Biomolecular modeling I

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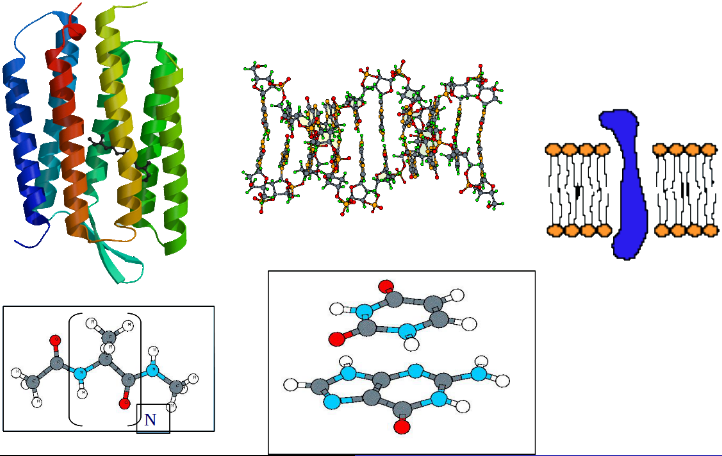
Biomolecular structure

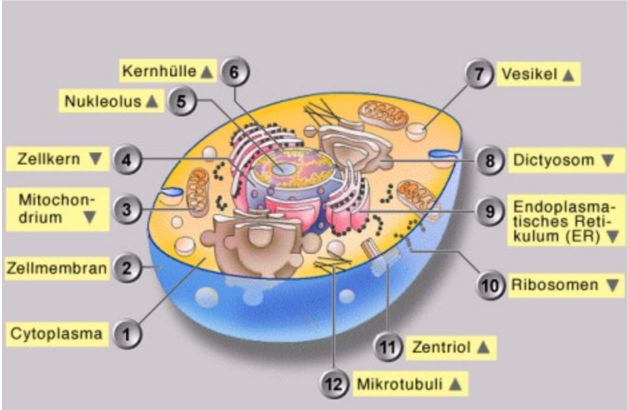
Structural elements of life

Biomolecules – proteins, nucleic acids, lipids, carbohydrates ...



Biomolecular structure

Biomolecules → biomolecular complexes → aggregates → . . . → organelles → a cell



Biomolecular function

Biophysical processes

- Bioenergetics
  – reception, transformation and utilization of energy
- Catalysis
  – synthesis of substances, metabolism
- Transport
  – exchange of small molecules . . . proteins with surroundings
- Sensing
  – detection / recognition / binding in presence of a stimulus

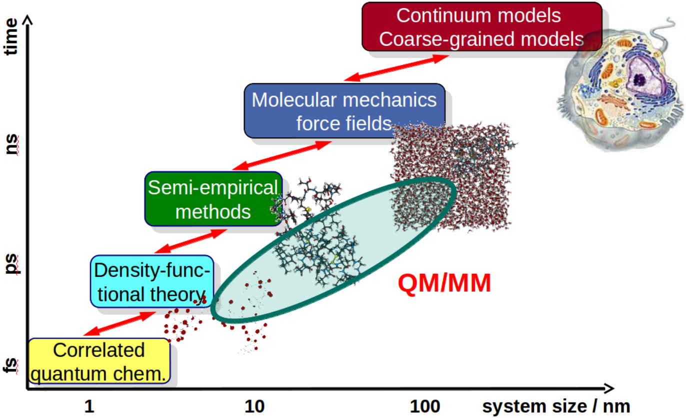
Theoretical / computational biophysics

– create a model and perform a "pseudo-experiment"

Molecular modeling

- Focus: understanding on the atomic scale
- The structure and dynamics determine
  the properties and function of biological molecules
- Prediction of properties of interest
  (e.g., experimentally relevant data)
- Molecular design of materials with desired properties
- The way to the goal – in general:
  solution of quantum mechanical many-body problem
- QM many-body approach would be too inefficient
  → apply more approximative methods

Methods



Continuum models
Coarse-grained models

Molecular mechanics
force fields

Semi-empirical
methods

Density-functional theory

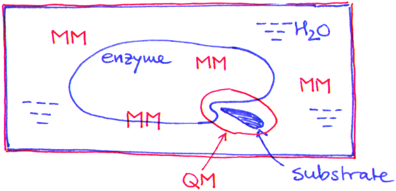
Correlated quantum chem.

QM/MM

A hybrid approach – QM/MM

- Quantum chemistry (QM)
  - – bonds created/broken
  - – computionally costly
  - – DFT or ab initio, up to 100 atoms
  - – semi-empirical, up to 1000 atoms
- Molecular mechanics (MM)
  - – efficient for up to 100,000 atoms
  - – generally – structural properties
- Hybrid QM/MM
  - – chemical reactions

    etc.

