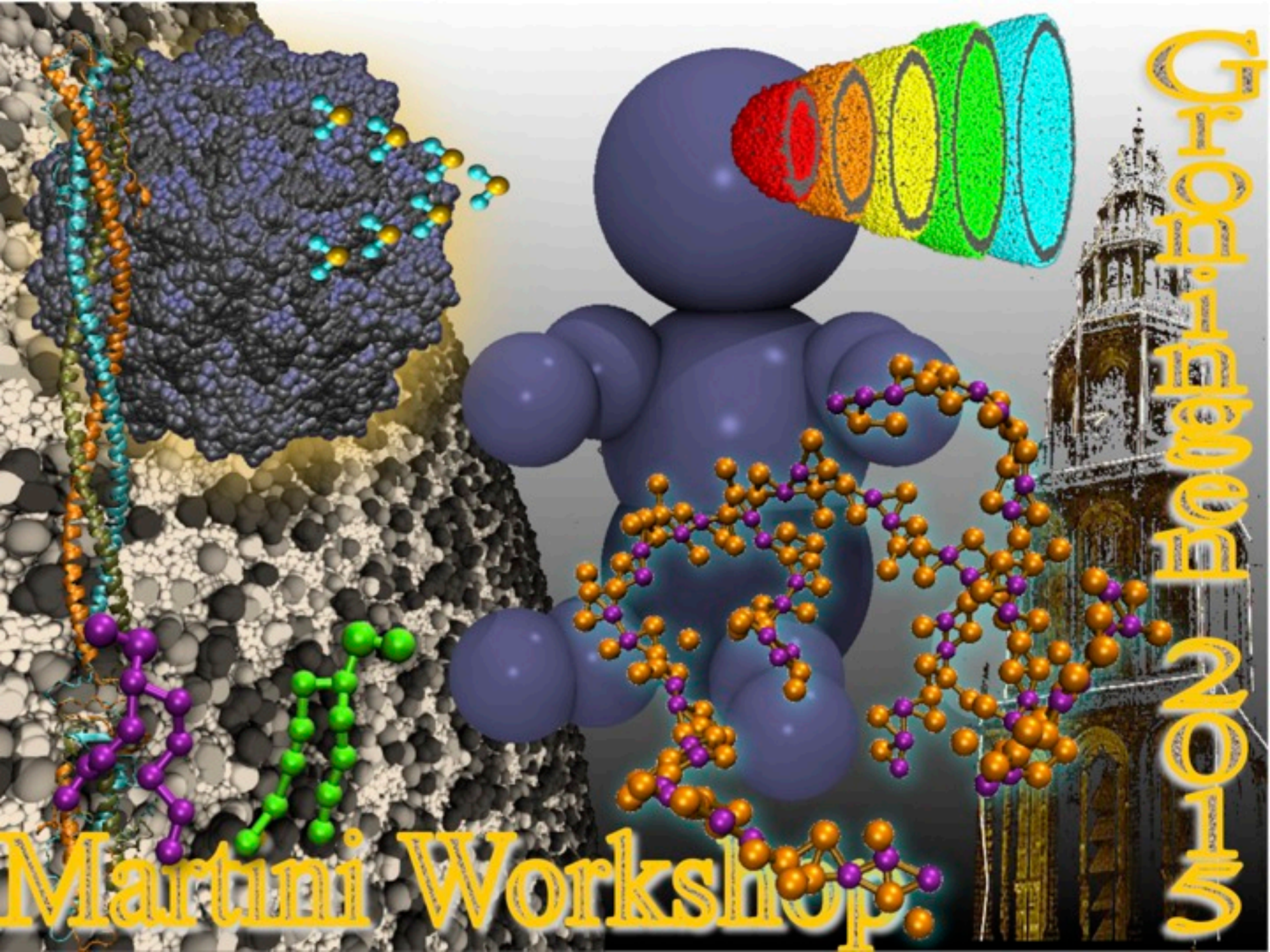

Martini Workshop
UCL Chemistry

university of groningen

Martini Workshop 2015

Coarse Graining Basics

Alex de Vries

Every word or concept, clear as it may seem to be,
has only a limited range of applicability

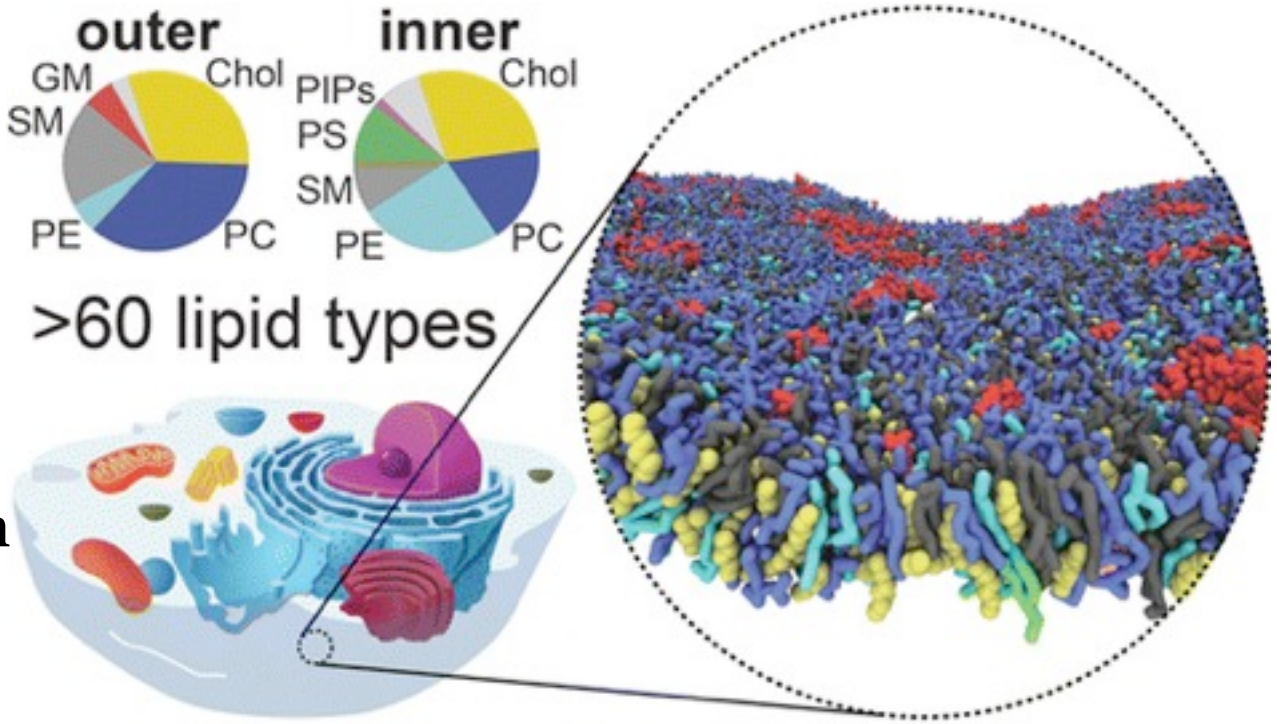
Werner Heisenberg

university of groningen

Recent MARTINI work

› Mammalian membrane simulation of unprecedented complexity and duration.

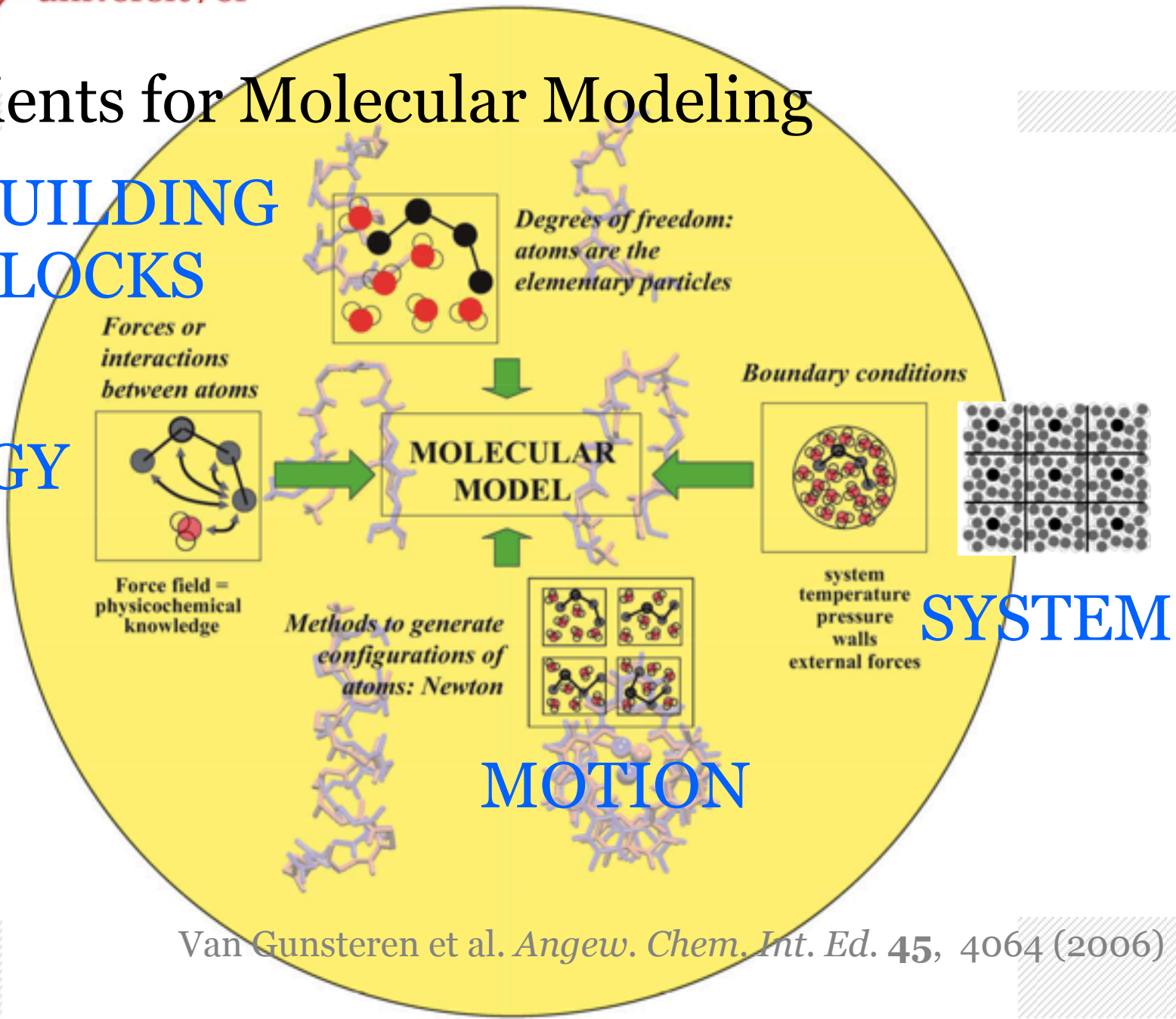
- 63 different lipids, asymmetric layers.
- ~0.5 Mbeads, 40 μs
- enables the high-resolution study of the distribution and dynamics of lipids interacting with each other.
- the next step is to add proteins.



Ingólfsson et al. *J. Amer. Chem. Soc.* **136**, 14554 (2014)

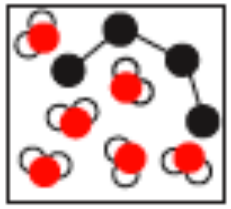
university of

Ingredients for Molecular Modeling



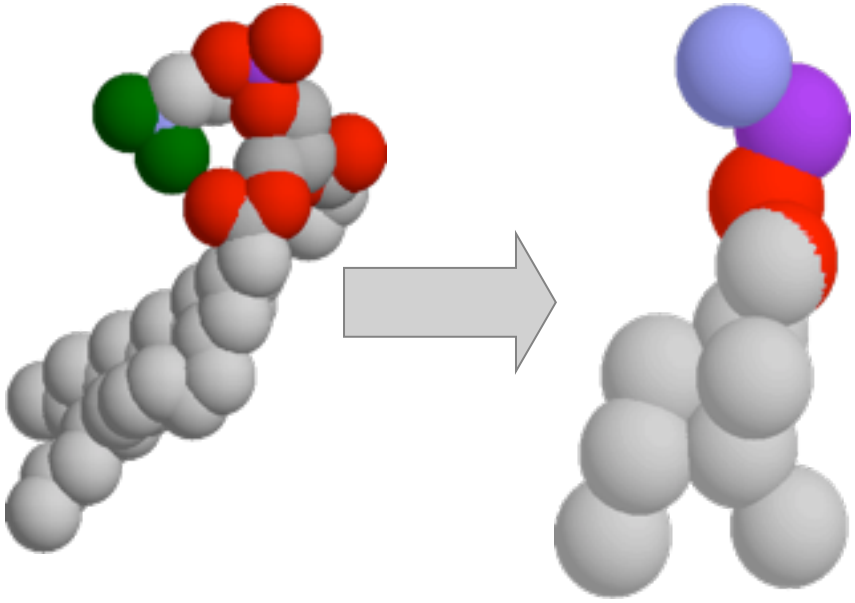
Van Gunsteren et al. *Angew. Chem. Int. Ed.* **45**, 4064 (2006)

university of groningen



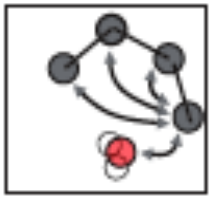
Popular Molecular Models

- All Atoms (OPLS-AA/L, CHARMM, AMBER)
  - Each atom is treated as a particle
- United Atoms (GROMOS)
  - Each atom is treated as a particle, except aliphatic CH, CH_2, CH_3
- Coarse grained superatoms (MARTINI)
  - A group of (~4 for Martini) united atoms is treated as a particle



- DPPC molecule (a lipid) in UA and CG (MARTINI) representations

university of groningen



Common Potentials in Molecular Models

› BONDED: Simple harmonic/cosine bonds & angles

* $V(d) = \frac{k}{2}\left(d - d_0\right)^2$

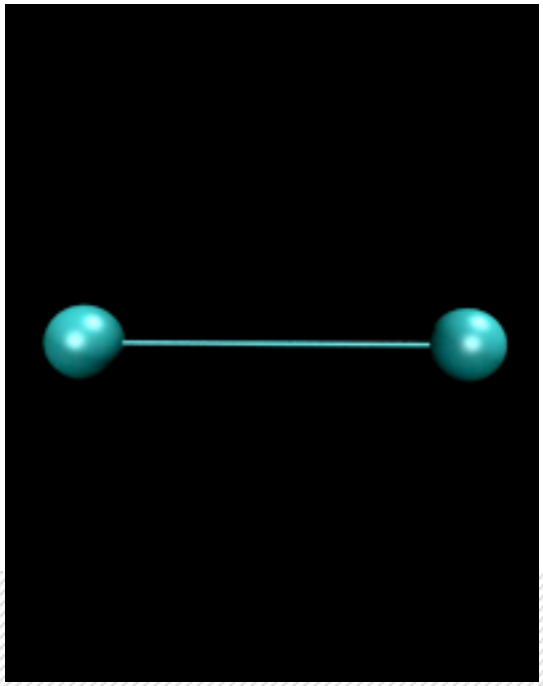
$V(\theta) = \frac{k_\theta}{2}\left(\theta - \theta_0\right)^2$

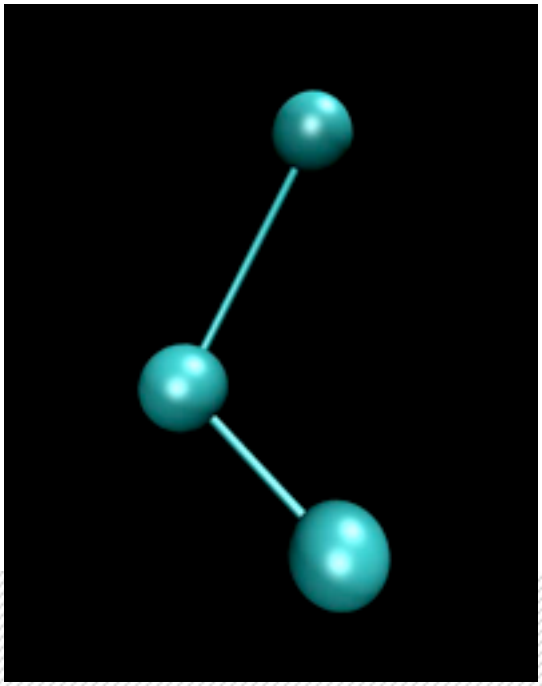
* $V(\phi) = \sum_n K_n \left[1 + \cos\left(n\phi + \delta\right)\right]$

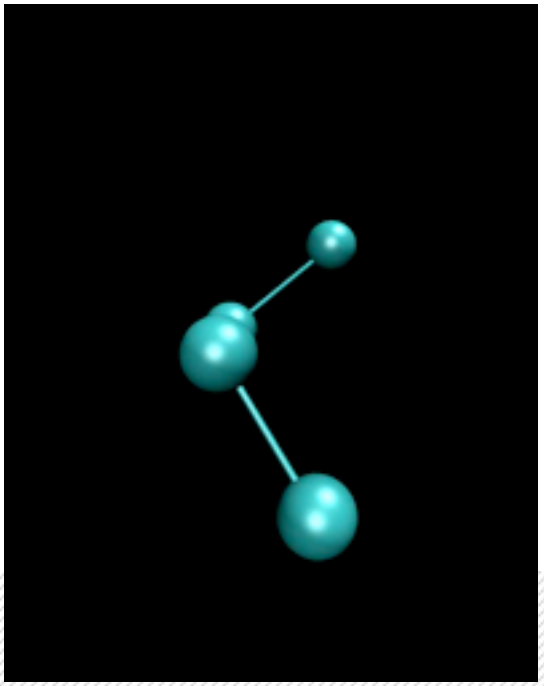
$V(d) = \frac{k}{4}\left(d^2 - d_0^2\right)^2$

* $V(\theta) = \frac{k_\theta}{2}\left(\cos\theta - \cos\theta_0\right)^2$

* type used in standard Martini



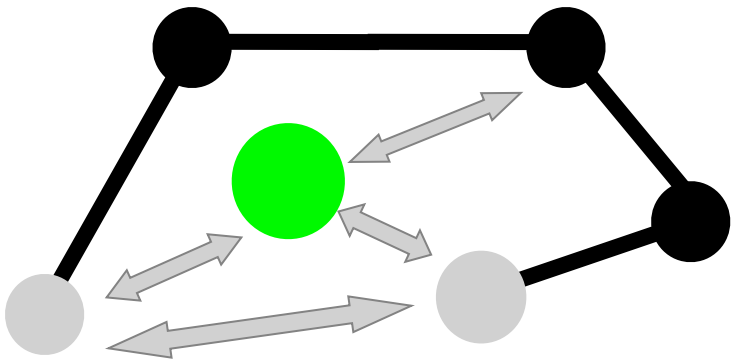




university of groningen

Common Potentials in Molecular Models

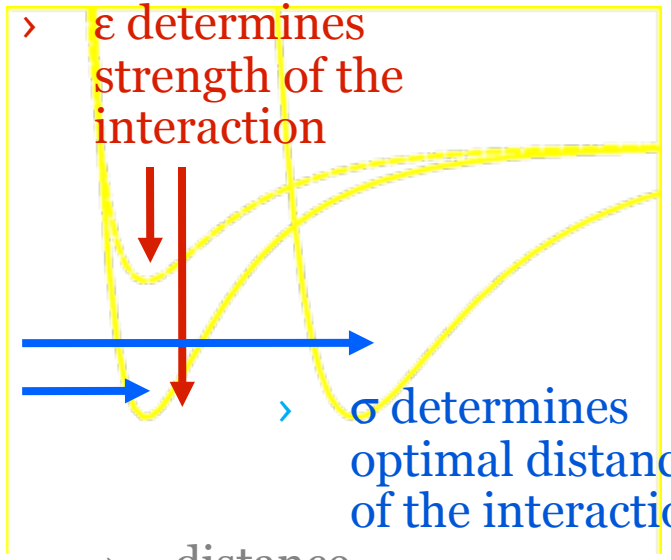
- NON-BONDED: Coulomb interaction between partial charges (electrostatics) and Lennard-Jones potential (long-range dispersion and short-range repulsion)



$$E_{Coulomb} = \frac{q_1 q_2}{r_{12}}$$

$$E_{LJ} = E_{dispersion} + E_{repulsion}$$

$$= 4\varepsilon\left(-\frac{\sigma^6}{r_{12}^6} + \frac{\sigma^{12}}{r_{12}^{12}}\right)$$



* Martini uses modified, smoothed variants of these!

