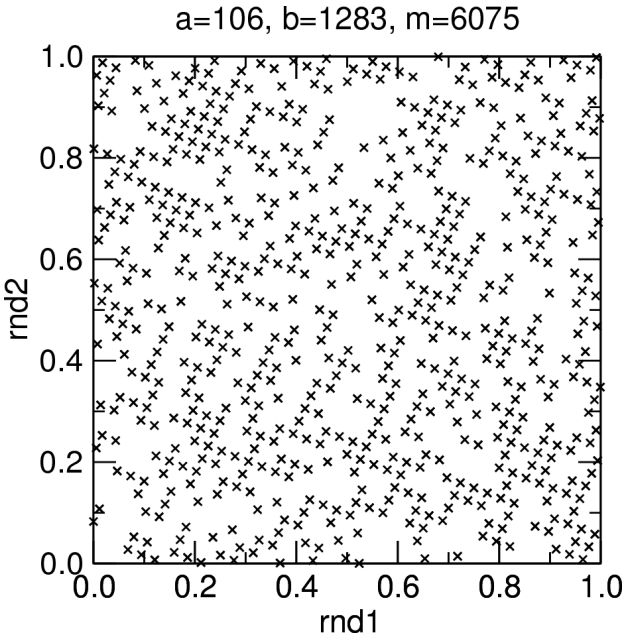
Very important – choose appropriate values of $a$, $b$ and $m$
Then, the generator will produce all possible values $0, \ldots, m-1$
and will start to repeat the sequence only after $m$ numbers.
Otherwise – the sequence starts to repeat itself much earlier,
and the randomness is severely limited.

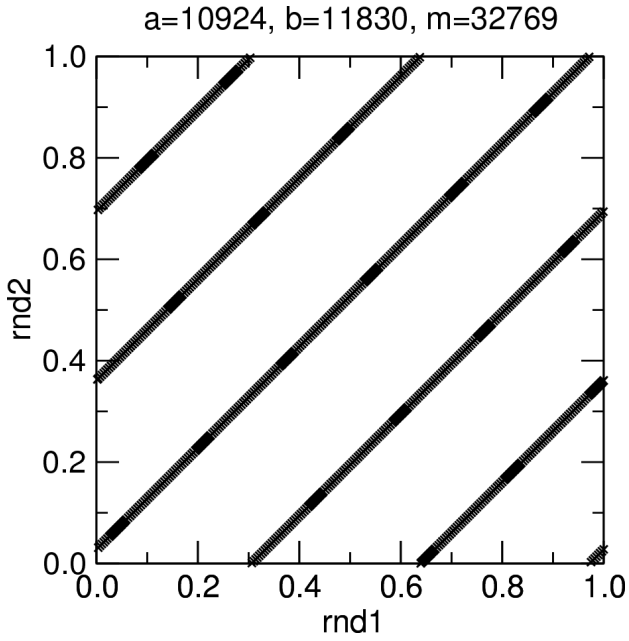
Disadvantage – if we generate points in an $N$-dimensional space,
these are not distributed uniformly in the space,
but rather they lie on at most $\sqrt[N]{m}$ $(N-1)$-dimensional planes
(i.e. on straight lines if we have a 2D space).
With really poor generators – much fewer than $\sqrt[N]{m}$ hyperplanes.

An example is RANDU: $\xi_0$ is odd and $\xi_{i+1} = 65539 \cdot \xi_i \bmod 2^{31}$.
All generated values are odd, the period is only $2^{29}$,
and the points $(\xi_i, \xi_{i+1}, \xi_{i+2})$ cumulate on as few as 15 planes in space.

# Linear congruential generators

A good and bad generator of pseudorandom numbers:




Each point (rnd1,rnd2) is a pair of consecutive numbers from LCG

# Generators of higher quality

Still, LCG are often used in MC simulations
because of extreme simplicity and computational efficiency.