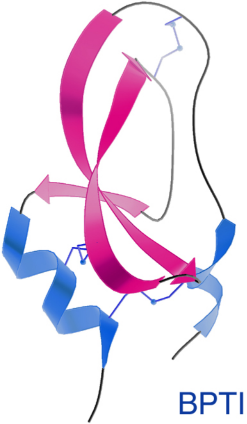


Timeline

- 1687 – equations of motion (Newton)
- similar – harmonic spring (Hooke)
- . . .
- 1946 – molecular mechanics
- 1950s – useful computers
- 1959 – molecular dynamics of a fluid (Alder & Wainwright)
- 1975 – molecular dynamics of a protein
  (Levitt & Warshel, Gelint & Karplus)
- 1976 – QM/MM proposed (Levitt & Warshel)
- 1990 – significant QM/MM work (Karplus)

Timeline

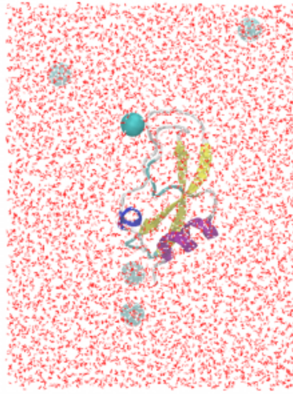
first simulation of protein dynamics
– BPTI, 58 AAs, in vacuo, 9.2 ps
– McCammon, Gelin & Karplus, Nature 1977
– starting point – crystal structure



Timeline

simulation of protein in aqueous solution
– BPTI + water, 210 ps
– Levitt & Sharon, PNAS 1988

today's standard – 100,000 atoms, 100 ns

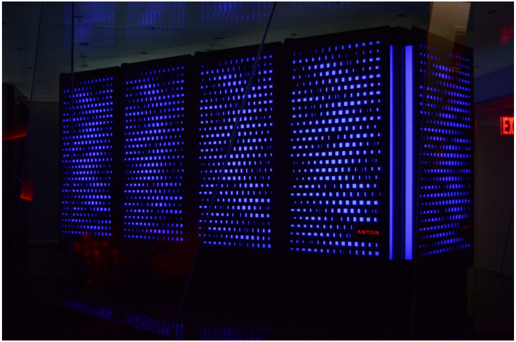


Any extra cash?

Anton

– massively parallel supercomputer
designed and built by D. E. Shaw Research (NYC)

– special-purpose system for MD simulations
of proteins and other biological macromolecules



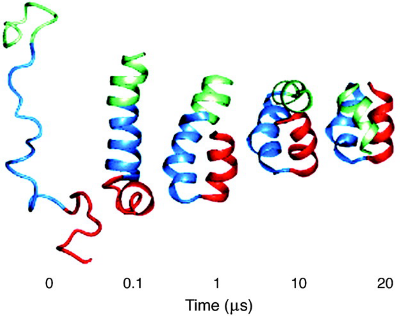
Contact with experimental reality

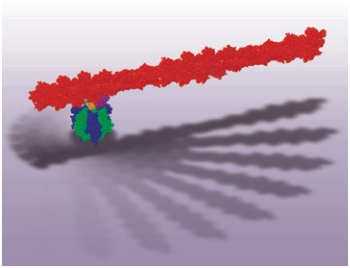
- X-ray and neutron diffraction
- STM/AFM imaging
- electronic / optical spectra
- electronic and nuclear magnetic resonance
- vibrational / IR spectra
- thermodynamic measurements – DSC, ITC

Applications

Structure and dynamics of complex biomolecular systems

- protein folding
- protein–ligand interaction
- proteins as nanomachines

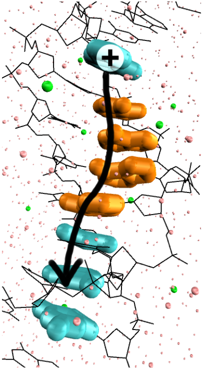


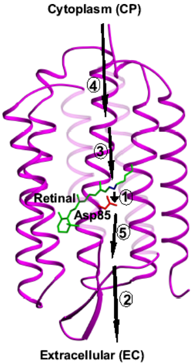


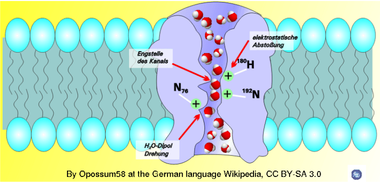
Applications

Transport

- electrons
- protons – across membrane
- water, ions, small molecules, . . .