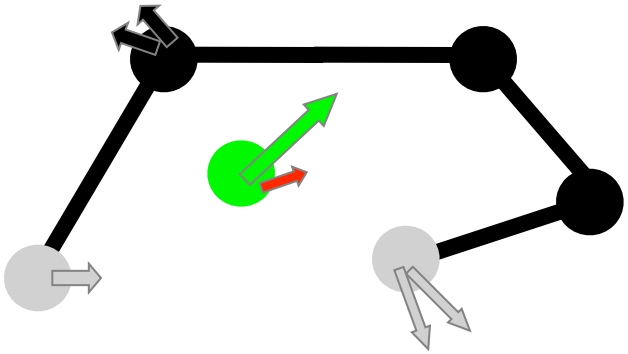
- Usually simple functions with some physical justification
  - Full descriptions of force fields implemented in GROMACS are described in the manual, Chapter 4

$$\Delta r = \dot{r}\Delta t + \frac{F}{2m}(\Delta t)^2$$

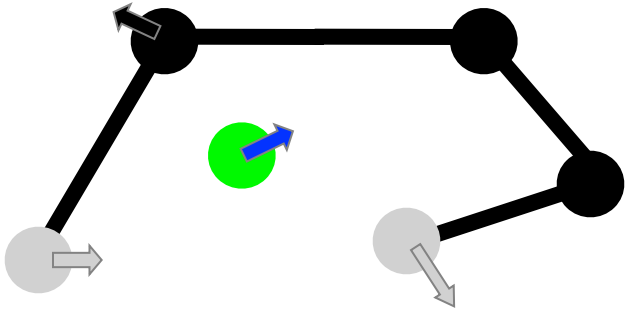
Basic MD Algorithm

$$ma = m\ddot{r} = F(r) = -\nabla E(r)$$

› Numerically integrate Newton's Law: F = m*a

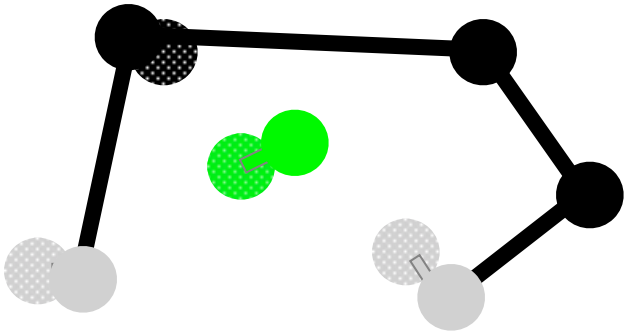


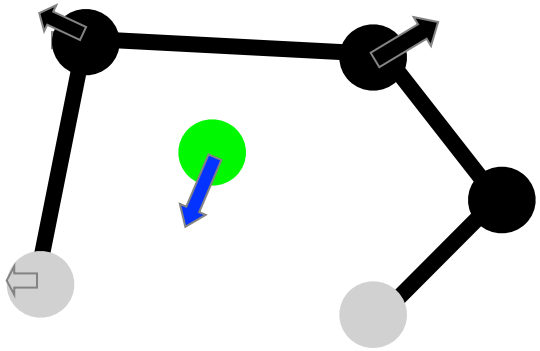
› Forces & velocities



› displacements

› t=0



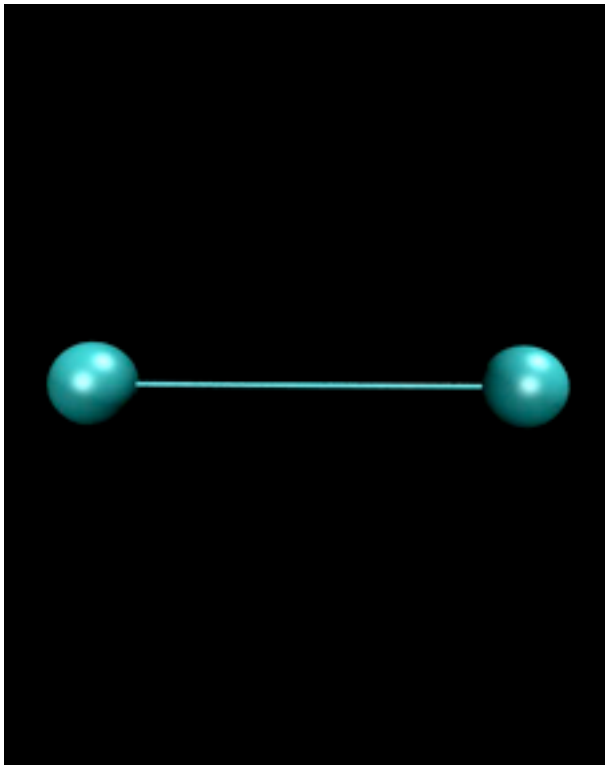


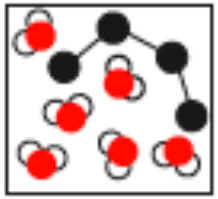
› t=1

› new displacements, etc…

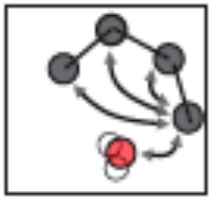
A Very Simple System

› Single oscillator treated classically in vacuo

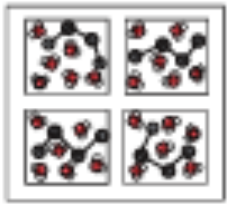




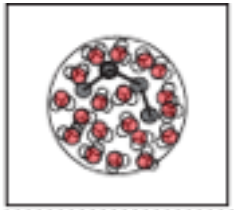
2 particles



$$V(\mathbf{R}) = \frac{1}{2}k\left(\mathbf{R} - \mathbf{R}_0\right)^2$$

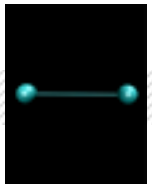


constant E

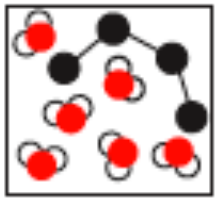


vacuum

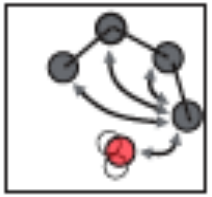
A Very Simple System



› Single oscillator treated classically in vacuo



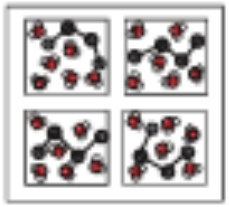
coordinates `.gro` or `.pdb`



$$V(\mathbf{R}) = \frac{1}{2}k\left(\mathbf{R} - \mathbf{R}_0\right)^2$$

`.top` or `.itp`

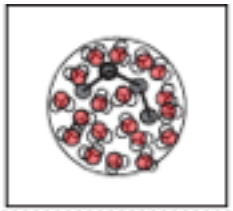
definition of the system and of the molecules and their bonded and nonbonded interactions



constant E

`.mdp`

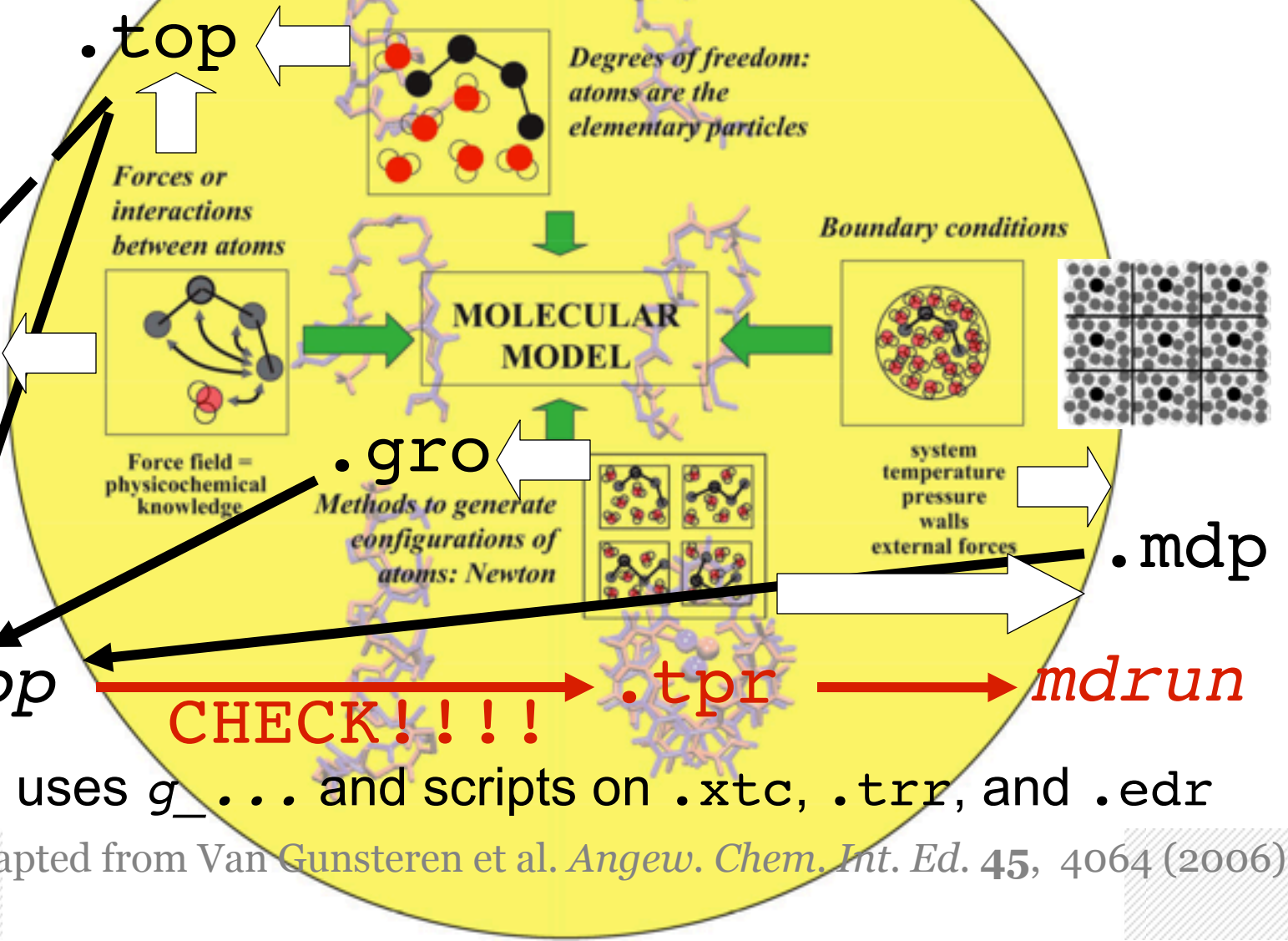
also algorithm for integration, number of steps, time step Δt, how often should we write output, and many other options!



vacuum

university of

GROMACS .files and *programs*

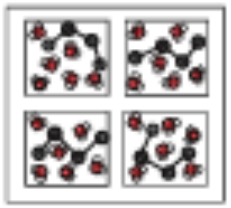


Analysis uses *g_...* and scripts on .xtc, .trr, and .edr

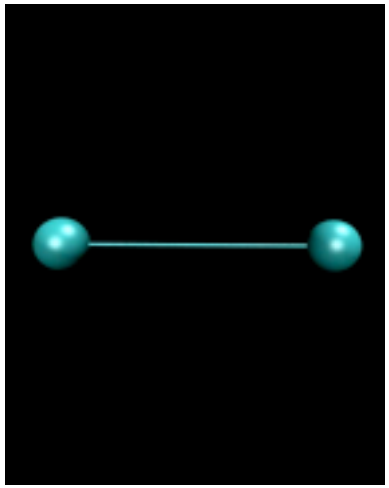
Adapted from Van Gunsteren et al. *Angew. Chem. Int. Ed.* **45**, 4064 (2006)

What comes out… using Gromacs

Time-traces

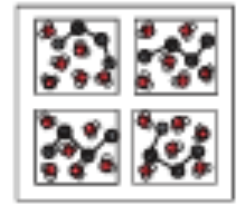


- Descriptions of the system
  - Positions — `.xtc` and/or `.trr`
  - Velocities
  - Forces
  - Energies — `.edr`
  - Other system information



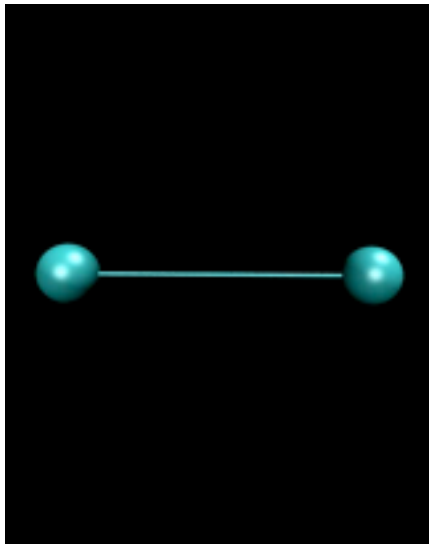
- The user must then extract this information and visualize it
  - Gromacs has many tools for this!
  - Always VISUALLY inspect your simulation (*ngmx*, *VMD*, *Pymol*, …)