Higher-quality pseudorandom number generators:

linear feedback shift register generators

- uses several bits from current number to generate new ones
- does not cumulate the generated numbers on hyperplanes

Mersenne twister

- current state of the art among generators
- extremely long period of $2^{19937} - 1$
- no cumulation of numbers on hyperplanes up to 623 dim.
- even suitable for cryptographic applications

# Alternative generators of random numbers

In Unix-like operating systems (with Linux being the first),
`/dev/random` (or `/dev/urandom`) is a special file
that serves as a random or pseudorandom number generator.

It accesses environmental noise collected from device drivers etc.

from Wikipedia

# Monte Carlo simulation of molecules

Easiest implementation – system of monoatomic molecules
(translational degrees of freedom only)
Polyatomic molecules – more complex situation,
most difficult if there is large conformational flexibility

Then, the internal degrees of freedom have to be free to vary
$\rightarrow$ overlap of atoms $\rightarrow$ energy grows steeply
$\rightarrow$ extremely low acceptance ratio

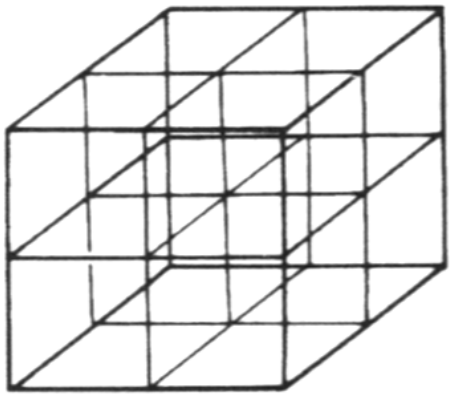
Rigid molecules – still quite easy to simulate with MC
– orientation in space being varied beside position in space
– rotation along an axis $x$, $y$ or $z$ by randomly chosen angle

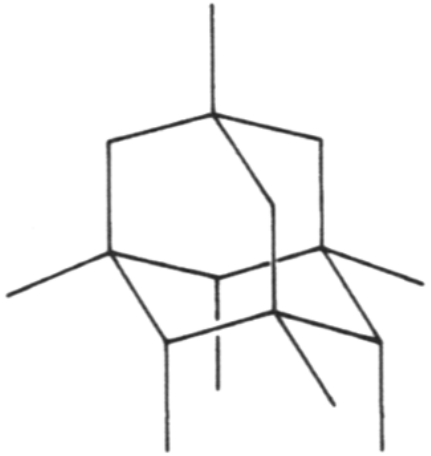
# Monte Carlo simulation of polymers

Macromolecular chemistry – particularly rich MC application area
Approximative polymer models are often suitable for MC
– a chain of monomer units, which are elementary particles

Potential energy function – usually rudimentary or even eliminated
(simplicity of the model + requirement of efficiency)

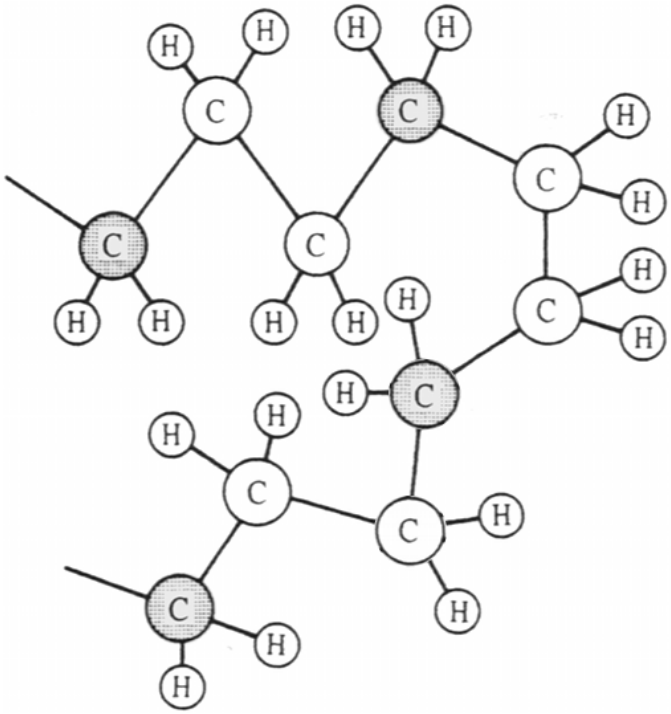
Lattice models – monomer units connected with a bond occupy neighboring lattice points on a cubic or tetrahedral lattice

