Biomolecular Modeling with Molecular Dynamics Introduction

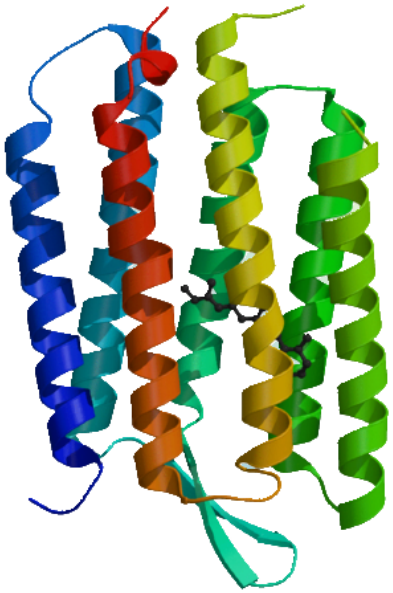
Marcus Elstner and Tomáš Kubař

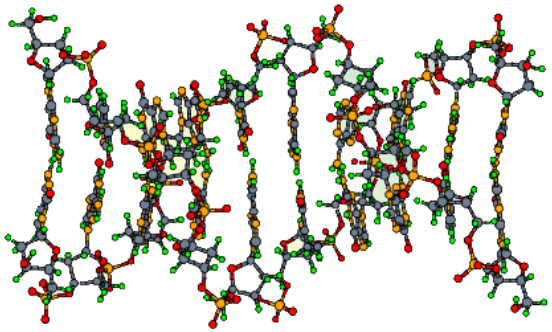
2018, April 20

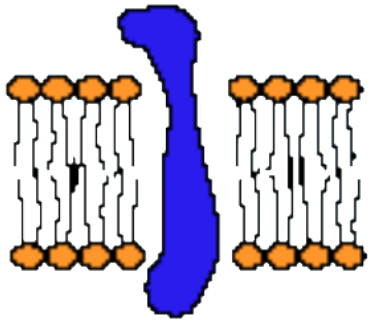
Biomolecular structure

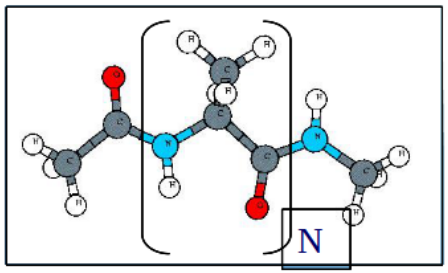
Structural elements of life

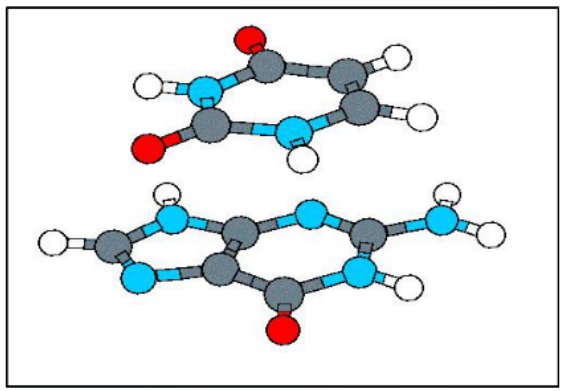
Biomolecules – proteins, nucleic acids, lipids, carbohydrates ...