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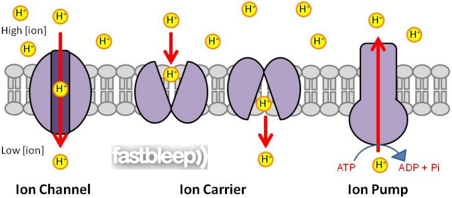
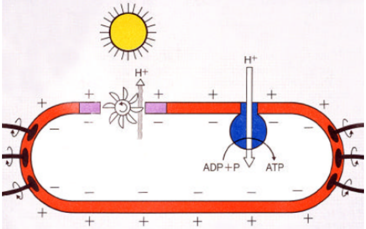
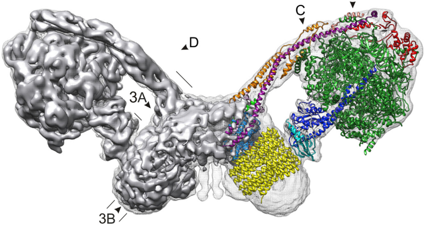


Applications

Enzymes

- catalyzed chemical reactions
- energy conversion (light, chem., mech., gradients)
- bioenergetics





Challenges

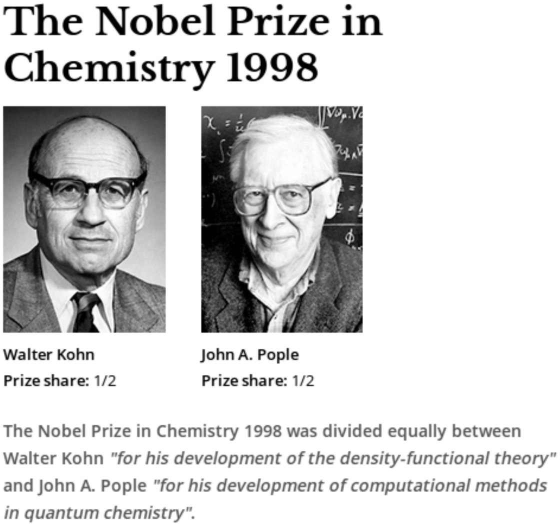
- system size limited to ca. 100,000 atoms
- time scales limited to few microseconds
- accuracy of description
  - bonded interaction (vibration, rotation)
  - non-bonded interaction (charge-transfer, polarizability)
- excited electronic states
- quantum character of movement of nuclei

Some can be tackled with

- further development of available methods
- combination of various methods
- optimization of algorithms

  parallelization, $\mathcal{O}(N)$ – linear scaling

Nobel prizes for computational chemistry



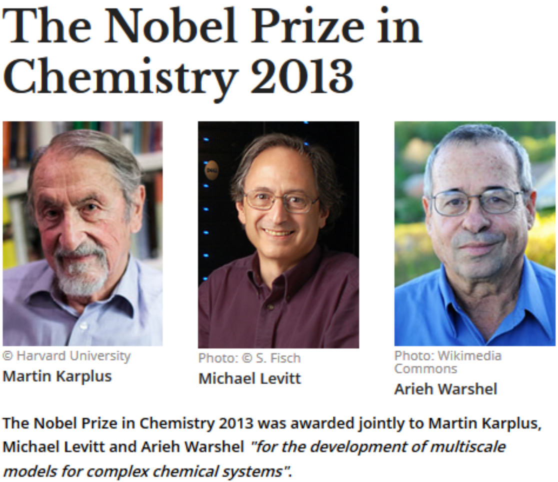
The Nobel Prize in Chemistry 1998

Walter Kohn
Prize share: 1/2

John A. Pople
Prize share: 1/2

The Nobel Prize in Chemistry 1998 was divided equally between Walter Kohn *"for his development of the density-functional theory"* and John A. Pople *"for his development of computational methods in quantum chemistry"*.

Nobel prizes for computational chemistry



The Nobel Prize in Chemistry 2013

© Harvard University
Martin Karplus

Photo: © S. Fisch
Michael Levitt

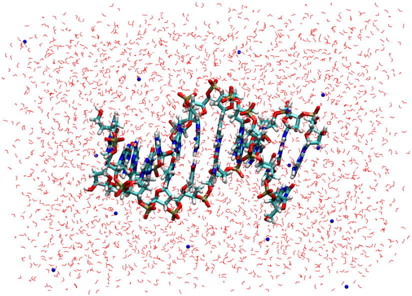
Photo: Wikimedia Commons
Arieh Warshel

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel *"for the development of multiscale models for complex chemical systems".*

Biomolecular simulation

Elementary body – atom

Usually – one molecule/complex of interest (e.g. protein, NA)