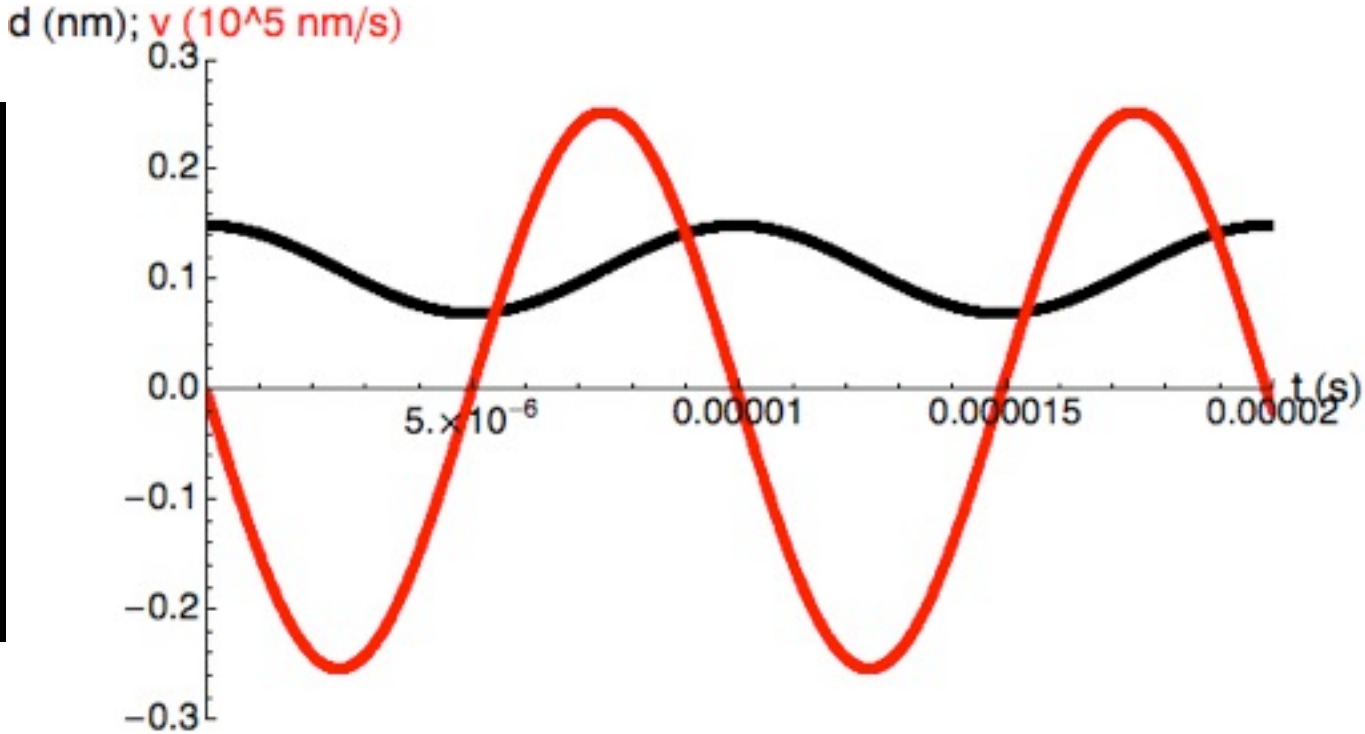
g_bond



Visualization of some results

› Time-trace data can extracted and visualized

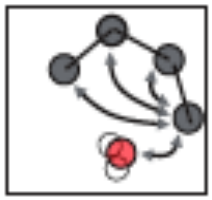


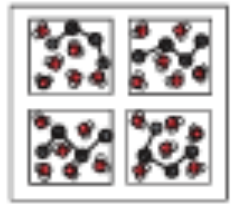


Bond distance and relative velocity as a function of time

university of groningen

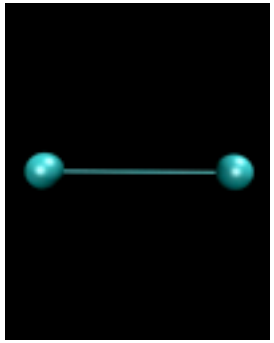
g_bond

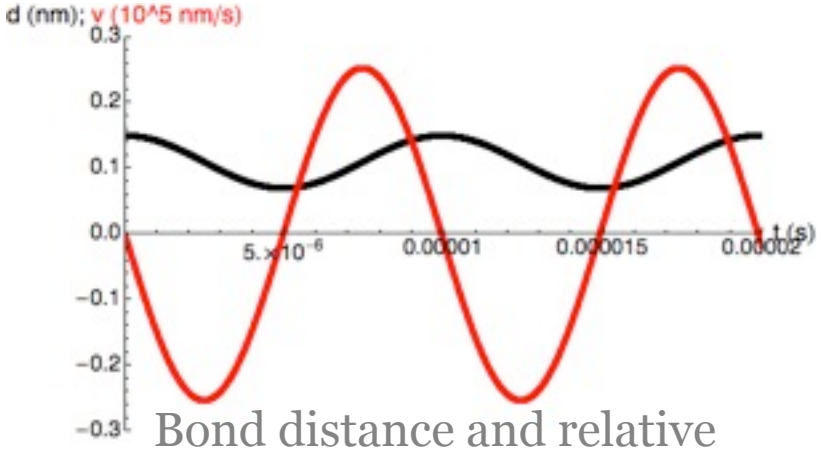




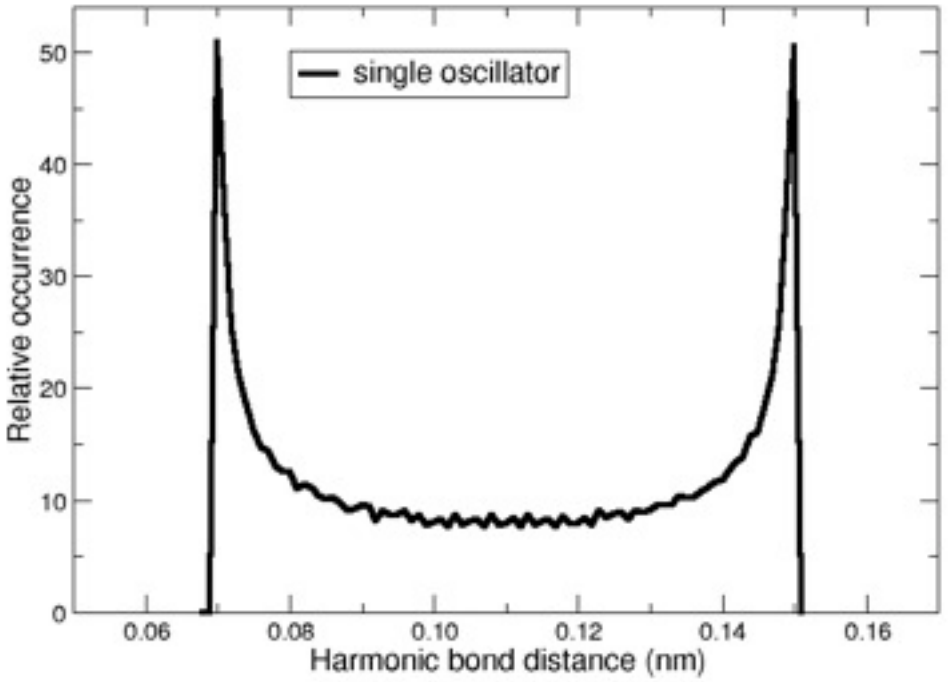
Sampling a Distribution

› Time-trace data can be collected in a distribution





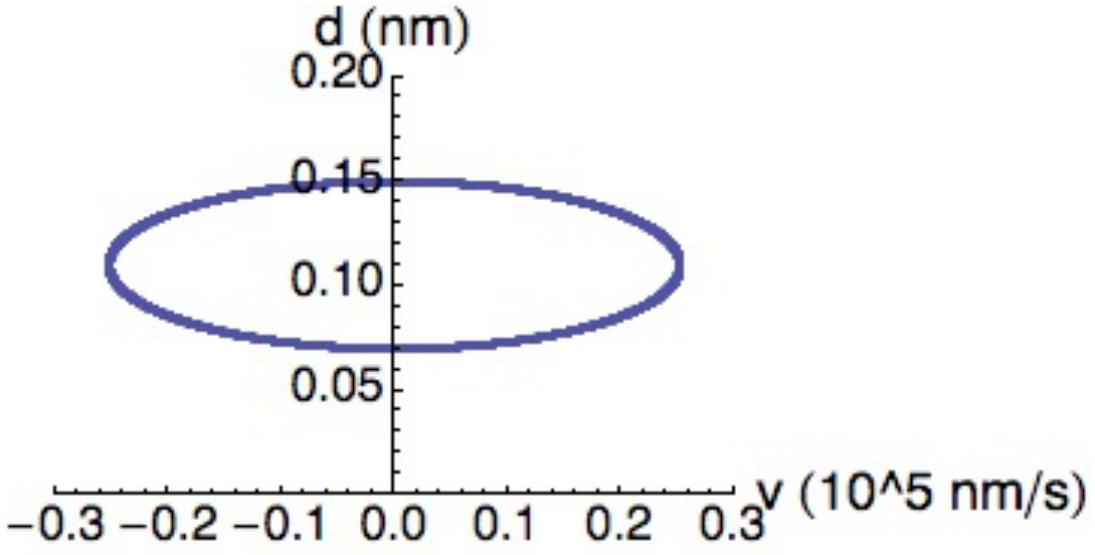
Bond distance and relative velocity as a function of time



Distribution of distances in harmonic oscillator model

Useful and Informative Description(s)

- Relevant or interesting degrees of freedom
- Harmonic oscillator traces out a simple path described by
  - Distance
  - Relative velocity



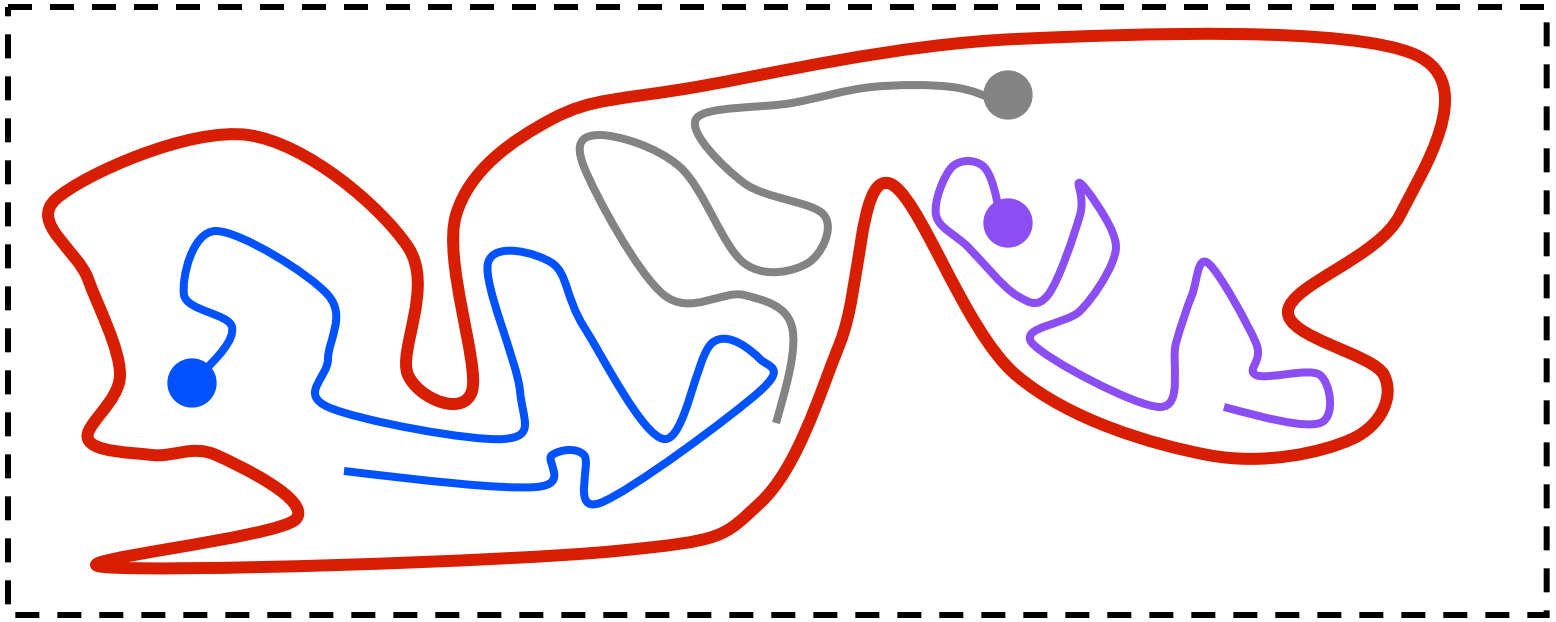
Distance (d) versus relative velocity (v) for a simple harmonic oscillator.

For an oscillator at constant energy, the ellipse constitutes its phase space. If the energy is not constant, many ellipses span its phase space, characterized by different amplitudes. (The path is traversed in counter clock-wise fashion.)

A Tasting (Sampling) of Classical Phase Space

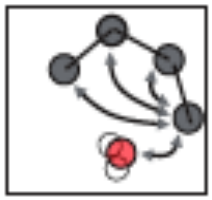
› Describes possible states of the system

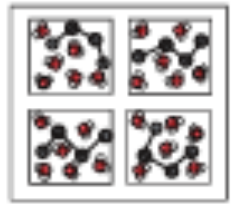
- Dimension $2*N_{dof}$ (**R**,**P**) or N_{dof} (**R**)
- A single system, in time, follows an allowed path through phase space visiting allowed states (**R**,**P**)



dof=degree(s) of freedom

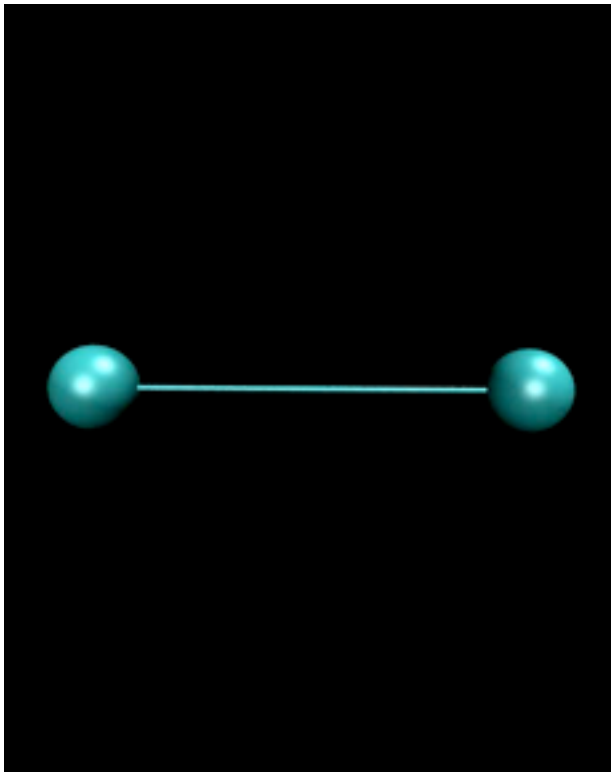
university of groningen

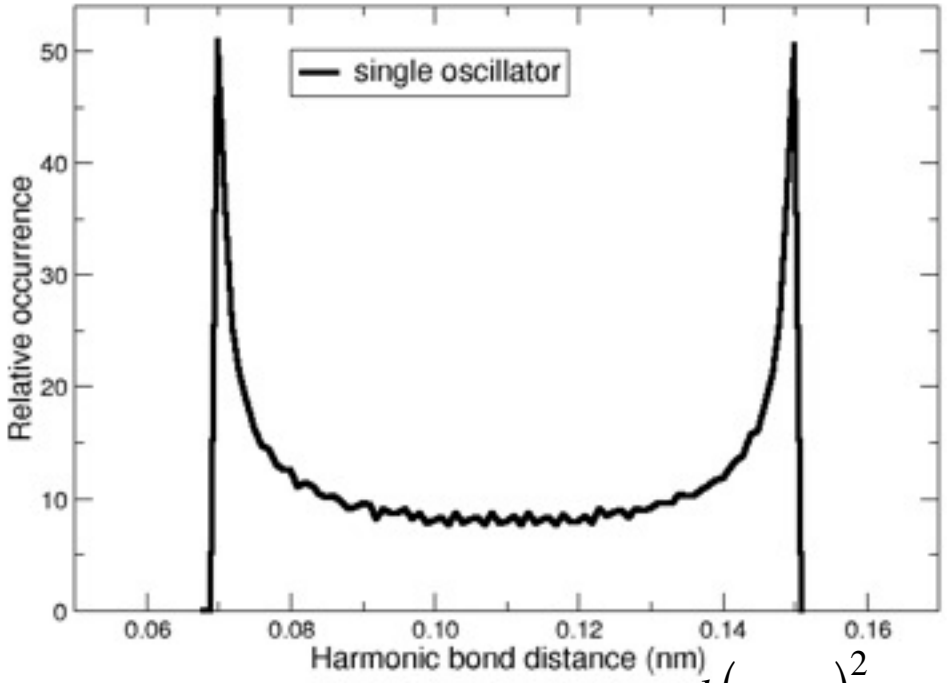




Potential and Distribution

- The Boltzmann distribution is **not** observed for a single harmonic oscillator in vacuo

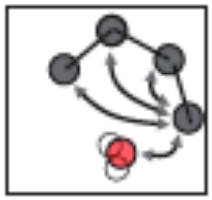


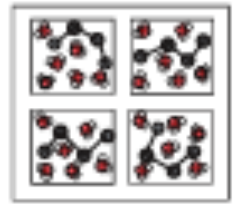


$$E(r) = \frac{k}{2}\left(r - r_0\right)^2$$

$$p(r) \overset{???}{\propto} e^{-\frac{E(r)}{k_B T}} = e^{-\frac{k\left(r - r_0\right)^2}{2 k_B T}}$$

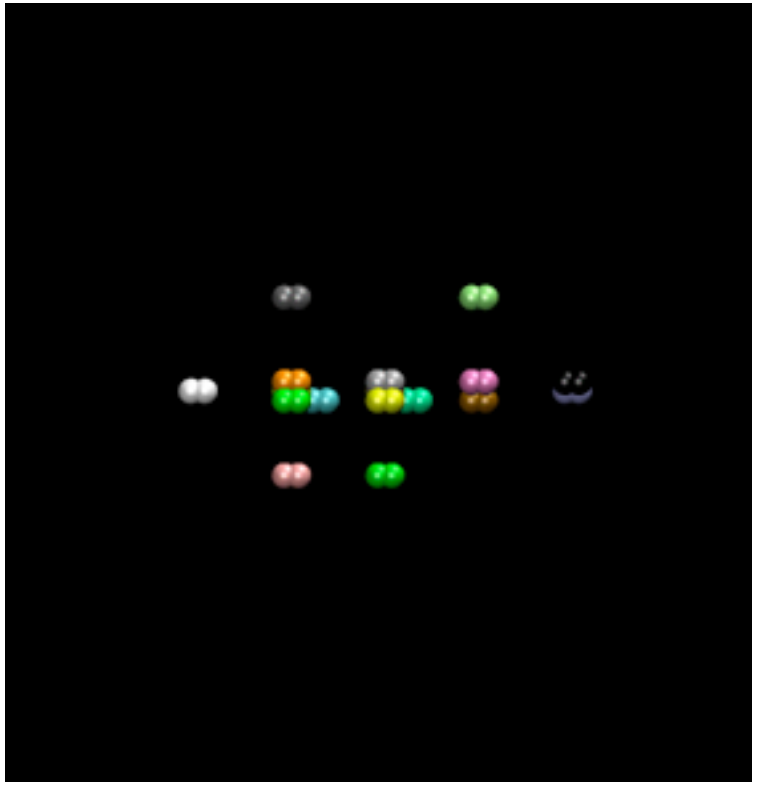
university of groningen

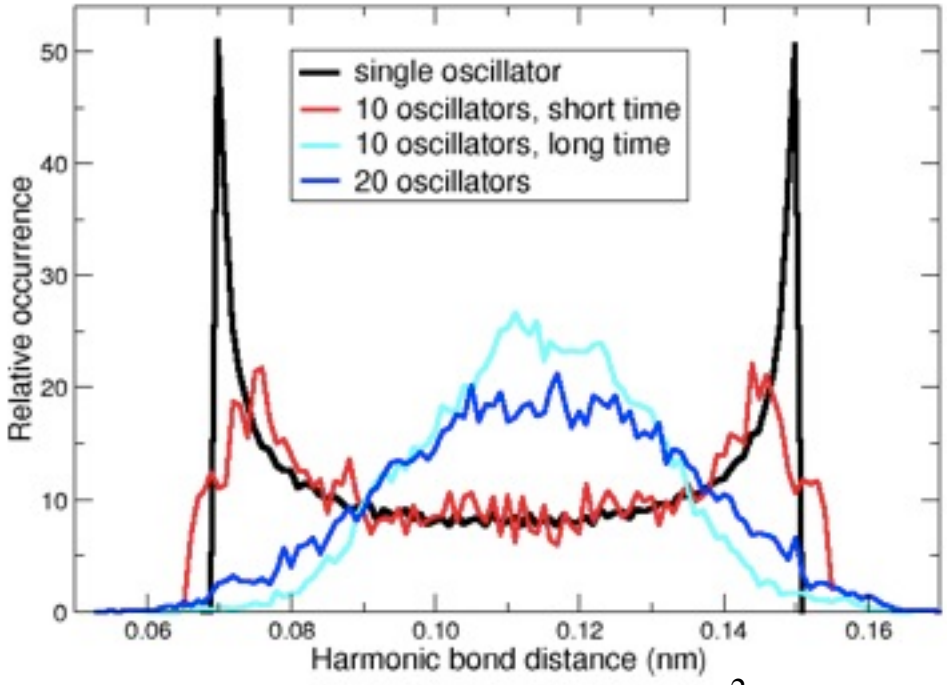




Potential and Distribution

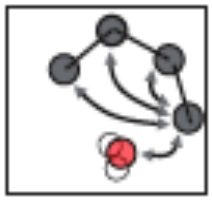
- The Boltzmann distribution is observed for anharmonically coupled oscillators