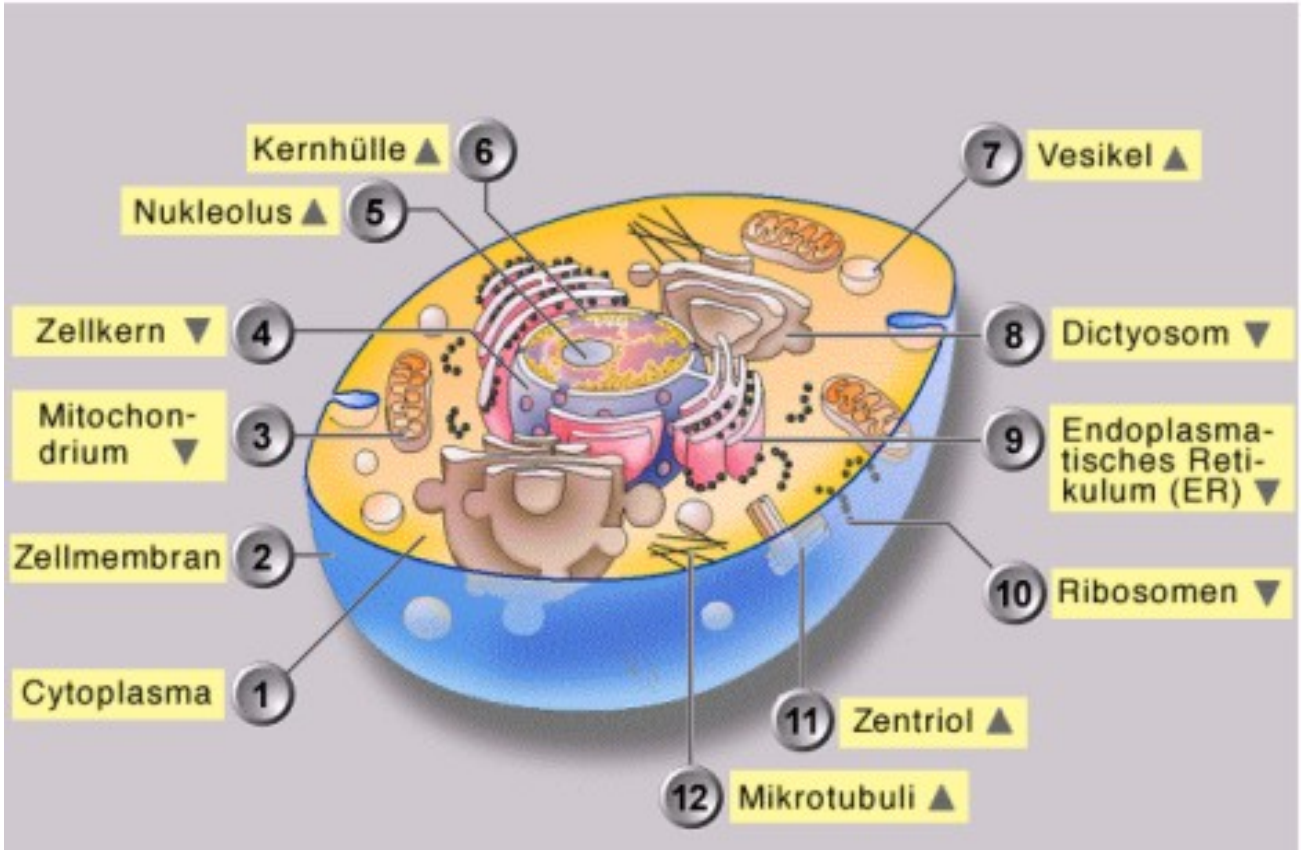






Biomolecular structure

Biomolecules $\rightarrow$ biomolecular complexes $\rightarrow$ aggregates $\rightarrow$ . . . $\rightarrow$ organelles $\rightarrow$ a cell