Simulation vs. reality

One molecule instead of many

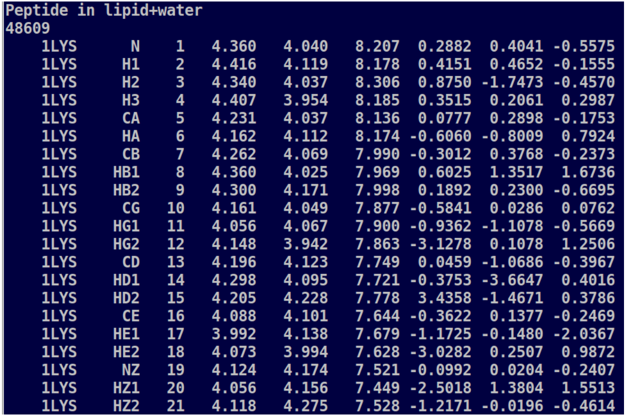
Tiny volume of $\approx 10^{-21}$ L
instead of $\approx 10^{-5}$ L

Dynamics – short time scale
of max. $\approx 10^{-5}$ s

Biomolecular simulation

Each atom – x, y, z coordinates

“A protein is a set of coordinates.” (Gromacs, A. P. Heiner)



```
Peptide in lipid+water
48609
    1LYS      N    1   4.360   4.040   8.207  0.2882  0.4041 -0.5575
    1LYS     H1    2   4.416   4.119   8.178  0.4151  0.4652 -0.1555
    1LYS     H2    3   4.340   4.037   8.306  0.8750 -1.7473 -0.4570
    1LYS     H3    4   4.407   3.954   8.185  0.3515  0.2061  0.2987
    1LYS     CA    5   4.231   4.037   8.136  0.0777  0.2898 -0.1753
    1LYS     HA    6   4.162   4.112   8.174 -0.6060 -0.8009  0.7924
    1LYS     CB    7   4.262   4.069   7.990 -0.3012  0.3768 -0.2373
    1LYS    HB1    8   4.360   4.025   7.969  0.6025  1.3517  1.6736
    1LYS    HB2    9   4.300   4.171   7.998  0.1892  0.2300 -0.6695
    1LYS     CG   10   4.161   4.049   7.877 -0.5841  0.0286  0.0762
    1LYS    HG1   11   4.056   4.067   7.900 -0.9362 -1.1078 -0.5669
    1LYS    HG2   12   4.148   3.942   7.863 -3.1278  0.1078  1.2506
    1LYS     CD   13   4.196   4.123   7.749  0.0459 -1.0686 -0.3967
    1LYS    HD1   14   4.298   4.095   7.721 -0.3753 -3.6647  0.4016
    1LYS    HD2   15   4.205   4.228   7.778  3.4358 -1.4671  0.3786
    1LYS     CE   16   4.088   4.101   7.644 -0.3622  0.1377 -0.2469
    1LYS    HE1   17   3.992   4.138   7.679 -1.1725 -0.1480 -2.0367
    1LYS    HE2   18   4.073   3.994   7.628 -3.0282  0.2507  0.9872
    1LYS     NZ   19   4.124   4.174   7.521 -0.0992  0.0204 -0.2407
    1LYS    HZ1   20   4.056   4.156   7.449 -2.5018  1.3804  1.5513
    1LYS    HZ2   21   4.118   4.275   7.528 -1.2171 -0.0196 -0.4614
```

Simulation vs. reality

Why should we want to simulate molecular systems?

Experiment – the molecule has its genuine properties
Simulation – we need a model to describe the interactions of atoms
– the quality of the model is decisive

Advantage of simulation – structure on atomic level defined

Structure → function

Combination of experiment and simulation – added value

Molecular mechanics

classical description of molecules

Motivation

- To investigate the function of biomolecules,
  we need to characterize its structure and dynamics.
- We will look how the molecules are moving
  – Molecular Dynamics
- For this, we need to calculate the forces on atoms
  and the energy of the system
- Energy from quantum mechanics / quantum chemistry
  seemingly easy $E = \left\langle \Psi \middle| \hat{H} \middle| \Psi \right\rangle$
  but not quite possible for large molecular systems