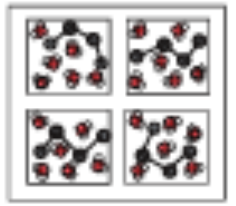




$$p(r) \overset{!!!}{\propto} e^{-\frac{k(r-r_0)^2}{2k_BT}}$$

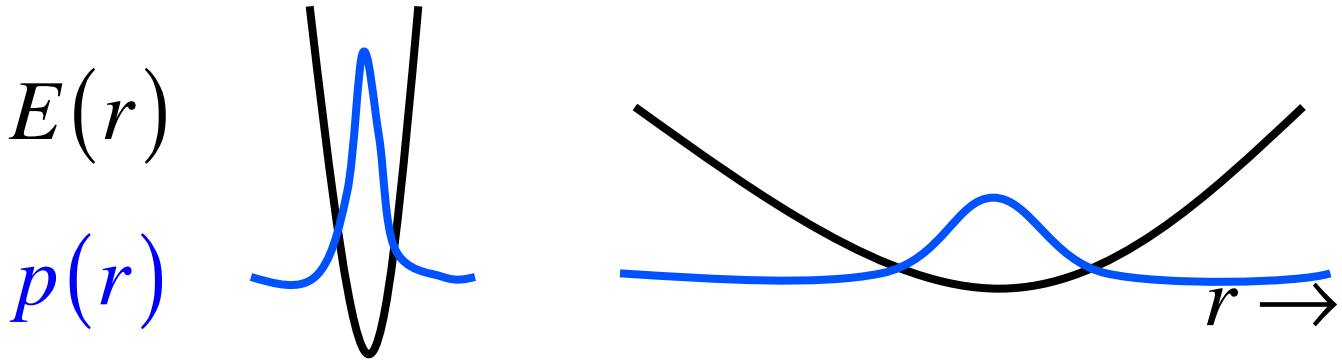
university of groningen





Potential and Distribution

› Close link between potential and distribution



- Can be used to extract potential from structural data

$$p(r) = \frac{e^{-\frac{E(r)}{k_B T}}}{Q} \Leftrightarrow E(r) = -k_B T \ln\left[p(r) Q \right]$$

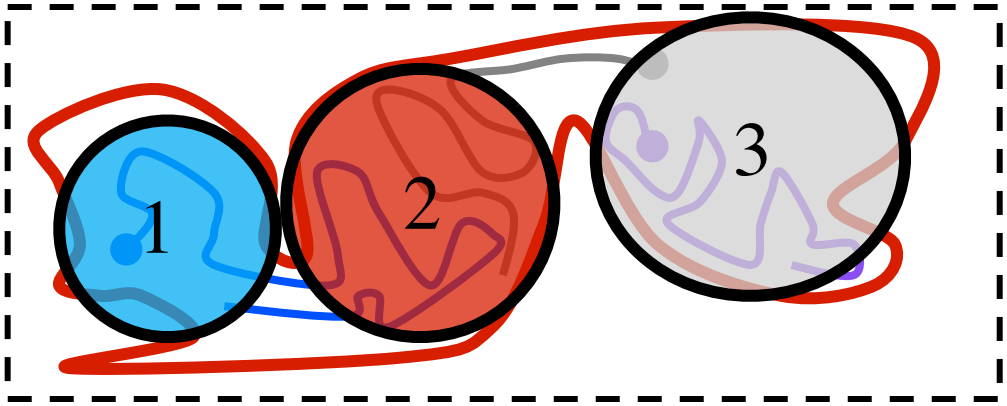
- Inverse Boltzmann techniques
- In MARTINI for fine-tuning bonded interactions

$$Q = \sum e^{-\frac{E_i}{k_B T}} \rightarrow Z = \int e^{-\frac{E(\mathbf{r})}{k_B T}} d\mathbf{r}$$

university of groningen

What we want to sample phase space for

- Define states as regions in phase space
  - Several realizations in the same state
  - Free energy difference between two states is related to the ratio of the number of realizations in each state and/or the probabilities of finding the system in a conformation belonging to a state



$$K_{12} = \frac{p_2^{eq}}{p_1^{eq}} = \frac{\sum_{i \in 2} e^{-\beta E_i}}{\sum_{j \in 1} e^{-\beta E_j}} = e^{-\beta \Delta G_{12}^0}$$

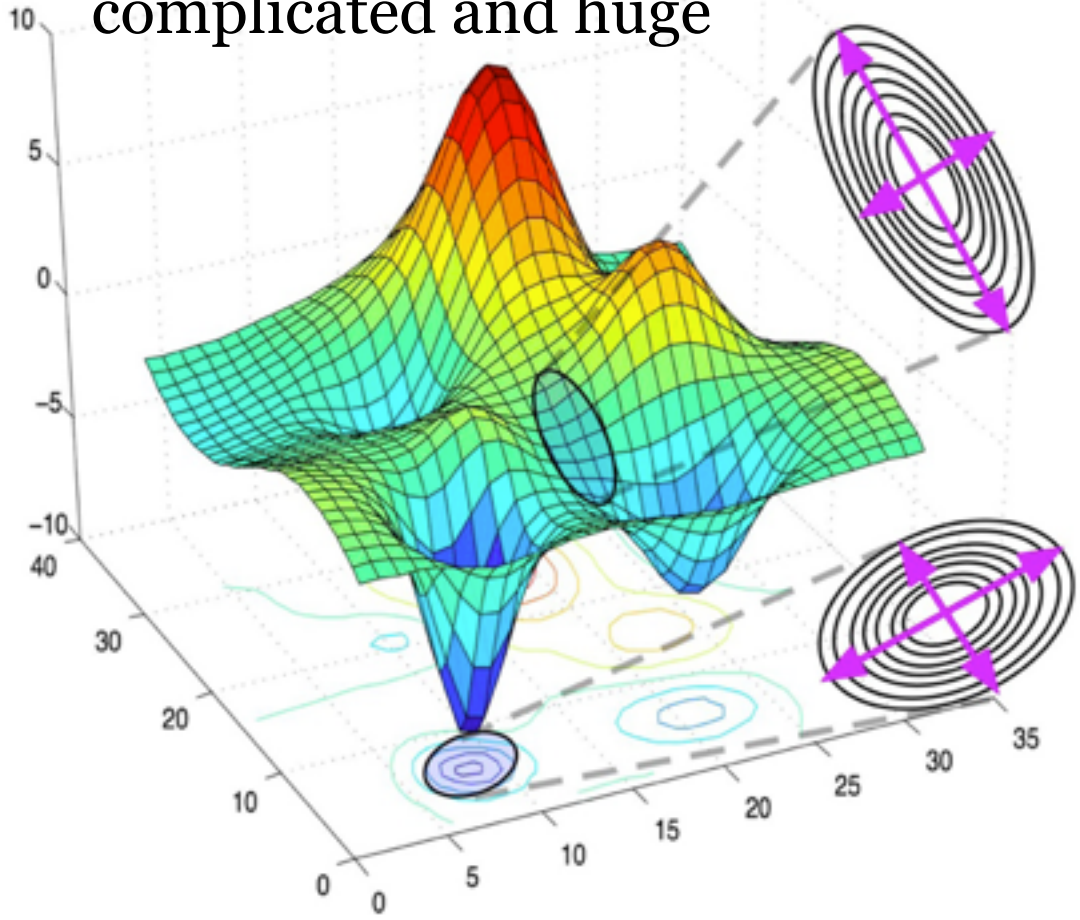
$$\beta = \frac{1}{k_B T}$$

  - The folded state of a protein is not a single conformation

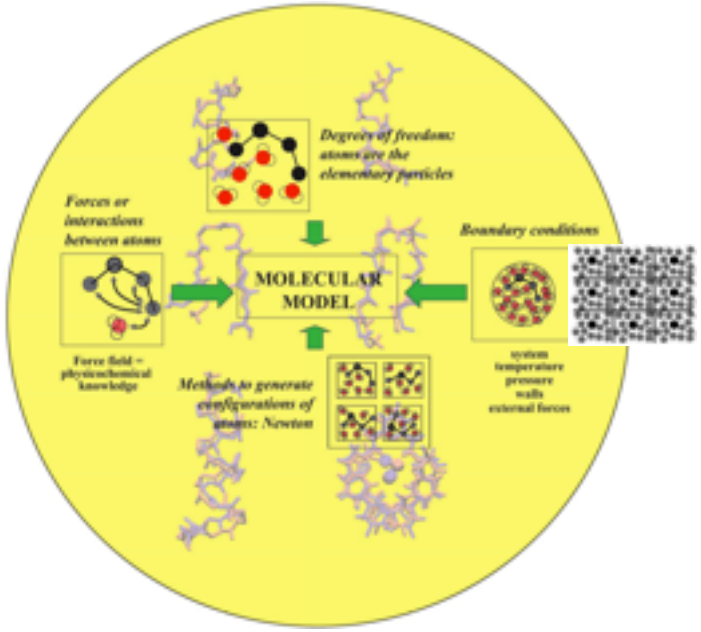
university of groningen

Sampling: a Problem?!

- (Free) energy landscape is complicated and huge



- Obtaining a complete picture of the possible conformations and their probability of occurring is hampered by the sheer number of them and the barriers between local minima in the (free) energy landscape



Pictures from presentation by Sander Pronk
and Van Gunsteren et al. *Angew. Chem. Int. Ed.* **45**, 4064 (2006)

university of

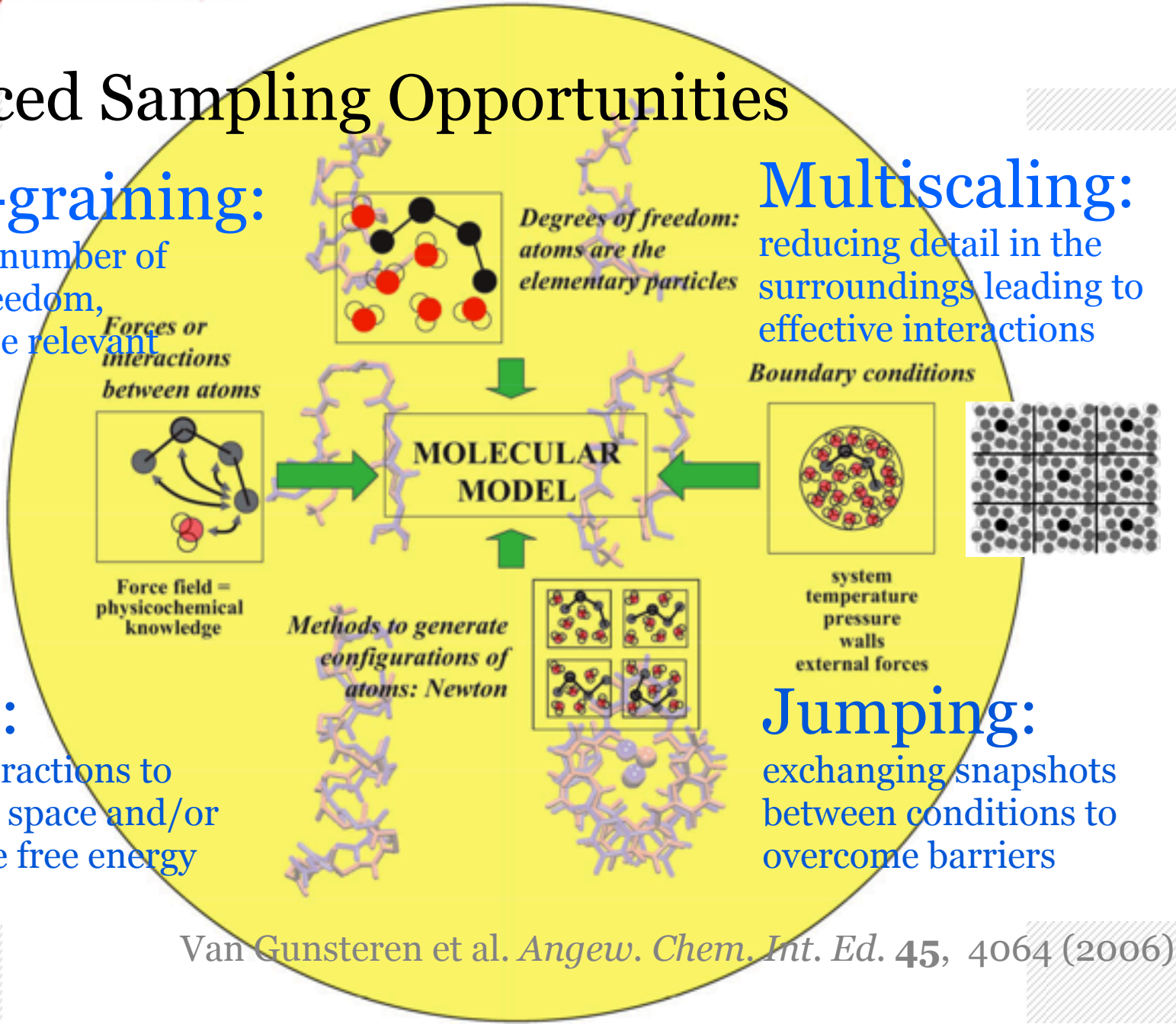
Enhanced Sampling Opportunities

Coarse-graining:

reducing the number of degrees of freedom, preserving the relevant physics

Multiscaling:

reducing detail in the surroundings leading to effective interactions



Biasing:

adapting interactions to reduce phase space and/or smoothen the free energy landscape

Jumping:

exchanging snapshots between conditions to overcome barriers

Van Gunsteren et al. *Angew. Chem. Int. Ed.* **45**, 4064 (2006)

university of

Enhanced Sampling Opportunities

Coarse-graining:

reducing the number of degrees of freedom, preserving the relevant physics

Multiscaling:

reducing detail in the surroundings, leading to effective interactions

Biasing:

adapting interactions to reduce phase space and/or smoothen the free energy landscape

Jumping:

exchanging snapshots between conditions to overcome barriers

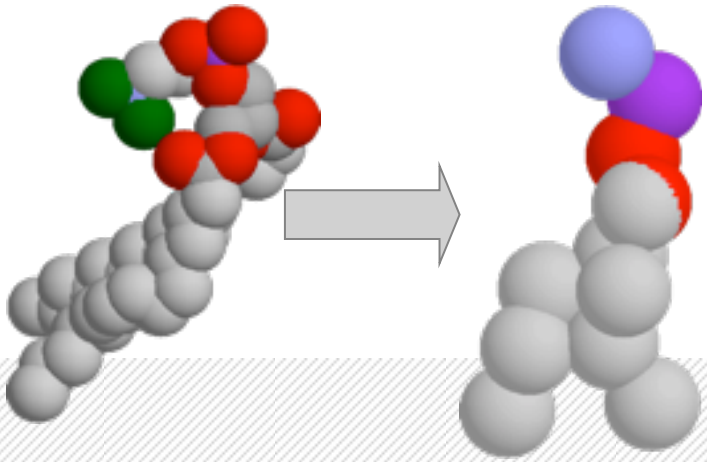
THERE IS NO SUCH THING AS A FREE LUNCH!

W. F. van Gunsteren et al. *Angew. Chem. Int. Ed.* **45**, 4064 (2006)

university of groningen

COARSE GRAINING BENEFITS

- Reduced Complexity
  - Physics: not all detail is relevant for our question
- Efficiency: increase length and time scales
  - Space: reduced density reduces number of interactions, e.g. in 4-to-1 mapping
    - 4 (number) x 4 (pairs)
    - 4 neighbor searching
  - Time: smoother energy landscape, increased time step
    - in the algorithm: 10-20
    - effective time: 4
  - Total: 2.5-5 10^3 speed-up



university of groningen

Martini Workshop 2015

COARSE GRAINING HowTo

Alex de Vries

A Simple(?) Example

Coarse-graining Caveats

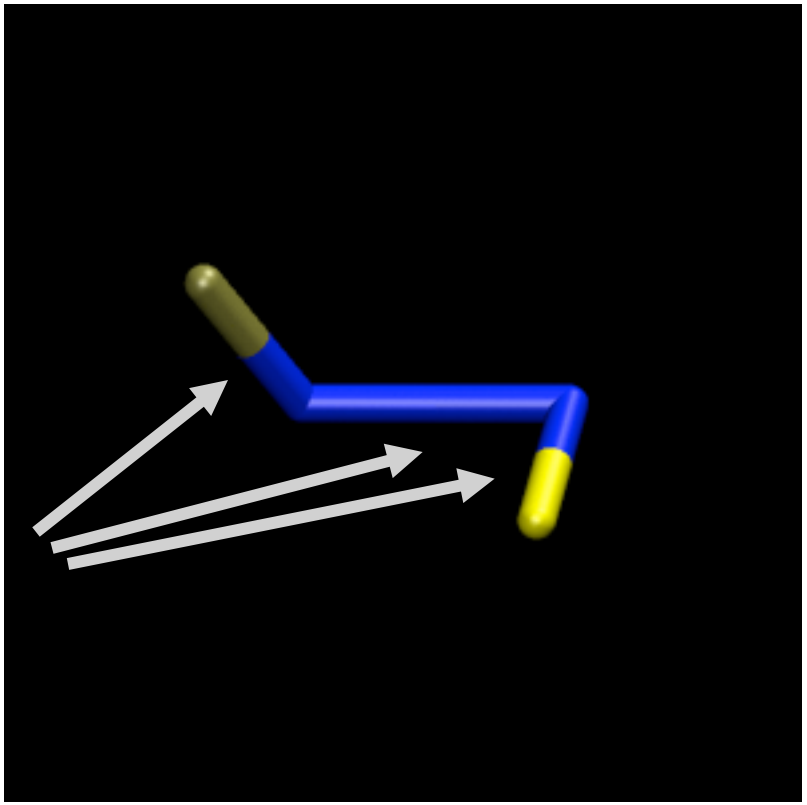
Coarse-graining Philosophies

university of groningen

A SIMPLE(?) EXAMPLE

- 2-to-1 mapping scheme unto simple oscillator
  - Weak coupling through collisions (gas)