Biomolecular function

Biophysical processes

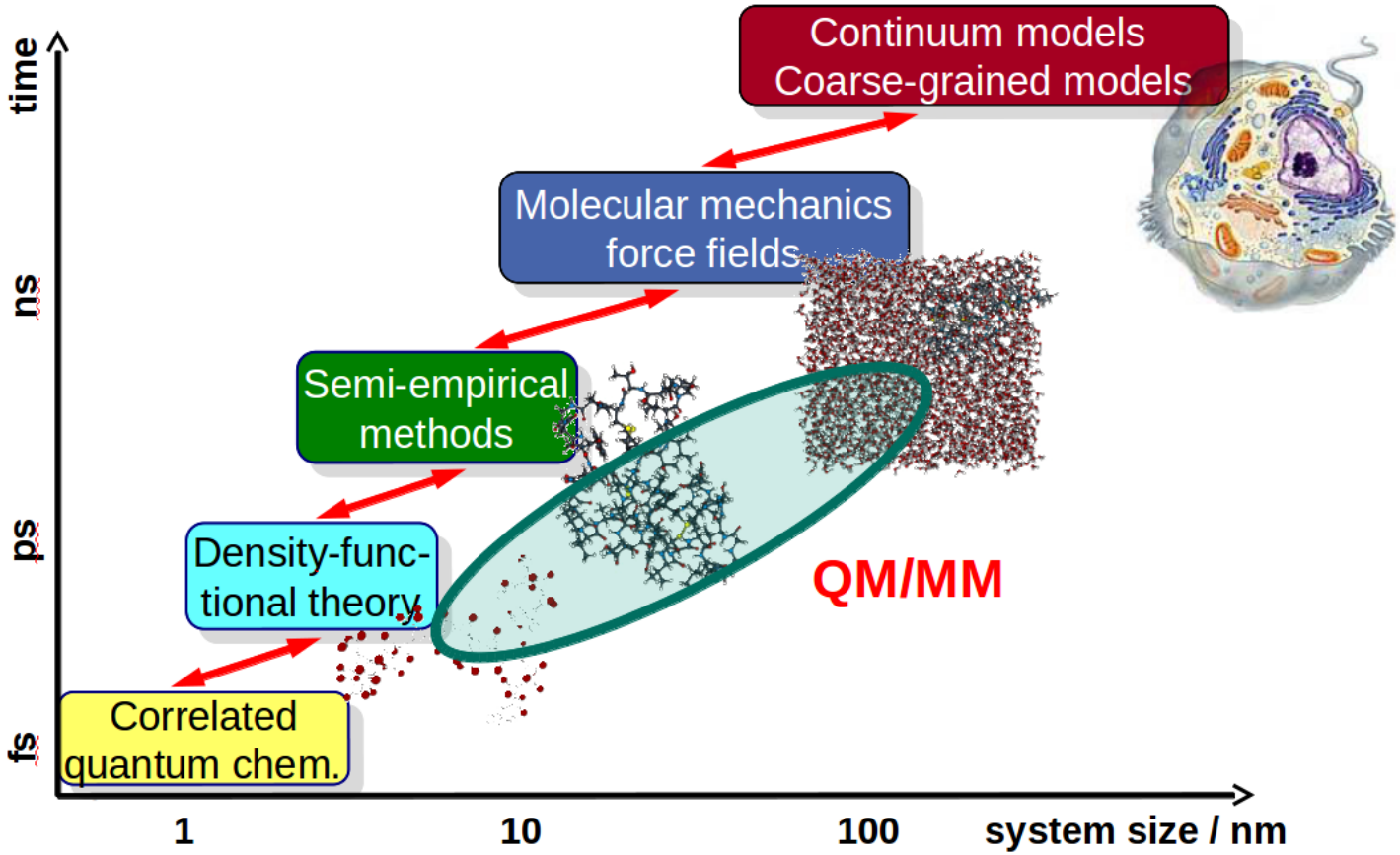
- Bioenergetics – reception, transformation and utilization of energy
- Catalysis – synthesis of substances, metabolism
- Transport – exchange of small molecules, ions up to proteins with the surroundings
- Sensing – detection / recognition / binding in presence of a stimulus

Theoretical / computational biophysics

Molecular modeling

- Focus: understanding on the atomic scale
- The structure and dynamics determine
  the properties and function of biological molecules
- Prediction of 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 MB approach would be too inefficient
  $\rightarrow$ apply more approximative methods