Motivation

$$\left[-\frac{\hbar^2}{2m_e\lambda^2}\nabla'^2 - \frac{e^2}{4\pi\varepsilon_0\lambda r'}\right]\phi' = \mathscr{E}\phi'$$

$$[ij|kl] = \int d\mathbf{x}_1\, d\mathbf{x}_2\, \chi_i^*(\mathbf{x}_1)\chi_j(\mathbf{x}_1) r_{12}^{-1}\chi_k^*(\mathbf{x}_2)\chi_l(\mathbf{x}_2)$$

$$\begin{aligned} F_{\mu\nu} &= \int d\mathbf{r}_1\, \phi_\mu^*(1) f(1) \phi_\nu(1) \\ &= \int d\mathbf{r}_1\, \phi_\mu^*(1) h(1) \phi_\nu(1) + \sum_a^{N/2} \int d\mathbf{r}_1\, \phi_\mu^*(1)[2J_a(1) - K_a(1)]\phi_\nu(1) \\ &= H_{\mu\nu}^{\text{core}} + \sum_a^{N/2} 2(\mu\nu|aa) - (\mu a|a\nu) \end{aligned}$$

$$|\Phi\rangle = c_0|\Psi_0\rangle + \sum_{ra} c_a^r|\Psi_a^r\rangle + \sum_{\substack{a<b\\ r<s}} c_{ab}^{rs}|\Psi_{ab}^{rs}\rangle + \sum_{\substack{a<b<c\\ r<s<t}} c_{abc}^{rst}|\Psi_{abc}^{rst}\rangle + \cdots$$

$$E_0^{(2)} = \sum_{a,b=1}^{N/2} \sum_{r,s=(N/2+1)}^{K} \frac{\langle ab|rs\rangle(2\langle rs|ab\rangle - \langle rs|ba\rangle)}{\varepsilon_a + \varepsilon_b - \varepsilon_r - \varepsilon_s}$$

Idea of molecular mechanics

- often – well localized bonding orbitals (organic molecules)
- idea 1 – similar bonds have similar strength and properties
  e.g. similar C–H σ-orbitals → all C–H bonds are 'similar'

- idea 2 – model the bonds with a simple function (harmonic)

$$\begin{aligned} E(x) &= \frac{1}{2}k(x-x_0)^2 \\ F(x) &= -\frac{\partial E(x)}{\partial x} = -k(x-x_0) \end{aligned}$$

- 2 parameters k and x_0 with defined meaning
  – can be obtained from spectroscopy

Concept of (atom, bond. . .) type

- let us use harmonic springs for covalent bonds
- we do not want to parametrize k and x_0 each bond separately
- use just several sets (k, x_0), for different types of bonds

Why can we expect such ‘unification’ to work?

Concept of (atom, bond. . .) type

Spectroscopy

- every C–H bond: length 1.06–1.11 Å,
  frequency ca. 3100 cm^{-1}, in any molecular environment

Thermochemistry

- heat of formation – roughly additive:
  $CH_4 \cong 4$ C–H
  $C_2H_6 \cong 6$ C–H + C–C

Concept of (atom, bond. . .) type

How to identify the atom types? – chemical ideas

i) hybridization

- different types for sp^3 carbon (4 bonds) and sp^2 C (3 bonds)
- different functions for bonds of types C–C, C=C and C≡C
- determine the parameters (k, x_0) with some selected molecules, typical for the binding situation
- example: use C_2H_6, C_2H_4, C_2H_2 and benzene for k, x_0

Concept of (atom, bond. . .) type

How to identify the atom types? – chemical ideas

ii) polarity

- an atom bonded to electronegative atom – electron deficient
  → affects its bonding to other atoms
- example: C–C bond in O=CH–C··· is affected
  and needs to be parametrized differently from apolar C–C
  → an atom type for carbonyl C introduced

Biomolecular force fields
– usually 20 types for C, 10 for N and 5 for O and H

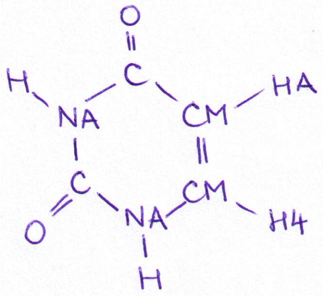
Concept of (atom, bond. . .) type

AMBER types for carbon:

C - sp2 C carbonyl group
CA - sp2 C pure aromatic (benzene)
CB - sp2 aromatic C, 5&6 membered ring junction
CC - sp2 aromatic C, 5 memb. ring HIS
CK - sp2 C 5 memb.ring in purines
CM - sp2 C pyrimidines in pos. 5 & 6
CN - sp2 C aromatic 5&6 memb.ring junct.(TRP)
CQ - sp2 C in 5 mem.ring of purines between 2 N
CR - sp2 arom as CQ but in HIS
CT - sp3 aliphatic C
CV - sp2 arom. 5 memb.ring w/1 N and 1 H (HIS)
CW - sp2 arom. 5 memb.ring w/1 N-H and 1 H (HIS)
C* - sp2 arom. 5 memb.ring w/1 subst. (TRP)

Concept of (atom, bond. . .) type

AMBER atom types in a molecule of uracil



Interactions between atoms

Bonded

- mediated by, and resulting directly from covalent bonds
- cover all of the quantum-mechanical phenomena between pairs of atoms with effective potentials
- harmonic springs between atoms (also angles and dihedrals)