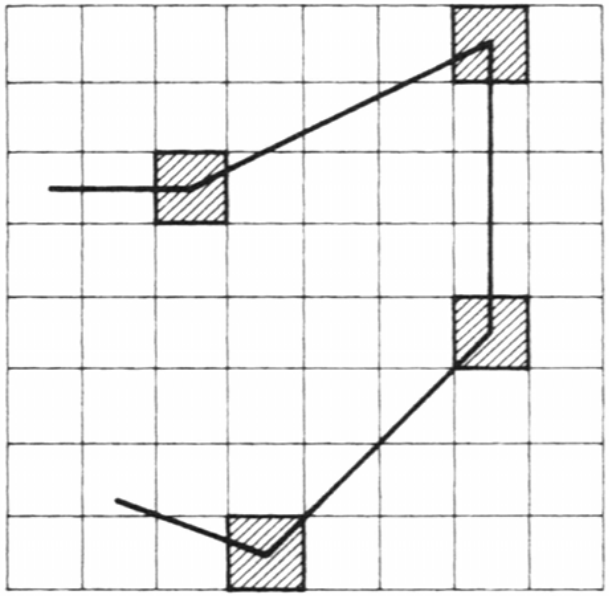




# Monte Carlo simulation of polymers

More realistic and complex – bond fluctuation model
- lattice is finer-grained compared to the bond length
- 'effective' bonds are not constrained to the edges of lattice



# Monte Carlo simulation of polymers

Simplest type of simulation – random walk

- the polymer chain is growing in random directions
  until the desired length is reached
- first implementation – excluded volume of previous segments
  is not considered $\rightarrow$ the chain is free to cross itself

structural properties – from averaging over growing simulations:

- end-to-end distance $\left\langle R_n^2 \right\rangle_0 = n \cdot L^2$
- radius of gyration $\left\langle s_n^2 \right\rangle_0 = \left\langle R_n^2 \right\rangle / 6$

  for a chain composed of $n$ bonds with length $L$

# Monte Carlo simulation of polymers

Excluded volume not described – may seem too crude,
but this is not necessarily a problem

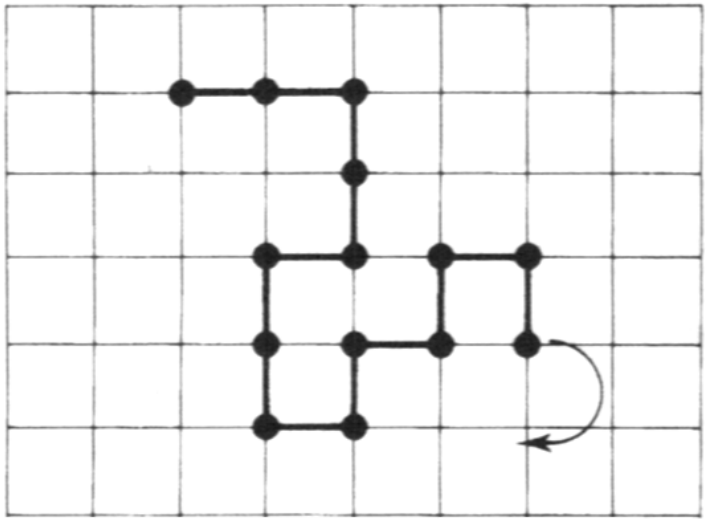
theta state ($\vartheta$ state) of a polymer

- the effects of excluded volume and attractive interactions compensate each other exactly
  (also, the second virial coefficient vanishes)
- equivalent to the Boyle temperature for real gas
- results derived with the simple random walk model are actually valid for a real polymer under real conditions
  (often designated with the subscript '0')

# Monte Carlo simulation of polymers

How to take the excluded volume into account?