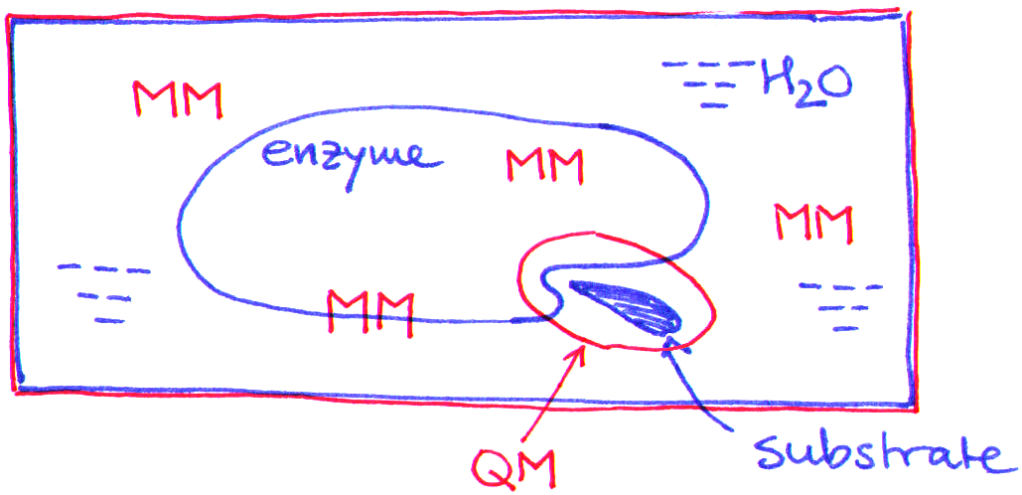
Methods


Continuum models
Coarse-grained models
Molecular mechanics
force fields
Semi-empirical
methods
Density-func-
tional theory
Correlated
quantum chem.
QM/MM
time
ns
ps
fs
1
10
100
system size / nm

Methods

- 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.

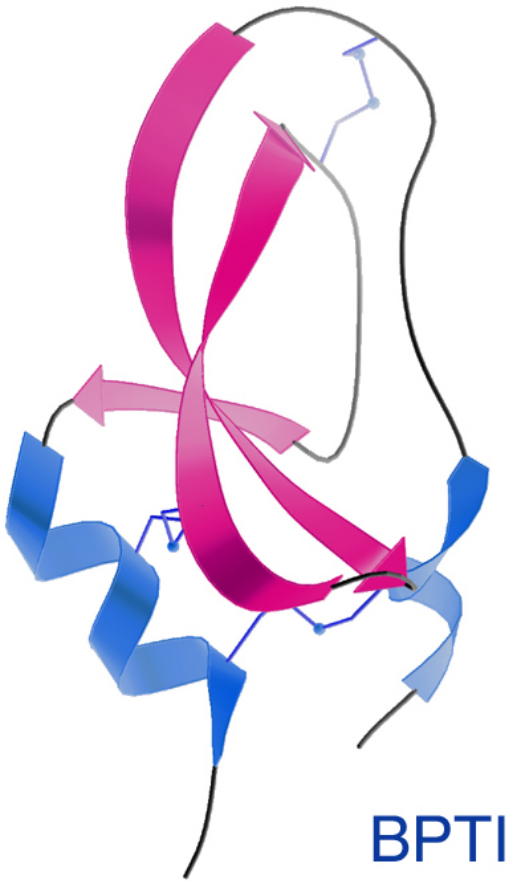


Timeline

- 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

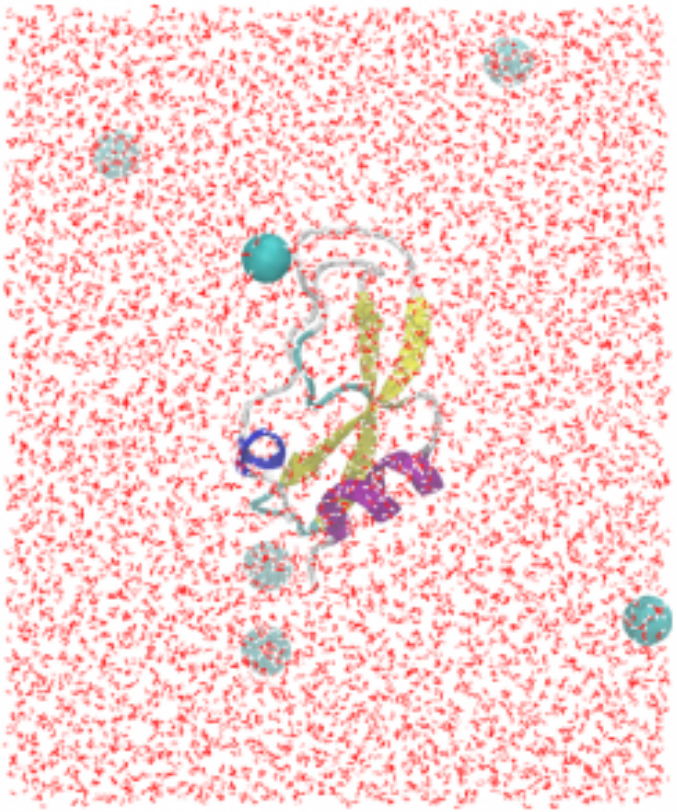
1st simulation of protein dynamics
– BPTI, 58 AAs, in vacuo, 9.2 ps
– McCammon, Gelin & Karplus, Nature 1977
– starting point – crystal structure