Non-bonded

- longer-range interactions
  – charge–charge (Coulomb) and van der Waals (vdW)
- between molecules and distant parts of one molecule

Coulomb interaction

- idea – condense electrons in each atom with the nucleus
  → effective atomic charge $q_i = -Q_i + Z_i$:

$$E_{QQ} = \frac{1}{2} \sum_{ij} \frac{q_i \cdot q_j}{R_{ij}}$$

- needs to be defined for every atom
  rather than atom type – this would be too crude

Possible improvement – polarizable force field

- atomic polarizability α_i is assigned to every atom i
- external field induces atomic dipole $\overrightarrow{\mu_i} = \overleftrightarrow{\alpha_i} \cdot \overrightarrow{E}$

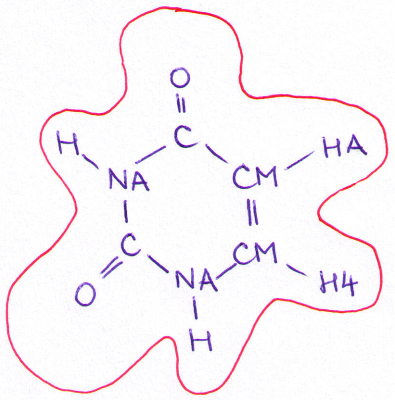
Coulomb interaction

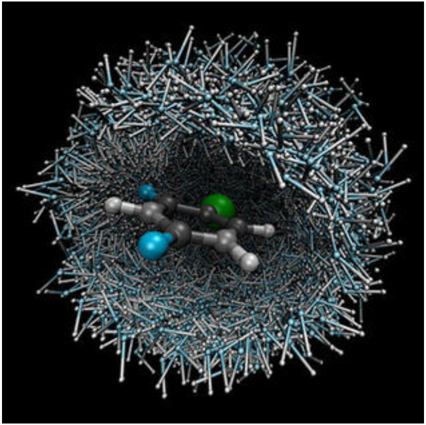
How to calculate atomic charges?

- from quantum-chemical calculations
  of typical (bio)molecular fragments
  – amino acid residues and peptide bonds for proteins
  – nucleobases, sugars and phosphate groups for DNA/RNA
- popular – potential-derived charges:
  1. calculate the electron density in the molecule
  2. get electrostatic potential at surface of the molecule
  3. fit point electric charges on atoms to reproduce the ESP

Coulomb interaction

surface of the uracil molecule

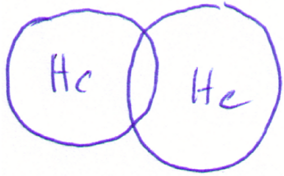




van der Waals interaction

Pauli repulsion

- electrons with the same spin avoid spatial overlap



- modeling:

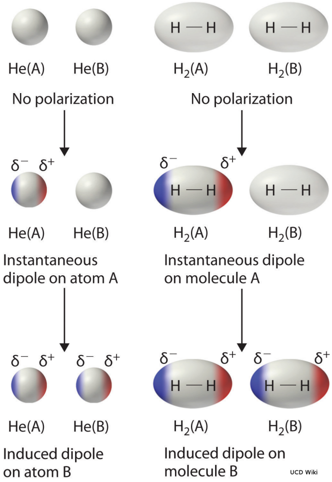
$$E_{\text{ex}} = \exp\left[a - b \cdot R_{ij}\right]$$

$$E_{\text{ex}} = \left(\frac{\sigma}{R_{ij}}\right)^{12}$$

van der Waals interaction

dispersion due to correlation

- correlation – between electrons
  irrespective of spin,
  retained on longer distances
- instantaneous dipole →
  induced dipole → interaction
- orientation of dipoles is correlated
  – attractive interaction
- R^{-6}-dependence,
  proportional to polarizabilities



UCD Wiki

van der Waals interaction

dispersion due to correlation

www.petrhejna.cz

news.softpedia.com

van der Waals interaction

most common function: Lennard-Jones 12-6 potential

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

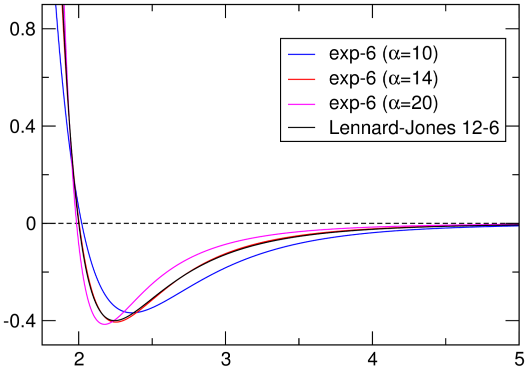
- 2 parameters – σ and ε

repulsive: $\exp\left[\alpha\left(1 - \frac{r}{\sigma}\right)\right]$ sometimes better than $\left(\frac{\sigma}{r}\right)^{12}$
→ exp-6 potential