- Weak LJ potential
- Harmonic springs

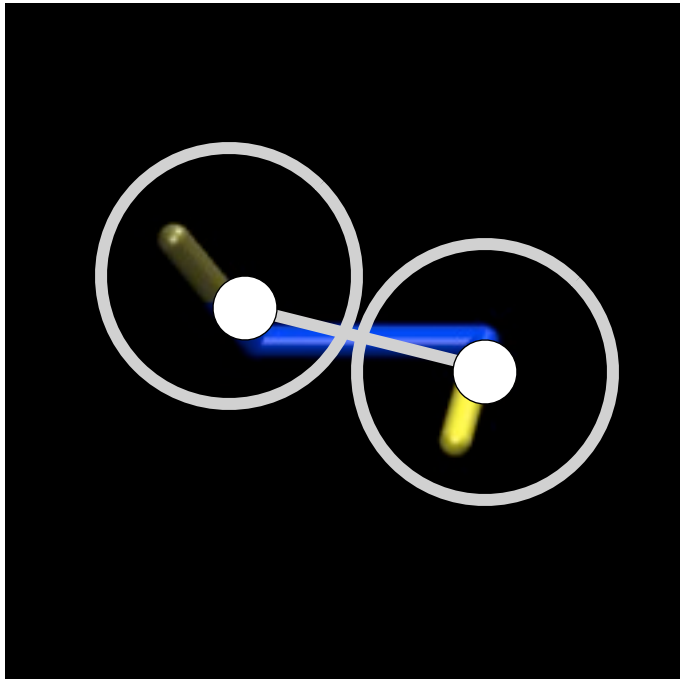


- Small mass
- Large mass

university of groningen

A SIMPLE(?) EXAMPLE

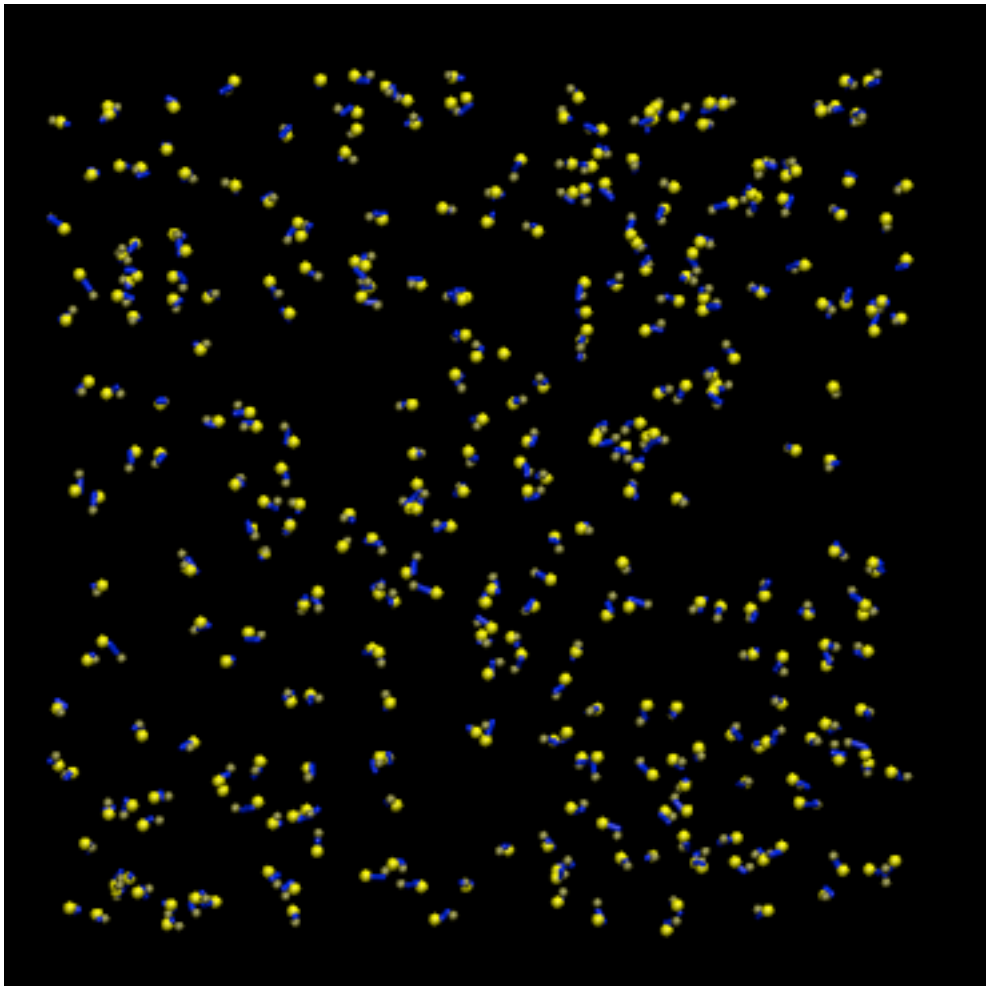
- 2-to-1 mapping scheme unto simple oscillator
  - Coarse grain on two centers of mass



university of groningen

A SIMPLE(?) EXAMPLE

- THE REFERENCE
  - A look at 100 ps trajectory for the system (looped)
  - Energy exchange through collisions
  - Run at constant Energy

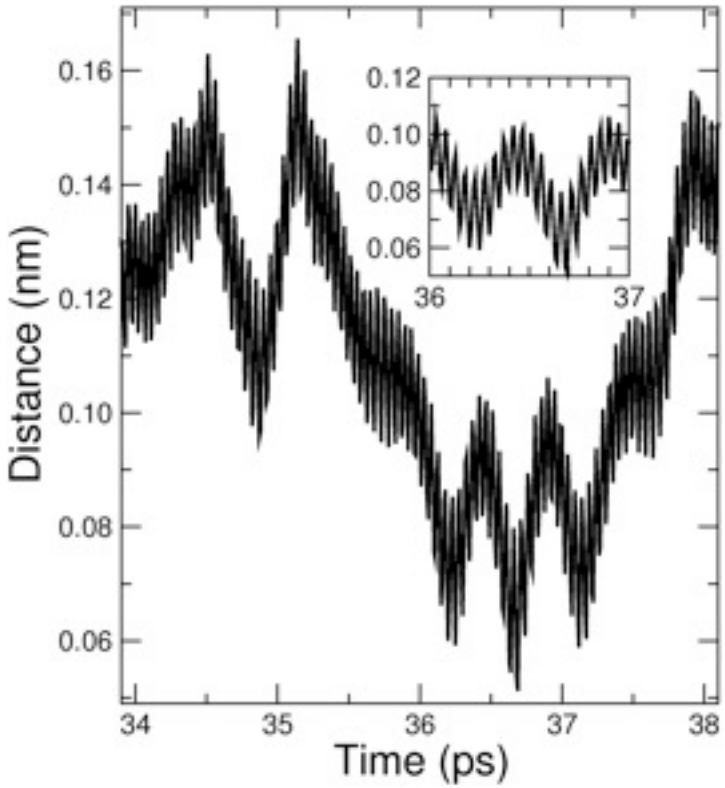


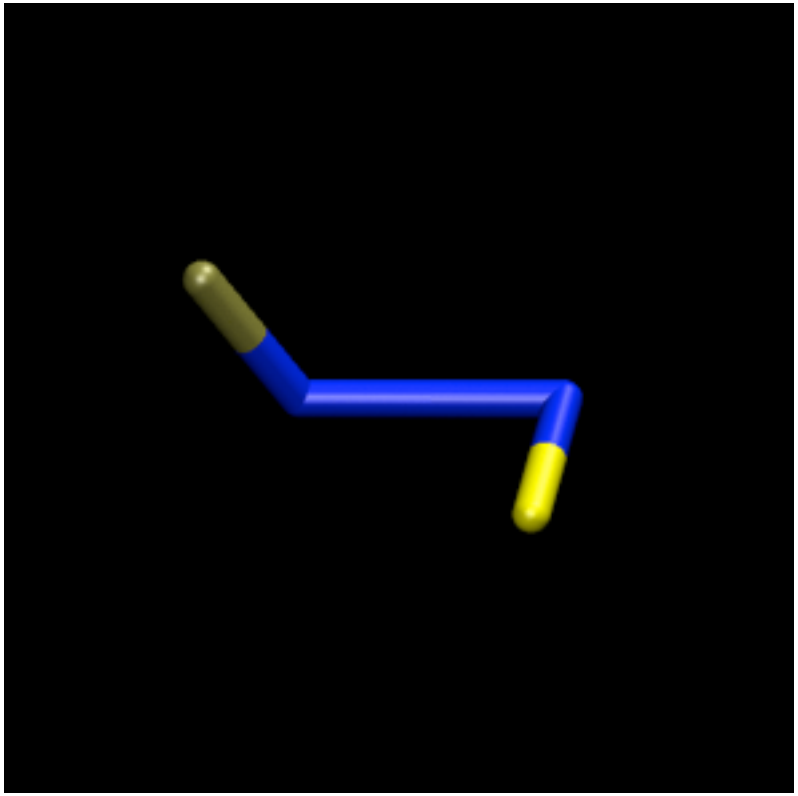
university of groningen

A SIMPLE(?) EXAMPLE

› COARSE-GRAINED BEHAVIOR

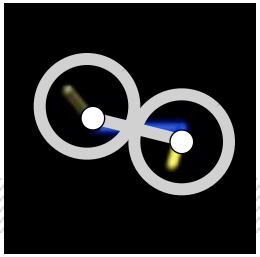
- A look at 10 ps trajectory for one oscillator





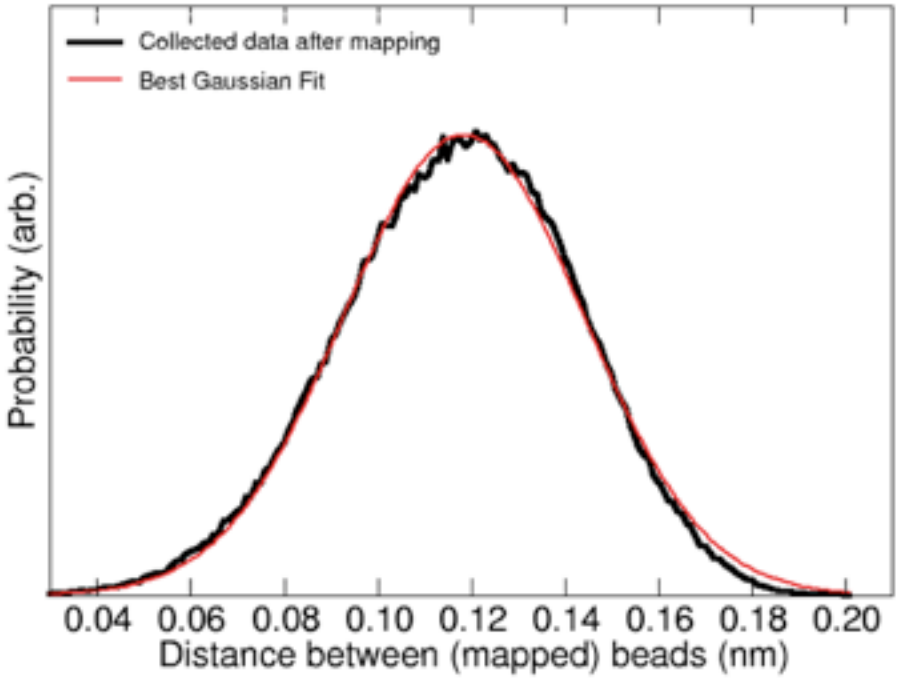
Distance between CG centers after 2-to-1 mapping

university of groningen



A SIMPLE(?) EXAMPLE

- COLLECT DISTRIBUTIONS OF INTEREST
  - Distribution reflects effective interaction
    - Can possibly be achieved by a simple potential



university of groningen

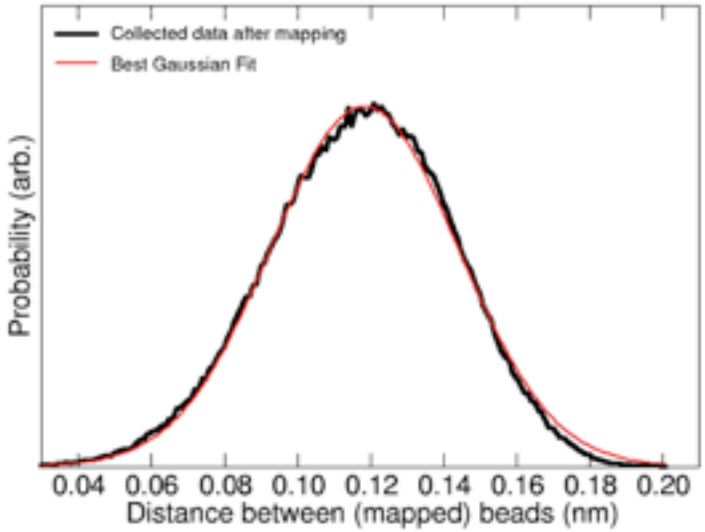
$$E(r) = \frac{k}{2}\left(r - r_0\right)^2$$

DERIVING POTENTIAL

- Harmonic force constant from normalized Gaussian distribution

$$p(r) \propto e^{-\frac{E(r)}{k_B T}} \propto e^{-\frac{k\left(r-r_0\right)^2}{2k_B T}}$$

$$\int \frac{1}{\sigma\sqrt{\pi}} e^{-\frac{\left(r-r_0\right)^2}{\sigma^2}} dr = 1$$



- Fit for best r_o and σ gives:

$$k = \frac{2k_B T}{\sigma^2}$$

$$p(r) = \frac{e^{-\frac{E(r)}{k_B T}}}{Q} \Leftrightarrow E(r) = -k_B T \ln\left[p(r)Q\right]$$

university of groningen

$$E(r) = \frac{k}{2}\left(r - r_0\right)^2$$

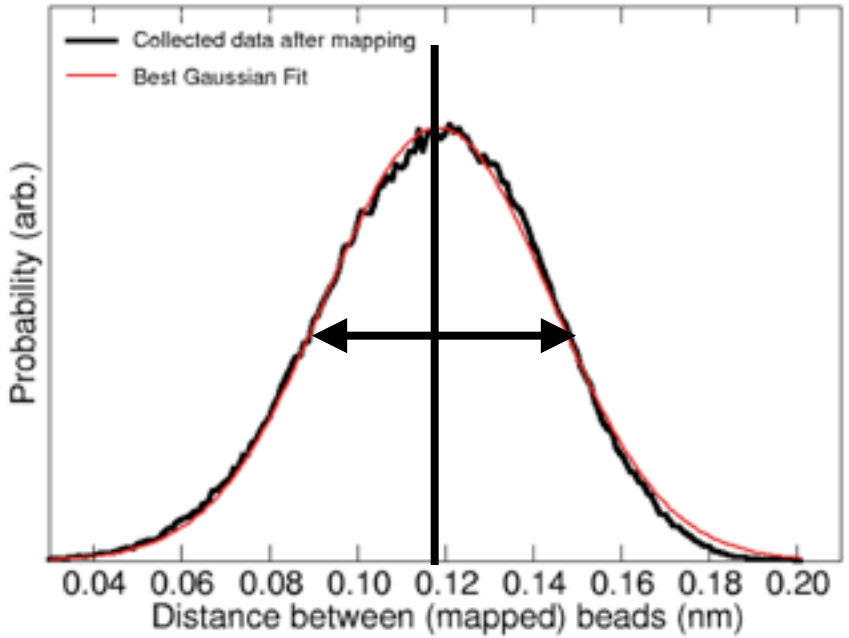
DERIVING POTENTIAL

- Harmonic force constant from Gaussian distribution

$$p(r) \propto e^{-\frac{k\left(r-r_0\right)^2}{2k_BT}}$$

- Fit for best r_o and σ:

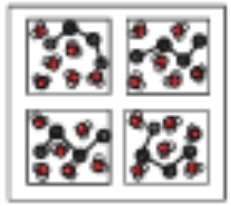
$$k = \frac{2k_BT}{\sigma^2}$$



$$k = 1{,}269\,\mathrm{kJ}\cdot\mathrm{mol}^{-1}\cdot\mathrm{nm}^{-2}$$

$$r_0 = 0.1185\,\mathrm{nm}$$

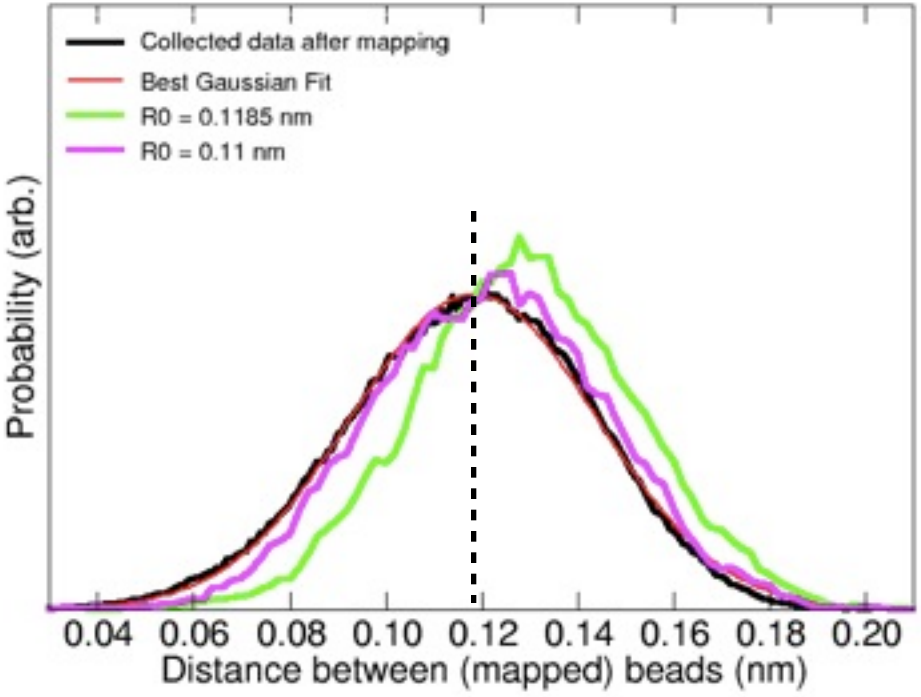
university of groningen



COARSE GRAINING CAVEATS

- Compare distributions at CG level
  - In this simple(?) example, there are already some complications

- Frequent collisions required to get good statistics
- Need to account for rotation that increases the bond length because of centrifugal force (*correlations* between degrees of freedom)
- Must use $r_0 \approx 0.11$ nm in CG model instead of the 0.1185 nm found by fitting
- K and r_0 will depend on total energy (temperature)