Timeline

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

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



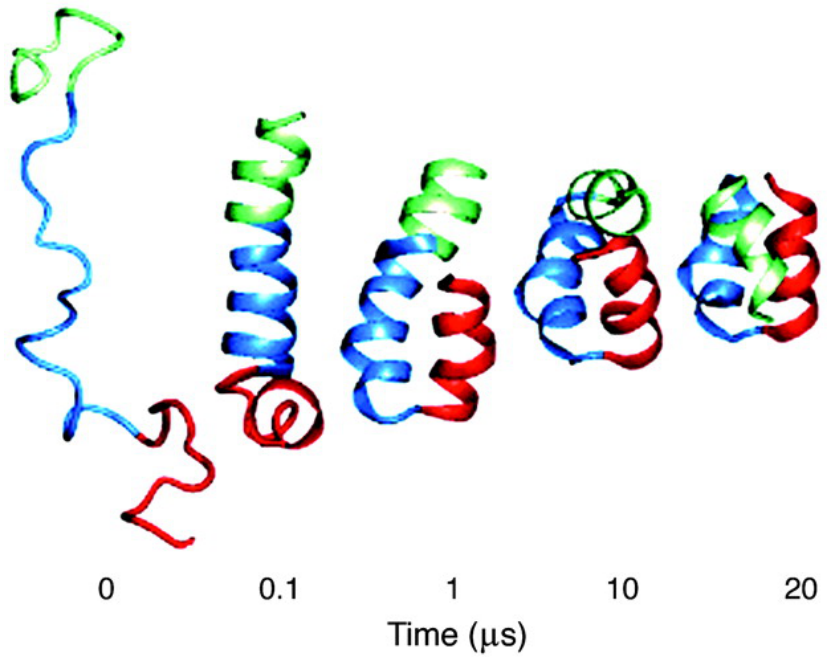
Contact with experimental reality

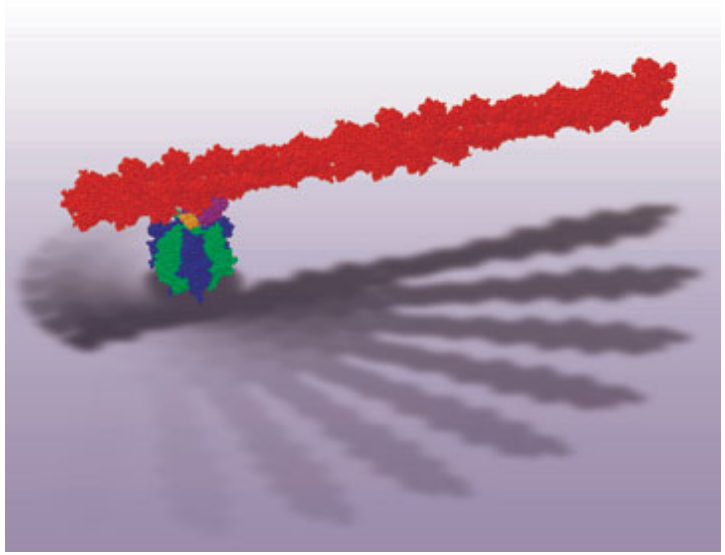
- X-ray and neutron diffraction
- electron cryomiscroscopy (cryo-EM)
- STM/AFM imaging
- electronic / optical spectra
- vibrational / IR spectra
- electronic and nuclear magnetic resonance
- thermodynamic measurements – DSC, ITC