- may be a better choice for phase transitions
- e.g. MM water would not freeze below 0 °C with LJ 12-6

note: phase transitions are difficult to simulate generally

van der Waals interaction



van der Waals interaction

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

parametrization

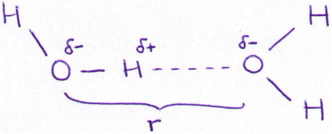
- challenging task in general
- fitting of params to experimental / quantum-chem. data
- e.g. relation to density and heat of vaporization
  – obvious in organic liquids – major interaction

Hydrogen bonding

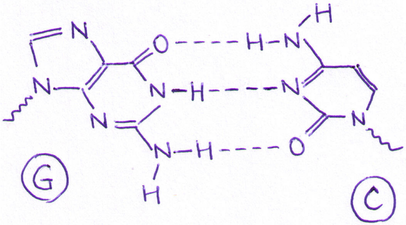
- crucial interatomic contacts in biomolecules
- interplay of several kinds of interactions
- typical binding energies: 20 kJ/mol
  higher for strongly polarized or even charged molecules
  or if there are several H-bonds (nucleobase pairs)
- early force fields – special potential functions for H-bonding
- modern force fields – no special treatment

Hydrogen bonding

H_2O dimer



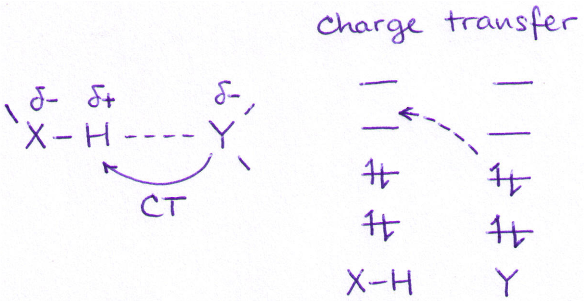
guanine:cytosine base pair



Hydrogen bonding

- Coulomb interaction is dominant
- vdW interaction
  - may become important, especially in weakly bound systems
  - crucial e.g. for angular dependence in $H_2CO \cdots H_2O$ etc.
- charge transfer contribution
  - cannot be covered by force fields due to constant charges
  - may be included in other terms effectively

Hydrogen bonding



charge transfer – into the σ^* orbital
→ weakening of the X–H bond → red shift in the IR spectrum

Parametrization of bonded interactions

Bonds

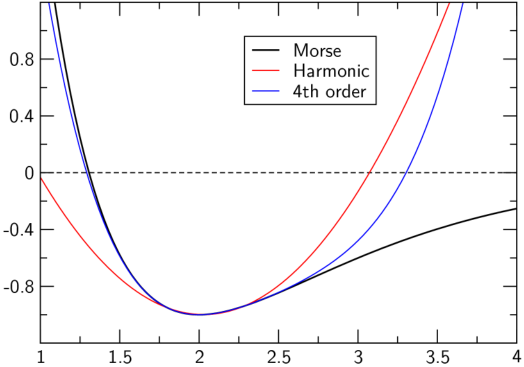
- harmonic approximation (Taylor expansion up to second order)

$$E(r) = \frac{1}{2}k(r - r_0)^2$$

  - parameters: equilibrium distance, force constant
  - works in a narrow interval of distances
  - often sufficient (vibrations are within the interval)
- does not work if bonds are created / broken (chemistry)

  another solution has to be sought
  → probably leave molecular mechanics ☹

Parametrization of bonded interactions



- for accurate vibration frequencies
  - quartic terms can be important to describe the curvature

Parametrization of bonded interactions

Angles

- harmonic approximation for the angle deformation

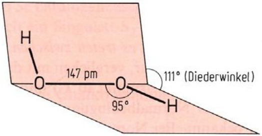
$$E_{\text{bend}}(\vartheta) = \frac{1}{2} k_{\vartheta} (\vartheta - \vartheta_0)^2$$

- parameters needed: equilibrium angle, and force constant
- from experiment (vib-rot spectra) or quantum chemistry