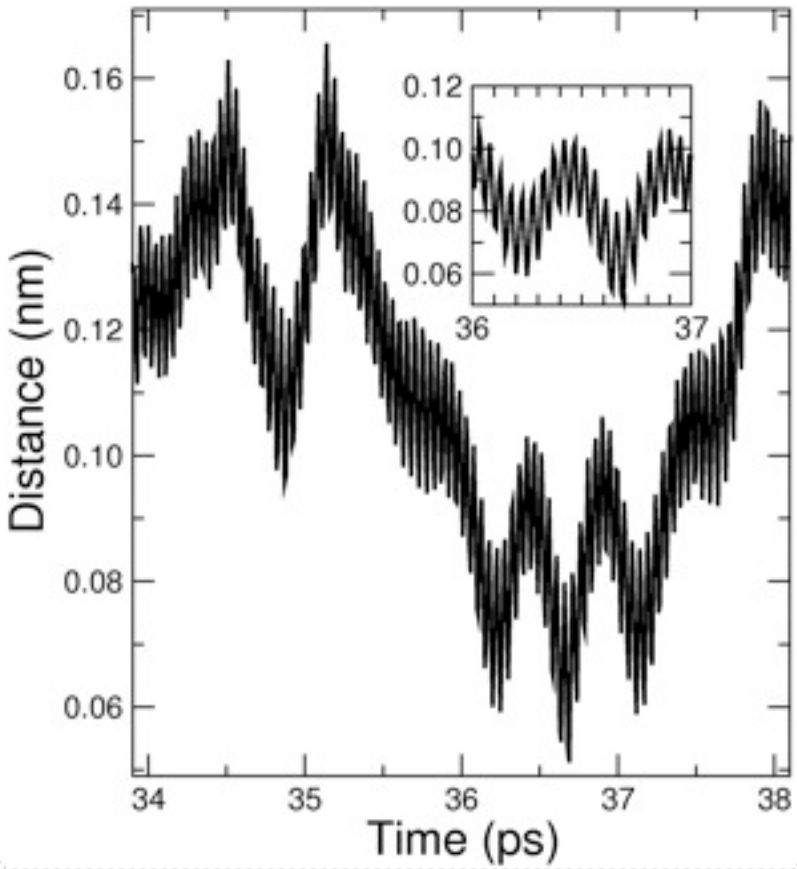


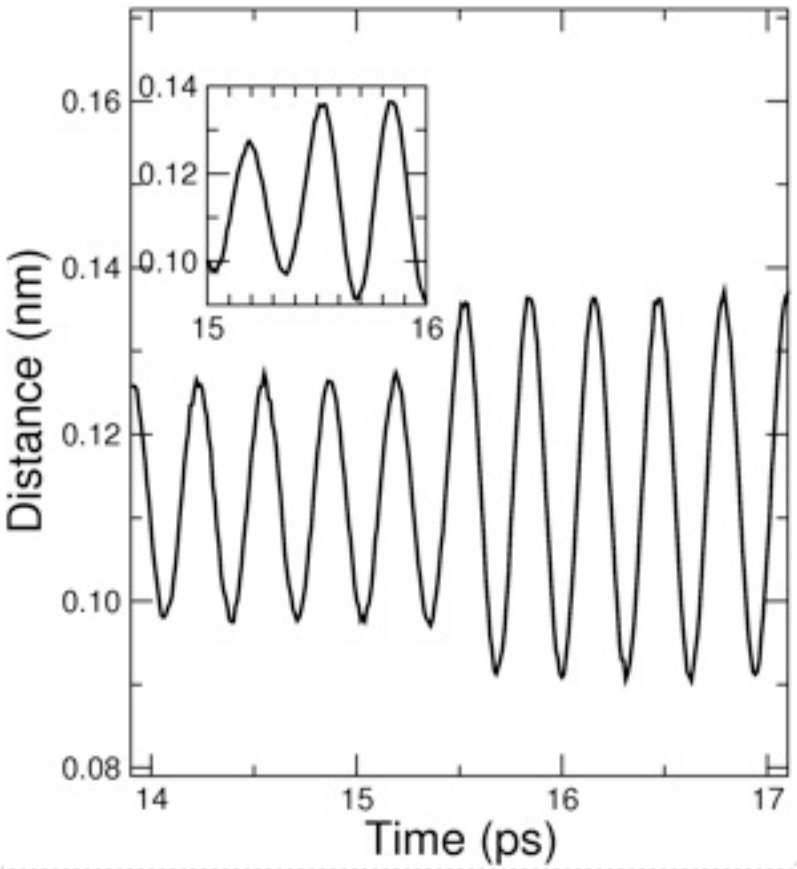
W.G. Noid et al, e.g. C.R. Ellis et al. *Macromol. Theory Simul.* **20**, 478 (2011)

university of groningen

COARSE GRAINING CAVEATS

› Smoother interaction, smoother motion





› Original, mapped

› Coarse-grained

university of groningen

COARSE GRAINING CAVEATS

- THE MEANING OF TIME
  - Smoother interaction, smoother motion
    - Enables larger time steps
    - Friction is lower, sampling speeds up
    - Barriers are more easily overcome

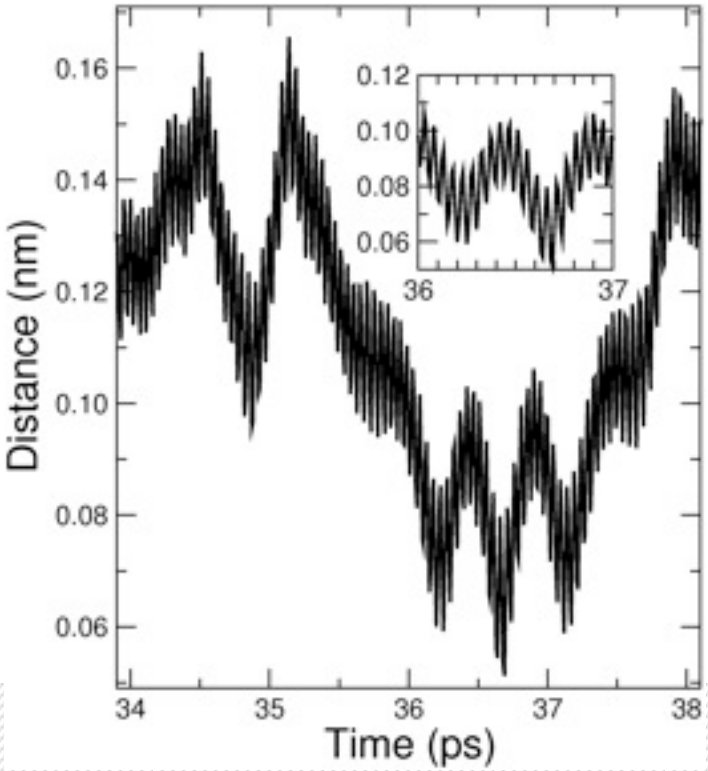
- DETAIL IS LOST
  - Physics may be different
  - Need to be careful in interpreting dynamics
  - Exchange of energy between modes may be less efficient

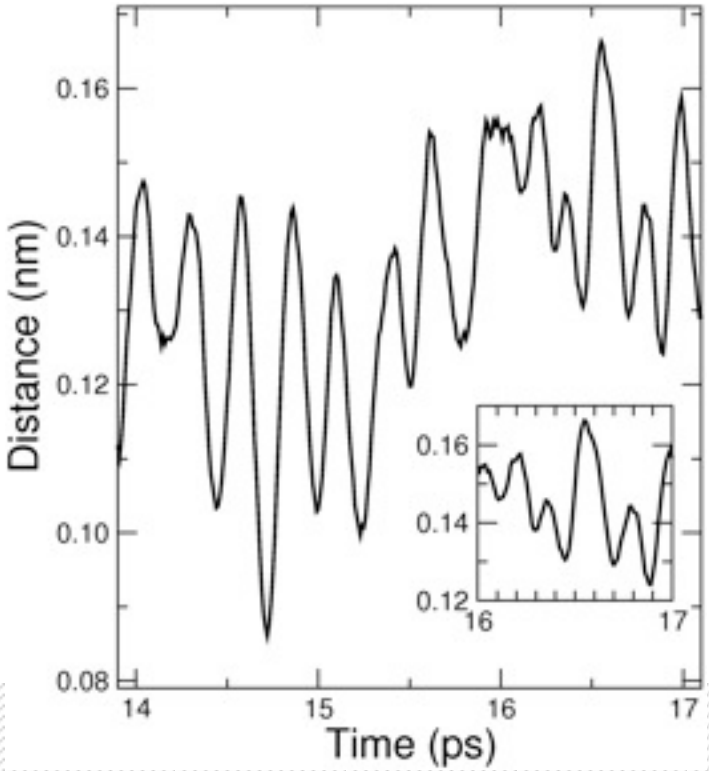
university of groningen

$$\Delta r = \dot{r}\Delta t + \frac{F}{2m}(\Delta t)^2 + \xi$$

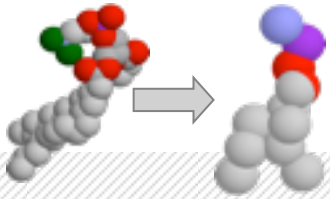
COARSE GRAINING CAVEATS

- THE MEANING OF TIME
  - Re-introduce friction through stochastic term
    - Part of benefit is gone, but dynamics may appear more realistic





university of groningen



Coarse-graining Philosophies

- HIERARCHICAL MODELING
  - From quantum mechanics to evolution of galaxies
    - Interactions at less detailed level are the result of the collective interactions at more detailed level
    - General method applicable to any system (like an algorithm)

- EFFICIENT MODEL AT CERTAIN SCALE
  - Reproduce faithfully certain chosen properties
    - Developed with certain application in mind
    - Nevertheless aiming at wide use through considering the physics of the problems in mind

university of groningen

Hierarchical modeling: pros and cons

- PRO
  - UNBIASED
    - Physics follows through the hierarchy of models
  - STRAIGHTFORWARD MULTISCALING
    - Enables reliable combination of levels of modeling
    - Entirely general approach

- CON
  - REQUIRES LARGE WORK LOAD
    - Need detailed level simulations to derive CG potentials
    - Complicated numerical potentials
  - LIMITED VALIDITY
    - Strictly valid for one state point only (new system, new potentials)

university of groningen

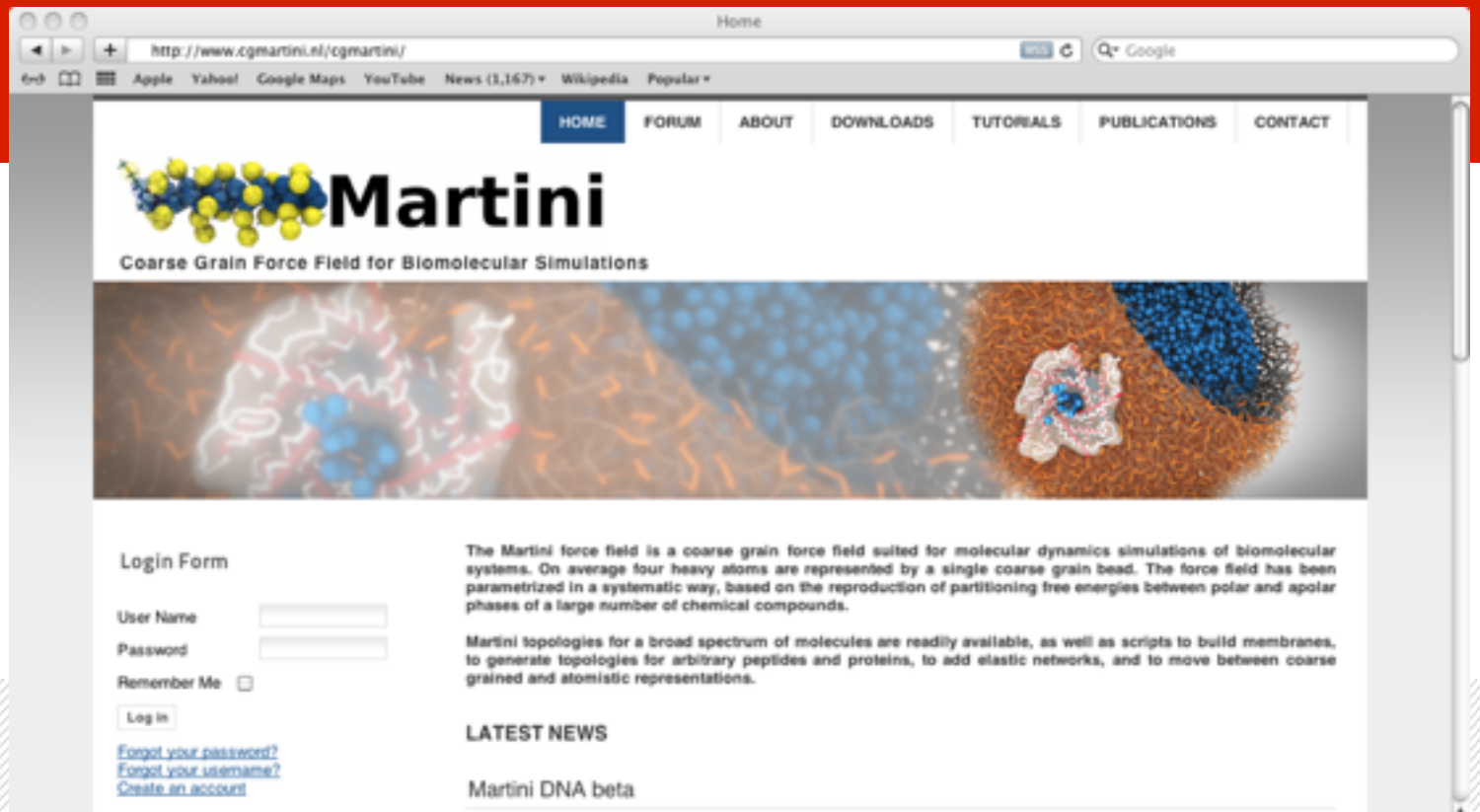
Semi-empirical modeling: pros and cons

- PRO
  - CHEAP
    - Parameterize on empirical data available
    - Simple analytical potentials
  - TRANSFERABLE
    - After parameterizing building blocks, many similar systems can be treated straightforwardly

- CON
  - BIASED
    - Toward parameterized properties
  - PROBLEMATIC MULTISCALING
    - Different levels do not need to correspond closely
    - Extensive validation required

university of groningen

MARTINI MODEL IS A SEMI-EMPIRICAL FORCE FIELD



university of groningen

What do we expect of the Martini CG model?

- For an empirical CG model
  - Results of complex systems should be consistent with experiment even though not explicitly parameterized on that complex system

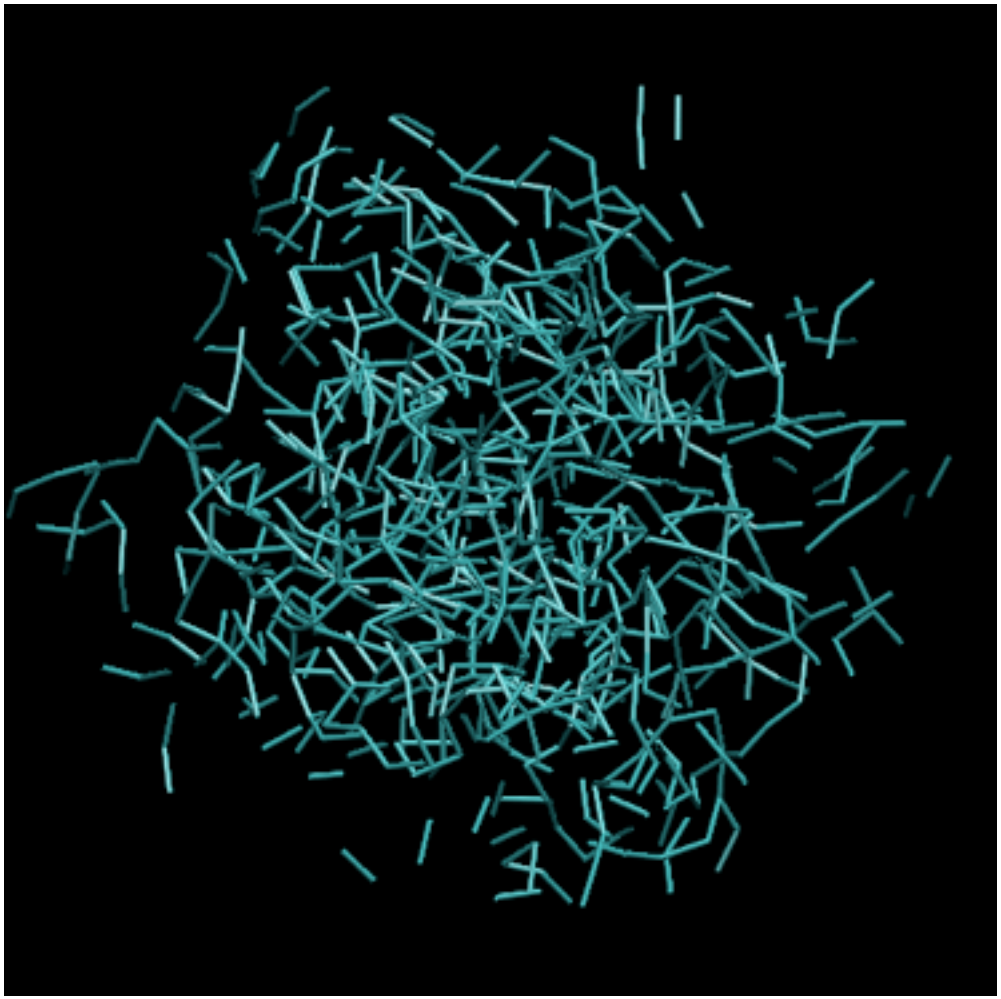
- MARTINI does pretty well for lipids
  - Many examples are described in literature
- MARTINI extensions
  - Proteins
  - Sugars
  - Polymers
  - …

Marrink and Tieleman *Chem. Soc. Rev.* **42**, 6801 (2013)
Check out http://www.cgmartini.nl

university of groningen

Example: liquid hexadecane

- Standard Martini model* compared to mapped GROMOS 53A6 model
- Movie shows CG representation and is looping over 0.2 ns
- 320 hexadecane molecules in the system
- T = 300 K