- do not allow the chain to extend to already occupied points
- self-avoiding walk



# Monte Carlo simulation of polymers

How to take the excluded volume into account?

- do not allow the chain to extend to already occupied points
- self-avoiding walk

SAW was used to generate all possible configurations
of a polymer of given length on a given lattice
→ partition function → all thermodynamic properties

'potential energy' – simple interaction model for nearby monomers
also – copolymers with two different types of monomer units

particular attention – structural properties – end-to-end distance:

$$\left\langle R_n^2 \right\rangle \approx n^{1.18} \cdot l^2 \qquad \text{for } n \to \infty$$

# Monte Carlo simulation of polymers

rotational isomeric state model (Flory, 1969)

- a 'continuous' polymer model – no lattice involved
- several rotational states are pre-defined for the links,
  and every link is always in one of these states
- these states, dihedral angles, are minima of pot. energy
- e.g., trans, gauche(+) and gauche(–) in a polyalkane chain
- conformations of chain are generated with probability
  distributions corresponding to their statistical weights,
  which are a component of the model (in a matrix form)
- best availabe approximative description of polymer chains

# Monte Carlo simulation of polymers

rotational isomeric state model (Flory, 1969)

matrix of statistical weights for an example of polyalkane chain:

$$U \equiv \begin{pmatrix} u_{tt} & u_{tg^+} & u_{tg^-} \\ u_{g^+t} & u_{g^+g^+} & u_{g^+g^-} \\ u_{g^-t} & u_{g^-g^+} & u_{g^-g^-} \end{pmatrix} = \begin{pmatrix} 1.00 & 0.54 & 0.54 \\ 1.00 & 0.54 & 0.05 \\ 1.00 & 0.05 & 0.54 \end{pmatrix}$$

$u_{ab}$ – statistical weight of dihedral state $b$
following a link in the dihedral state $a$

if there are different atoms/groups along the polymer chain:
→ more than 1 matrix needed
– e.g.: polyoxyethylene – 3 different matrices

# Monte Carlo simulation of polymers

rotational isomeric state model (Flory, 1969)

Starting on one end of the chain, a conformation is generated
by calculating the dihedral angles sequentially,
until the whole chain is finished

The probability of each dihedral angle is determined with MC
using the a priori probabilities of the dihedral states
and the state of the previous dihedral angle

A large number of such chains will be grown,
and structural data will be calculated and averaged:

- pair correlation functions,
- scattering functions
- force–elongation profiles

# Grand canonical Monte Carlo simulation

grand canonical ensemble: $\mu$VT
(compare with canonical ensemble: NVT)
constant chemical potential, variable number of particles

GCMC

- explicitly accounts for density fluctuations
  at fixed volume and temperature
- trial insertions and deletions of molecules

# Grand canonical Monte Carlo simulation

trial step:

- choose randomly if a particle insertion or deletion is attempted
- if insertion: place a particle with uniform probability density inside the system / defined part of the system
- if deletion: delete one out of $N$ particles randomly

calculation of the acceptance probability:

$$\mathcal{P}(N \to N+1) = \frac{V\Lambda^{-3}}{N+1} \cdot \exp[\beta\mu] \cdot \exp[-\beta(U_{N+1} - U_N)]$$

$$\mathcal{P}(N \to N-1) = \frac{N}{V\Lambda^{-3}} \cdot \exp[-\beta\mu] \cdot \exp[-\beta(U_{N-1} - U_N)]$$

($\beta = \frac{1}{k_B T}$, de Broglie thermal wavelength $\Lambda = \sqrt{\frac{h^2}{2\pi m k_B T}}$)

note: practical implementations differ a little

# Grand canonical Monte Carlo simulation

Applications:

- interfaces – e.g. studies of adsorption
- protonation states of amino acid side chains in a protein
  – chemical potential of protons is related to pH
- water molecules in a binding pocket / another cavity
  – work with the chemical potential of water