Applications

Structure and dynamics of complex biomolecular systems

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

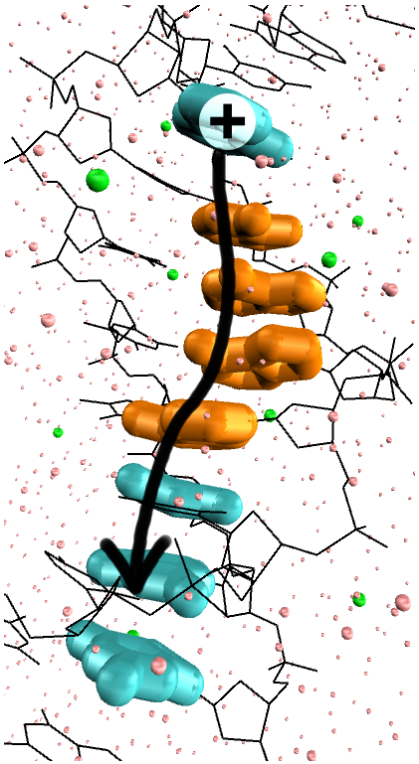


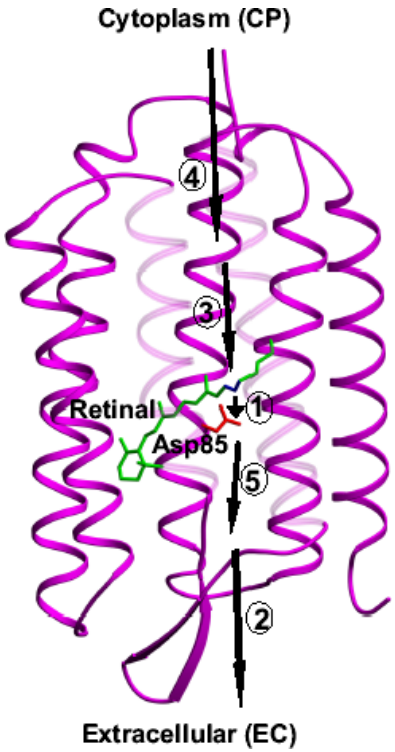


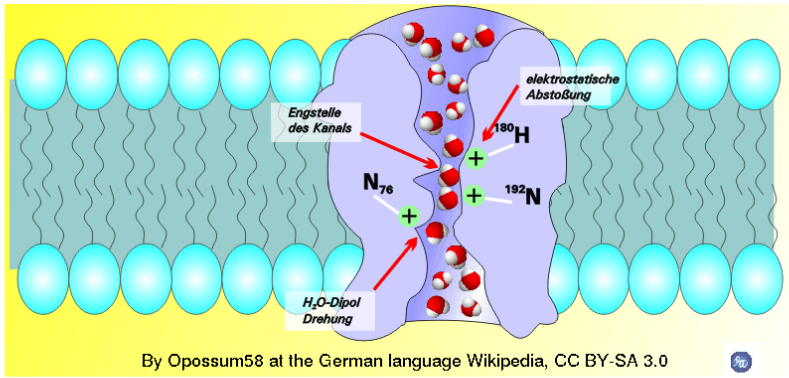
Applications

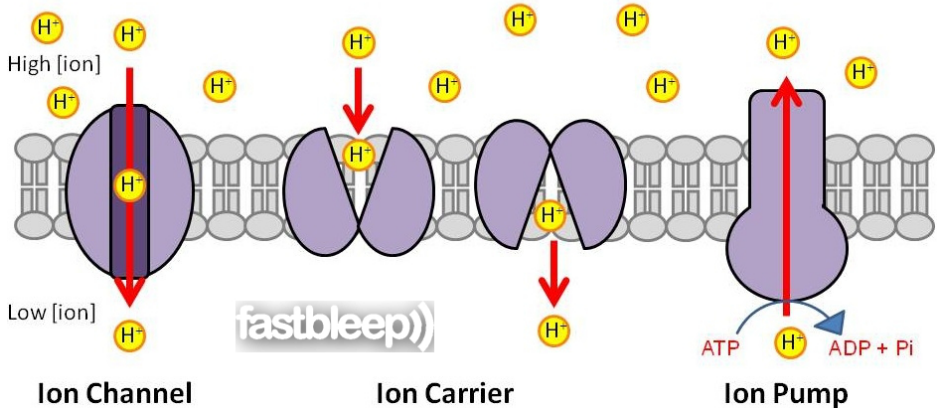
Transport

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