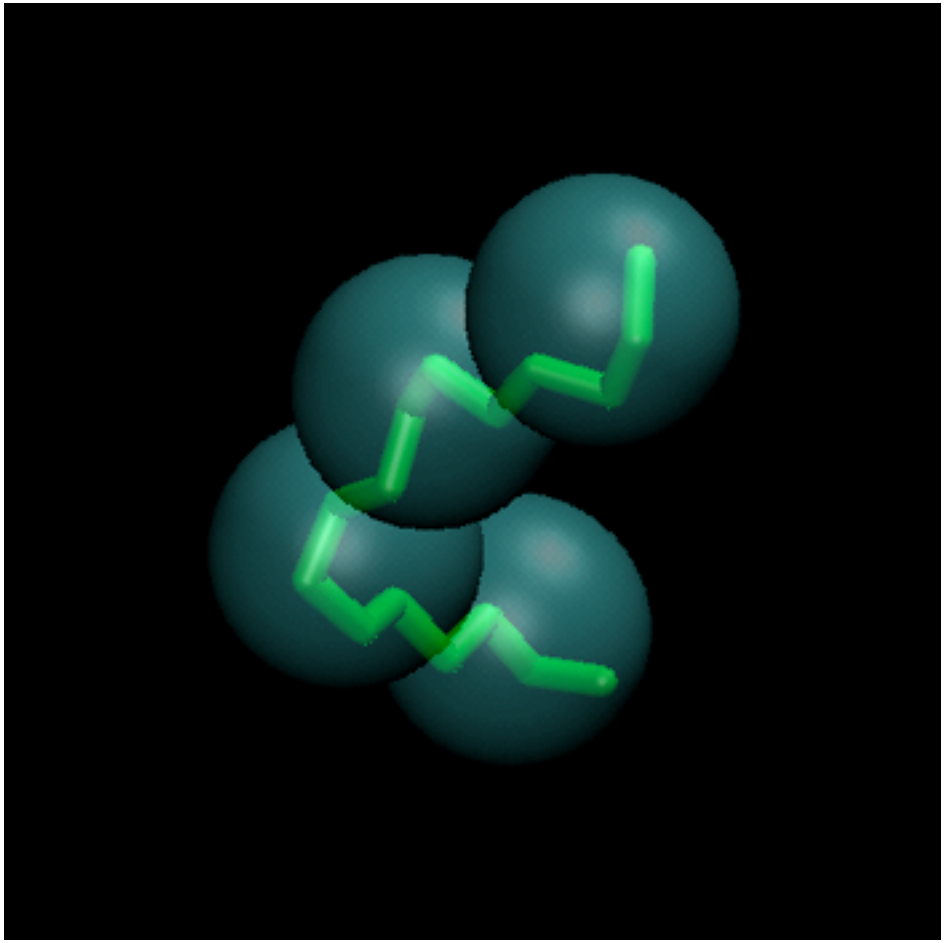


- * Parameterization discussed in the next lecture

university of groningen

Example: liquid hexadecane

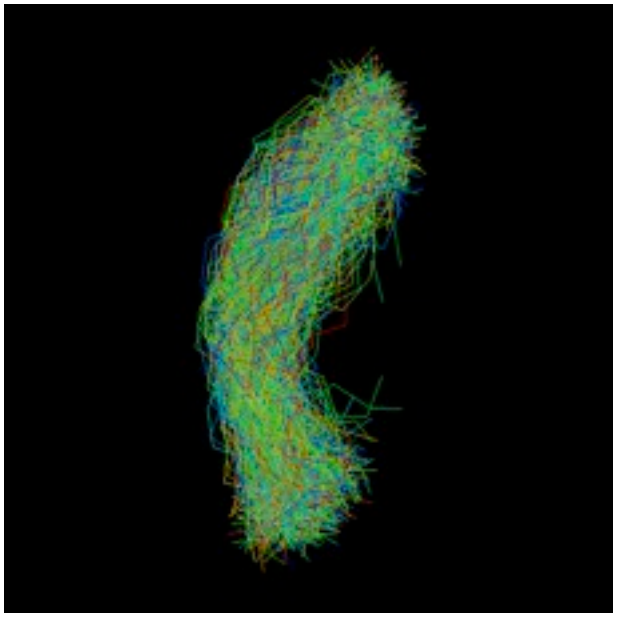
- Movie is looping over 5 ns
- 1 hexadecane molecule of 320 in the system
- Overall translation and rotation of the molecule is removed



university of groningen

Characterizing a collection of structures

- Are conformations realistic?
- Time scale of sampling



- Schlitter's formula for configurational entropy
  - Upper bound
  - Approximation for harmonic oscillator

$$S_{true} \leq S = \frac{k_B}{2} \ln \left\| 1 + \frac{k_B T e^2}{\hbar^2} \mathbb{D} \right\|$$

Mass-weighted covariance matrix

- Procedure
  - Fit (part of) the structure to remove translation (and rotation)

J. Schlitter *Chem. Phys. Lett.* **215**, 617 (1993)

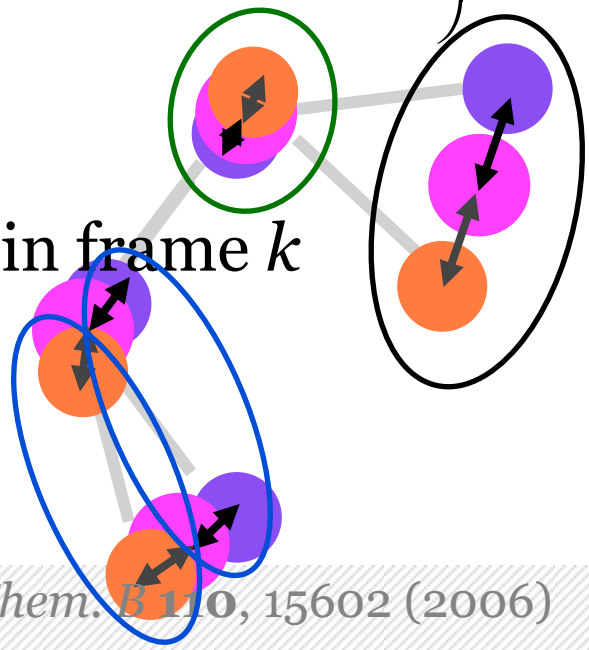
university of groningen

$$S_{true} \le S = \frac{k_B}{2} \ln \left\| 1 + \frac{k_B T e^2}{\hbar^2} \mathbb{D} \right\|$$

Mass-weighted covariance matrix

$$\mathbb{D} = \begin{pmatrix} \frac{m_1}{K} \sum_k \left(r_1^k - \langle r_1 \rangle \right)^2 & \cdots & \frac{1}{K} \sum_k \left(r_1^k - \langle r_1 \rangle \right)\left(r_N^k - \langle r_N \rangle \right) \\ \vdots & \ddots & \vdots \\ \frac{1}{K} \sum_k \left(r_N^k - \langle r_N \rangle \right)\left(r_1^k - \langle r_1 \rangle \right) & \cdots & \frac{m_N}{K} \sum_k \left(r_N^k - \langle r_N \rangle \right)^2 \end{pmatrix}$$

- Here, K is the number of conformations
- r_1^k is the position of atom/bead number 1 in frame k
- m_1 is the mass of atom/bead 1
- Note similarity to variance!



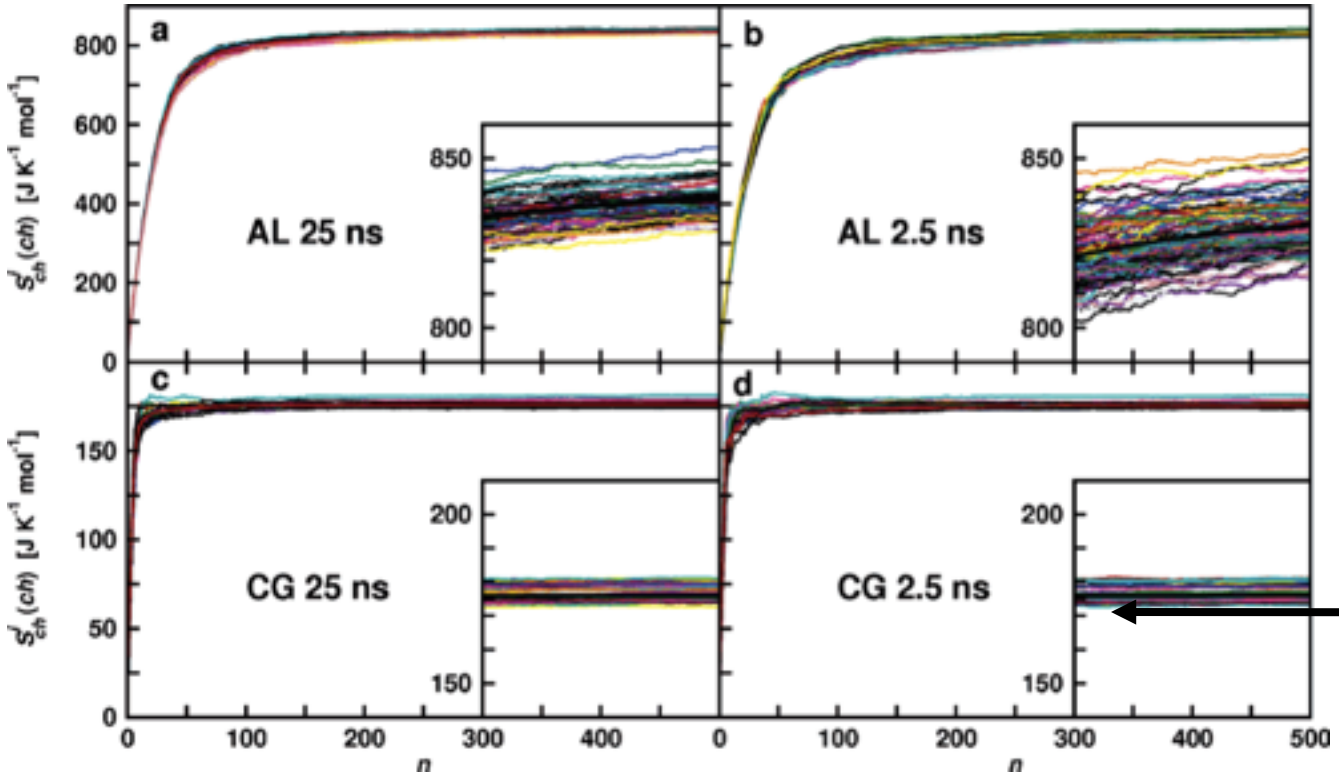
Baron et al *J. Phys. Chem. B* **110**, 15602 (2006)

university of groningen

$$S_{true} \leq S = \frac{k_B}{2} \ln \left\| 1 + \frac{k_B T e^2}{\hbar^2} \mathbb{D} \right\|$$

Configurational Entropy

- MARTINI versus GROMOS 53A6
  - Studied at FG (AL) and CG levels by Baron et al.



- Mapped FG

Baron et al *J. Phys. Chem. B* **110**, 8464 (2006)

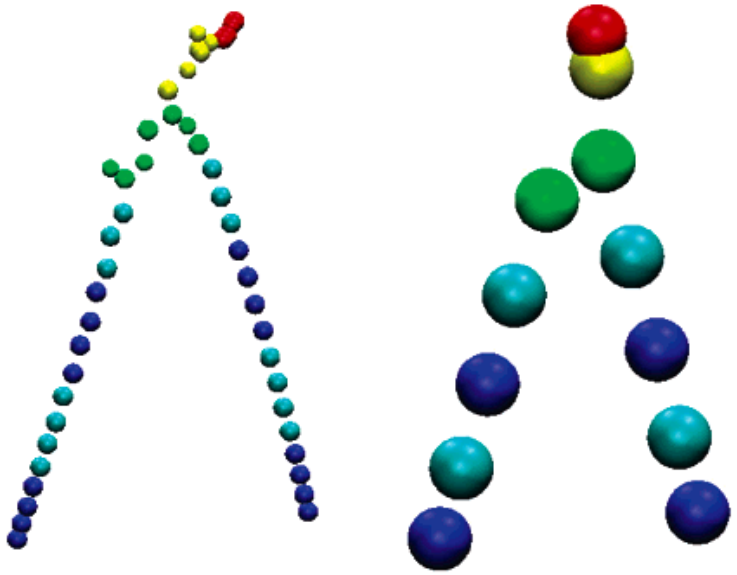
university of groningen

$$S_{true} \le S = \frac{k_B}{2} \ln \left\| 1 + \frac{k_B T e^2}{\hbar^2} \mathbb{D} \right\|$$

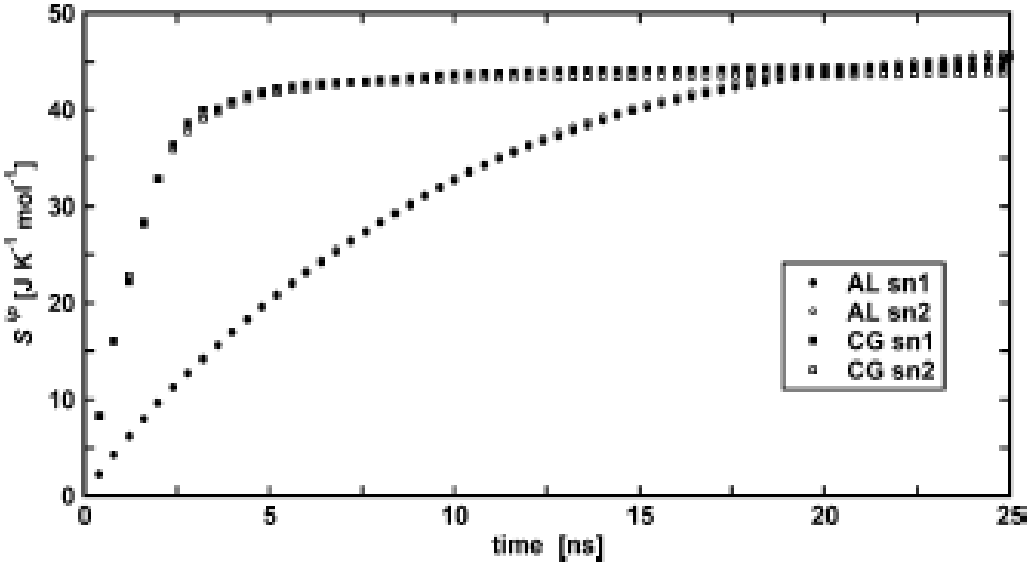
Configurational Entropy: Time Scale

› For phospholipid DPPC in bilayer

Average structures



Build-up of sampling after mapping

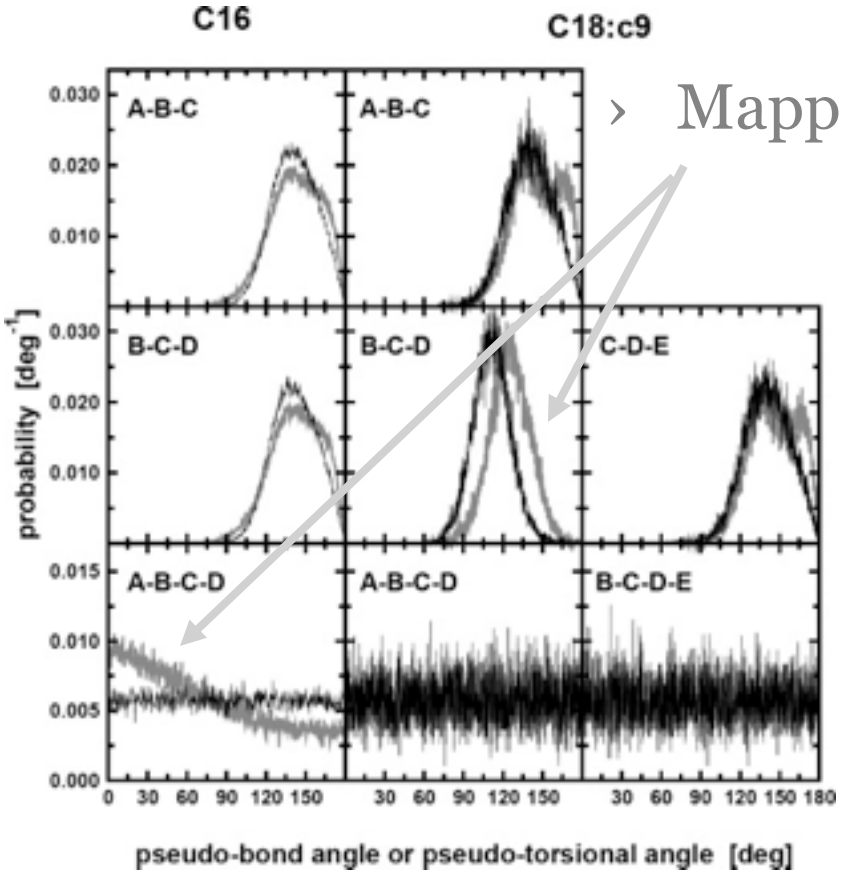


Baron et al. *J. Phys. Chem. B* **110**, 15602 (2006)

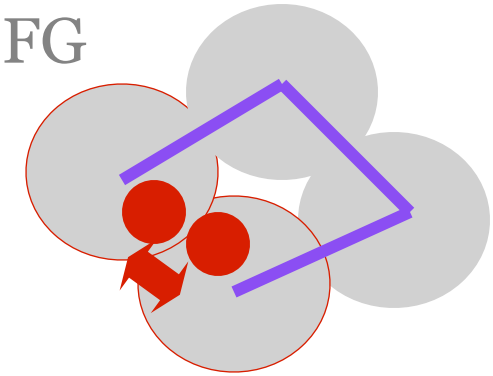
university of groningen

Bonded interactions: compare to FG model

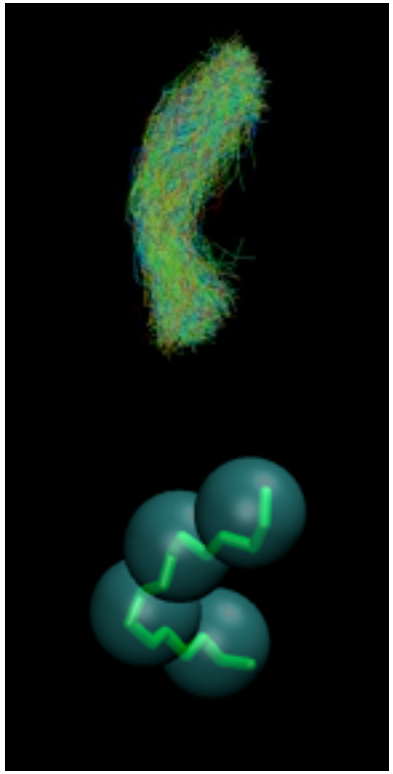
- MARTINI versus GROMOS 53A6
  - Bonded distributions MARTINI and mapped FG differ



- Mapped FG



- Some conformations of hexadecane are more favorable in FG because of short contacts but overlapping vdW spheres in CG



Baron et al *J. Phys. Chem. B* **110**, 8464 (2006)

university of groningen

COARSE GRAINING SUMMARY

- SPEEDING UP SEARCH IN PHASE SPACE
  - Use an effective interaction from distribution
    - Smooths Potential Energy Surface
    - Reduces number of interactions
    - Increases effective time

- DETAIL IS LOST
  - Beneficial: detail may not be required
  - Detrimental: some system characteristics are gone

university of groningen

Thank you for your attention

$$\mathbf{p}_i(t) = m_i \frac{d\mathbf{r}_i(t)}{dt}; \quad \mathbf{F}_i(t) = \frac{d\mathbf{p}_i(t)}{dt}$$

Integrating equations of motion

- To compute a new position after a time interval Δt

$$\mathbf{r}_i(t+\Delta t) = \mathbf{r}_i(t) + \int_t^{t+\Delta t} \frac{\mathbf{p}_i(\tau)}{m_i} d\tau \approx \mathbf{r}_i(t) + \frac{\bar{\mathbf{p}}_i(t)}{m_i} \Delta t$$

- Similarly, for the new momentum

$$\mathbf{p}_i(t+\Delta t) = \mathbf{p}_i(t) + \int_t^{t+\Delta t} \mathbf{F}_i(\tau) d\tau \approx \mathbf{p}_i(t) + \bar{\mathbf{F}}_i(t) \Delta t$$

- Combining these from t = 0

$$\mathbf{r}_i(\Delta t) = \mathbf{r}_i(0) + \frac{1}{m_i} \int_0^{\Delta t} \left[\mathbf{p}_i(0) + \int_0^{\tau} \mathbf{F}_i(\tau') d\tau' \right] d\tau$$

$$\approx \mathbf{r}_i(0) + \frac{\bar{\mathbf{p}}_i(0)}{m_i} \Delta t + \frac{\bar{\mathbf{F}}_i(0)}{2m_i} (\Delta t)^2$$

$$\mathbf{F} = m\mathbf{a} = m\frac{d\mathbf{v}}{dt} = m\frac{d}{dt}\left(\frac{d\mathbf{r}}{dt}\right) = m\frac{d^2\mathbf{r}}{dt^2}$$