Parametrization of bonded interactions

Dihedral angles

- describe the rotation around covalent bonds



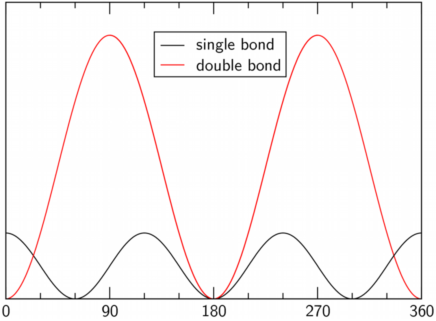
- defined by 4 atoms
- potential energy – periodic function of the dihedral angle:

$$E(\omega) = \sum_{n=1,2,3,4,6} V_n \cos\left[n \cdot \omega - \gamma_n\right]$$

- V_n – amplitude (barrier), n – periodicity, γ_n – phase shift

Parametrization of bonded interactions

Dihedral angles – example: C–C single and C=C double bonds



The complete equation

$$E(R^N) =$$

$$\begin{aligned} = \quad & \frac{1}{2}\sum_i k_i (r_i - r_i^0)^2 + \frac{1}{2}\sum_j k_j^\vartheta (\vartheta_j - \vartheta_j^0)^2 + \frac{1}{2}\sum_n V_n \cdot \cos\left[n\omega - \gamma_n\right] \\ + \quad & \sum_i^N \sum_{j=i+1}^N \left\{ 4\varepsilon_{ij} \left(\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6} \right) + \frac{1}{4\pi\varepsilon_0}\frac{q_i q_j}{r_{ij}} \right\} \end{aligned}$$

Molecular dynamics simulation

how to get things moving

Equations of motion

$$m \cdot \ddot{\vec{r}} = \vec{F}$$

ordinary differential equations of second order

- have to be solved numerically
- solution proceeds in discreet steps of length Δt
- numerical integration starts at time t_0,
  where the initial conditions are specified
  – the positions $\vec{r}_0$ and the velocities $\vec{v}_0$
- calculations of forces at $\vec{r}_0$ to get accelerations $\ddot{\vec{r}}_0$
- then, an integrator calculates $\vec{r}$ and $\vec{v}$ at time $t_0 + \Delta t$
- accelerations $\rightarrow$ step $\rightarrow$ accelerations $\rightarrow$ step $\rightarrow \ldots$

Verlet integration method

for the development of the method:

take a virtual step in positive time and in 'negative' time, and apply Taylor expansion up to second order:

$$\begin{aligned} r(t+\Delta t) &= r(t) + \dot{r}(t)\cdot\Delta t + \tfrac{1}{2}\ddot{r}(t)\cdot\Delta t^2 \\ r(t-\Delta t) &= r(t) - \dot{r}(t)\cdot\Delta t + \tfrac{1}{2}\ddot{r}(t)\cdot\Delta t^2 \end{aligned}$$

add both equations – eliminate the velocity $\dot{r}$:

$$\begin{aligned} r(t+\Delta t) &= 2\cdot r(t) - r(t-\Delta t) + \ddot{r}(t)\Delta t^2 \\ \ddot{r}(t) &= a(t) = \frac{F(t)}{m} = -\frac{1}{m}\frac{\partial V}{\partial r}(t) \end{aligned}$$

Verlet integration method

another, equivalent formulation – velocity Verlet

$$\begin{aligned} r(t+\Delta t) &= r(t) + v(t)\cdot\Delta t + \tfrac{1}{2}a(t)\cdot\Delta t^2 \\ v(t+\Delta t) &= v(t) + \tfrac{1}{2}\left(a(t) + a(t+\Delta t)\right)\cdot\Delta t \end{aligned}$$

yet another – Leap-frog

$$\begin{aligned} v(t+\tfrac{1}{2}\Delta t) &= v(t-\tfrac{1}{2}\Delta t) + a(t)\cdot\Delta t \\ r(t+\Delta t) &= r(t) + v(t+\tfrac{1}{2}\Delta t)\cdot\Delta t \end{aligned}$$

both: better numerical precision than Verlet normal form

Δt – crucial parameter

Let us say: we want to obtain a trajectory over a time interval T

– we perform M steps

– we have to evaluate the forces on atoms $M = T/\Delta t$ times

Computational cost of the calculation of forces

– major computational effort

– determines how many steps we can afford to make

Δt – crucial parameter

- we neglect contributions in Δt^3 and higher orders
  → error per step in the order of Δt^3
- keep the step short → make the error small
  but need too many steps to simulate certain time T
- make the step long → cut computational cost
  but increase the error and decrease stability
- compromise needed

Δt – crucial parameter

- fastest motion – hydrogen atoms, period around 10 fs
- rule of thumb – stable integration with $\Delta t \leq \frac{1}{10}$ fastest period
- practically, Δt of 1 fs is used,
  increase to 2 fs possible with a special treatment of bonds
- 1M calculations of forces needes for a trajectory of 1 ns
- large systems – multi-ns simulations routinely, μs possible