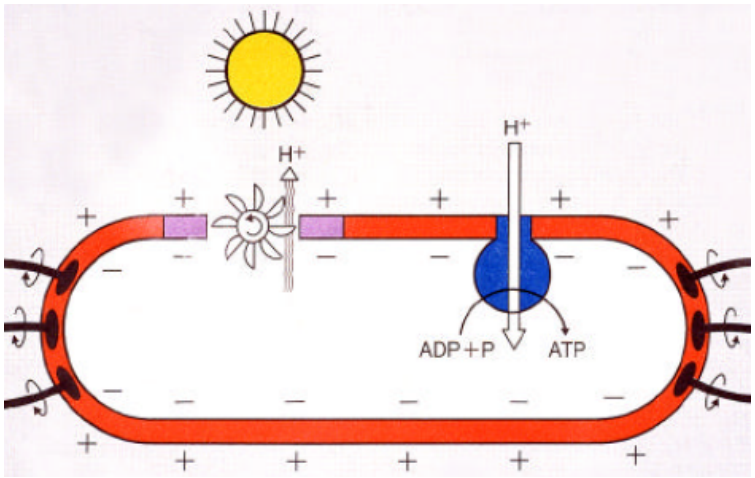


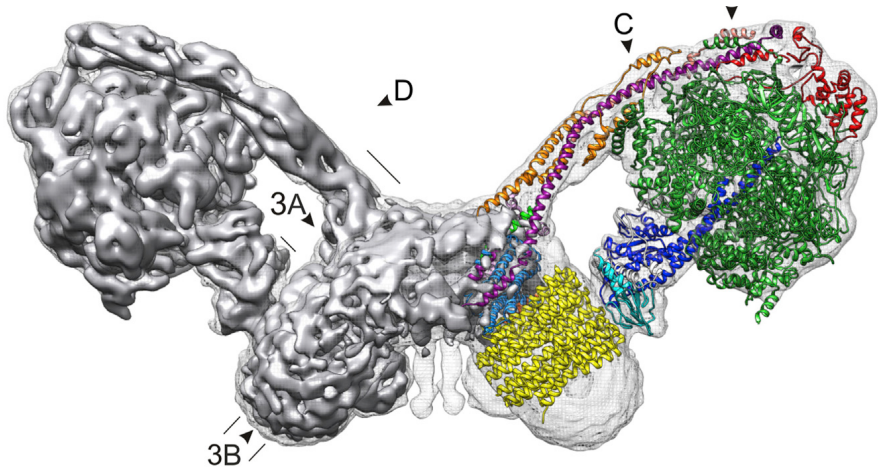


Applications

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

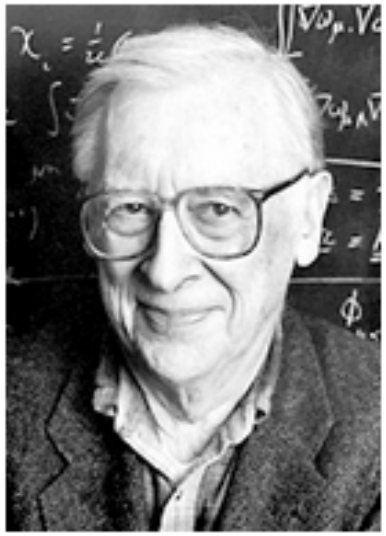
- further development of available methods
- combination of various methods
- optimization of algorithms
  parallelization, $\mathcal{O}(N)$ – linear scaling

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"*.