Verlet Integrator

$$\mathbf{r}(t+\Delta t) = \mathbf{r}(t) + \left.\frac{d\mathbf{r}}{dt}\right|_t \Delta t + \frac{1}{2!}\left.\frac{d^2\mathbf{r}}{dt^2}\right|_t (\Delta t)^2 + \ldots$$

$$\mathbf{r}(t-\Delta t) = \mathbf{r}(t) - \left.\frac{d\mathbf{r}}{dt}\right|_t \Delta t + \frac{1}{2!}\left.\frac{d^2\mathbf{r}}{dt^2}\right|_t (\Delta t)^2 - \ldots$$

$$\mathbf{r}(t+\Delta t) + \mathbf{r}(t-\Delta t) = 2\mathbf{r}(t) + \left.\frac{d^2\mathbf{r}}{dt^2}\right|_t (\Delta t)^2 + O((\Delta t)^4)$$

$$\Rightarrow \mathbf{r}(t+\Delta t) + \mathbf{r}(t-\Delta t) \approx 2\mathbf{r}(t) + \frac{\mathbf{F}}{m}(\Delta t)^2$$

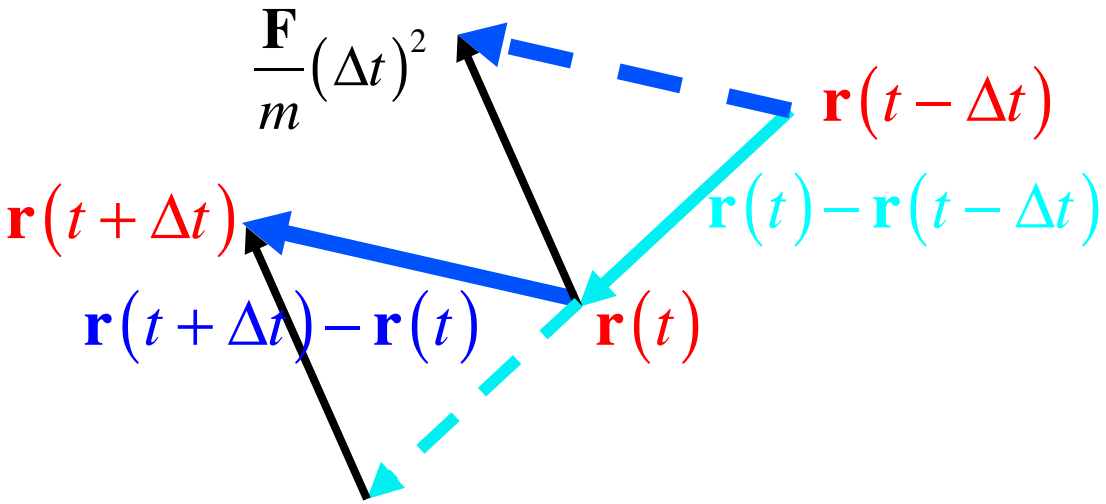
Taylor expansion of the position in time, assuming constant force

university of groningen

$$\mathbf{F} = m\frac{d^2\mathbf{r}}{dt^2}$$

Verlet integrator from Newton's Law

$$\left[\mathbf{r}(t+\Delta t)-\mathbf{r}(t)\right]-\left[\mathbf{r}(t)-\mathbf{r}(t-\Delta t)\right]=\frac{F(t)}{m}\Delta t^2$$



$$\mathbf{r}(t+\Delta t)-\mathbf{r}(t)\approx$$

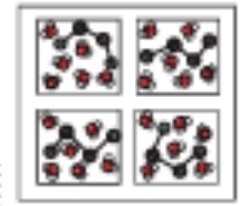
$$\mathbf{r}(t)-\mathbf{r}(t-\Delta t)$$

$$+\frac{\mathbf{F}}{m}(\Delta t)^2$$

$\frac{d^2\mathbf{r}}{dt^2}$ is the difference of the difference, or the change in the change

university of groningen

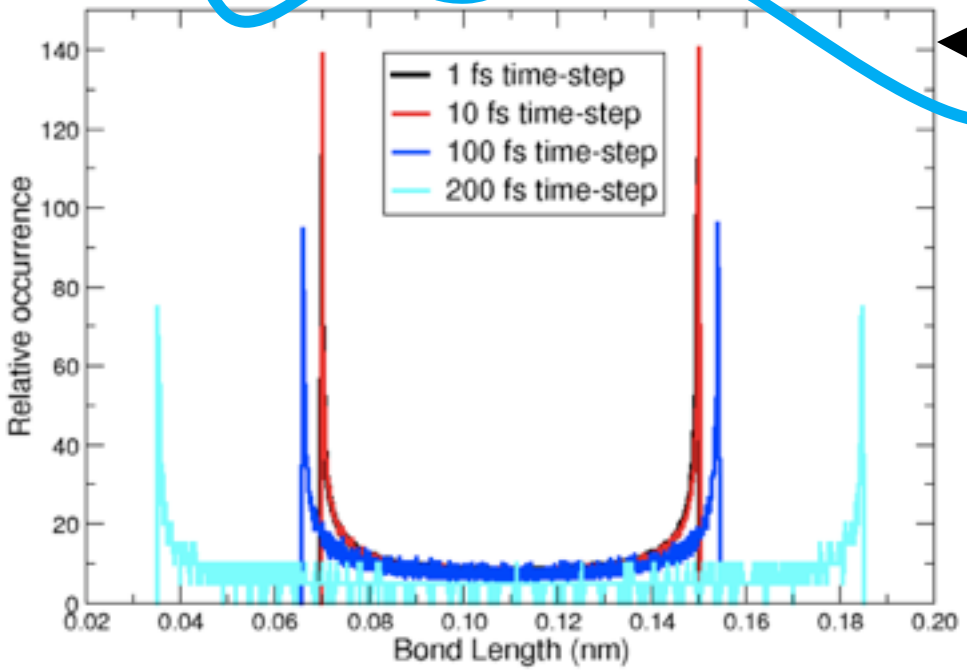
.mdp



Conservation of Energy

› In practice, even with small time-steps, conservation of energy is difficult to achieve

$$\Delta E = -W = -\int \mathbf{F} \bullet d\mathbf{R}$$



$$\Delta E = -W = -\mathbf{F} \bullet \Delta\mathbf{R}$$

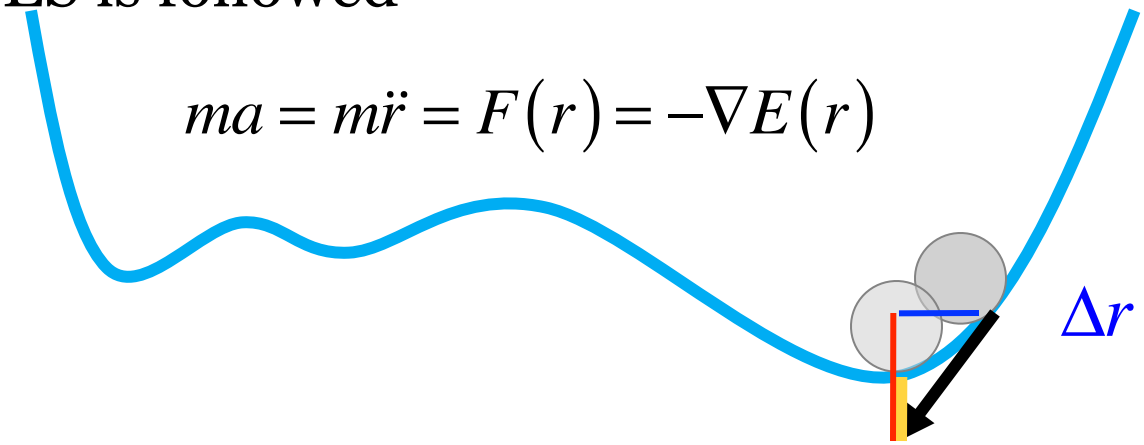
Too large a time-step takes the system away from its potential energy surface and leads to failure of energy conservation.

university of groningen

$$\Delta r = \dot{r}\Delta t + \frac{F}{2m}(\Delta t)^2$$

Practical considerations: Conservation of Energy

- In numerical approaches, time-step should be such that PES is followed



$$ma = m\ddot{r} = F(r) = -\nabla E(r)$$

$$\Delta E = -F(r) \bullet \Delta r$$

$$\Delta r \approx \frac{F(r)(\Delta t)^2}{2m}$$

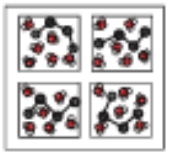
- We should end up at the potential energy we expect or energy is lost from/added to the system

$$\Delta E_{pred} \approx -F(r) \bullet \frac{F(r)(\Delta t)^2}{2m}$$

$E(r)$ and $U(r)$ are used interchangeably

$$\dot{r} = v = \frac{dr}{dt}; \quad \ddot{r} = a = \frac{d^2r}{dt^2}$$

university of groningen



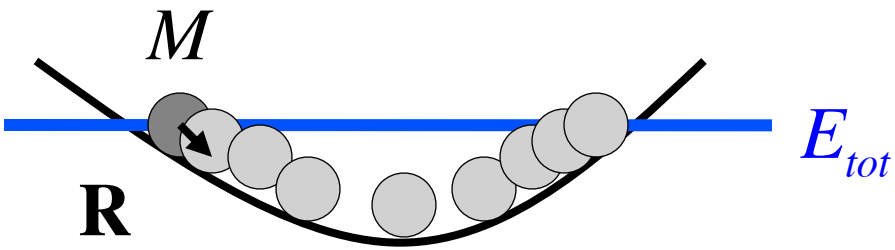
Appropriate time step for sampling

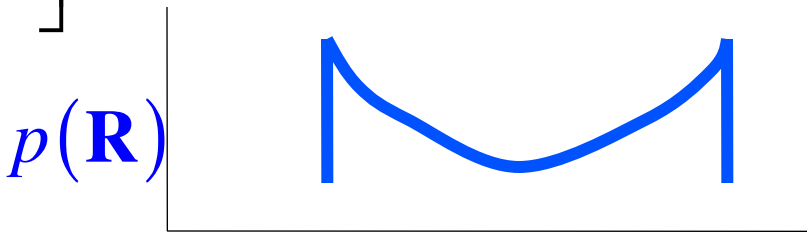
› At atomistic level, time step for fastest vibrations

$$1/\Delta t_{vib} = \nu_{IR} = c\tilde{\nu}_{IR} \approx$$

$$3*10^{8} * 3{,}000\left[ms^{-1}cm^{-1}\right]$$

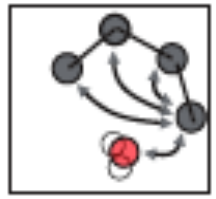
$$\approx 1*10^{14}\,Hz$$





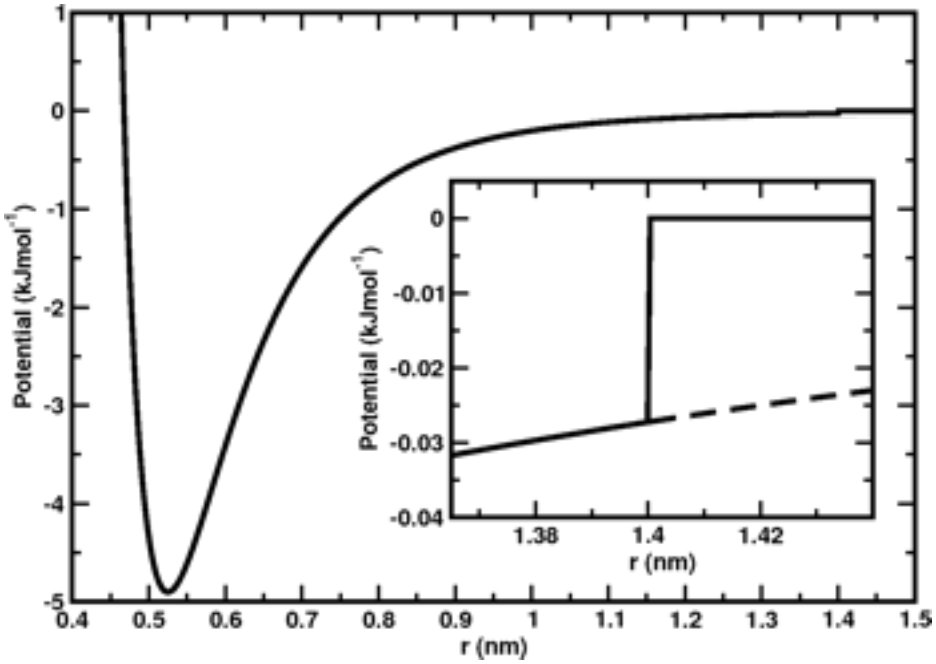
- Time step ~1 fs

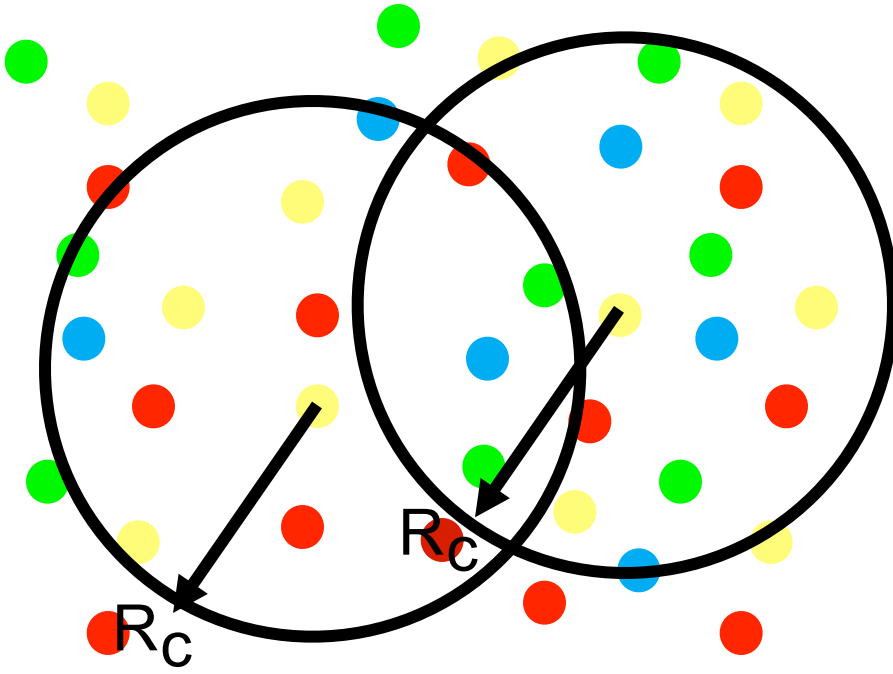
university of groningen



Cut-off noise

› Particles start/stop interacting at certain distance: **energy is not conserved**





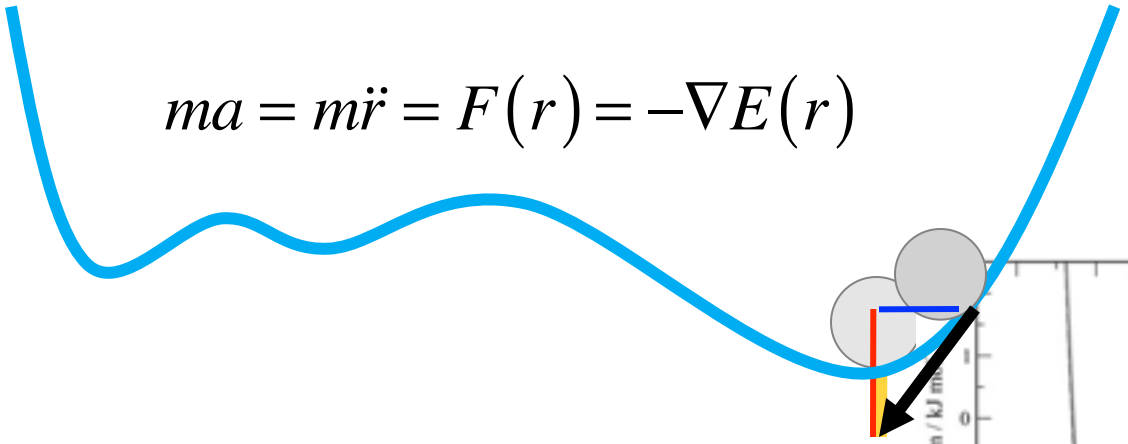
university of groningen

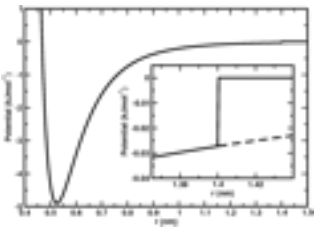
$$\Delta r = \dot{r}\Delta t + \frac{F}{2m}(\Delta t)^2$$

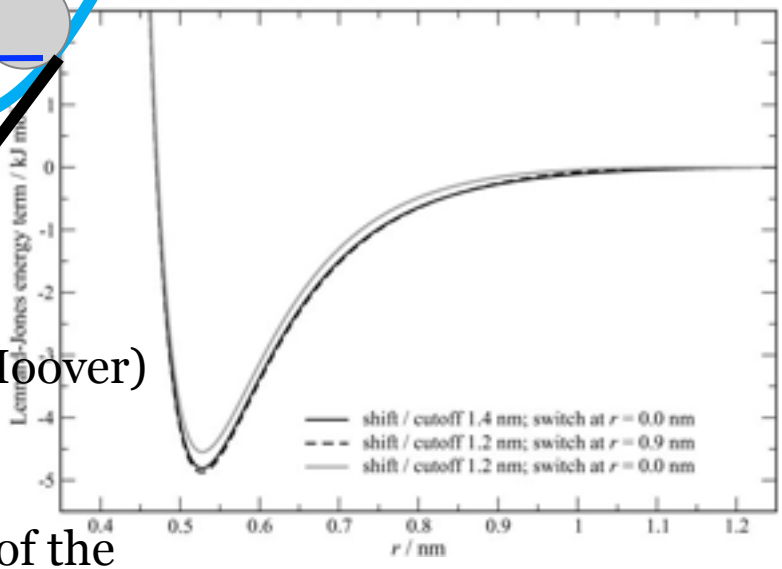
Practical considerations: Conservation of Energy

- In practice, energy conservation is impossible to achieve

$$ma = m\ddot{r} = F(r) = -\nabla E(r)$$







- Couple to heat bath to dissipate or gain heat
- Popular methods are velocity rescaling (e.g. Berendsen) or extended ensembles (e.g. Nose-Hoover)
- Strictly speaking, we are not doing Newtonian mechanics
- Time step and bath coupling strengths are part of the parameter set!
- Martini uses non-bonded potentials without jump at cut-off (shifted potentials)