The Nobel Prize in Chemistry 2013

© Harvard University

Martin Karplus

Photo: © S. Fisch

Michael Levitt

Photo: Wikimedia Commons

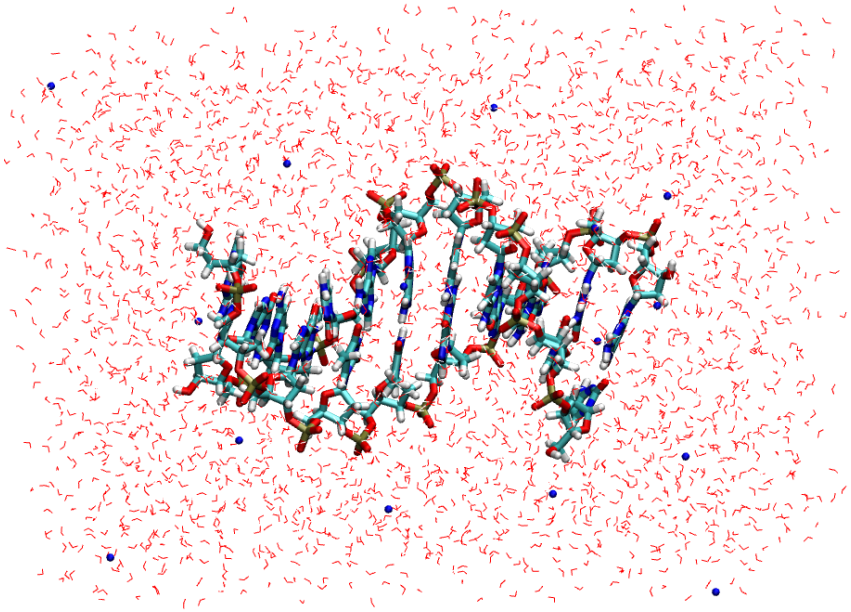
Arieh Warshel

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?

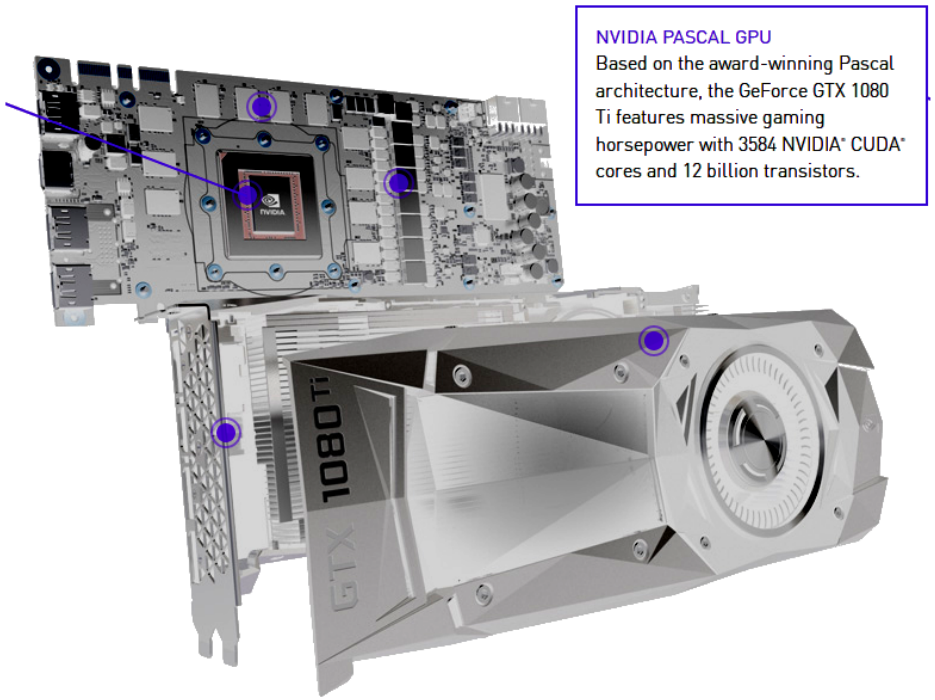
Experiment – the molecule has its genuine properties
Simulation – we need a model to describe the interactions of atoms
– the quality of the model is decisive

Advantage of simulation – structure on atomic level defined

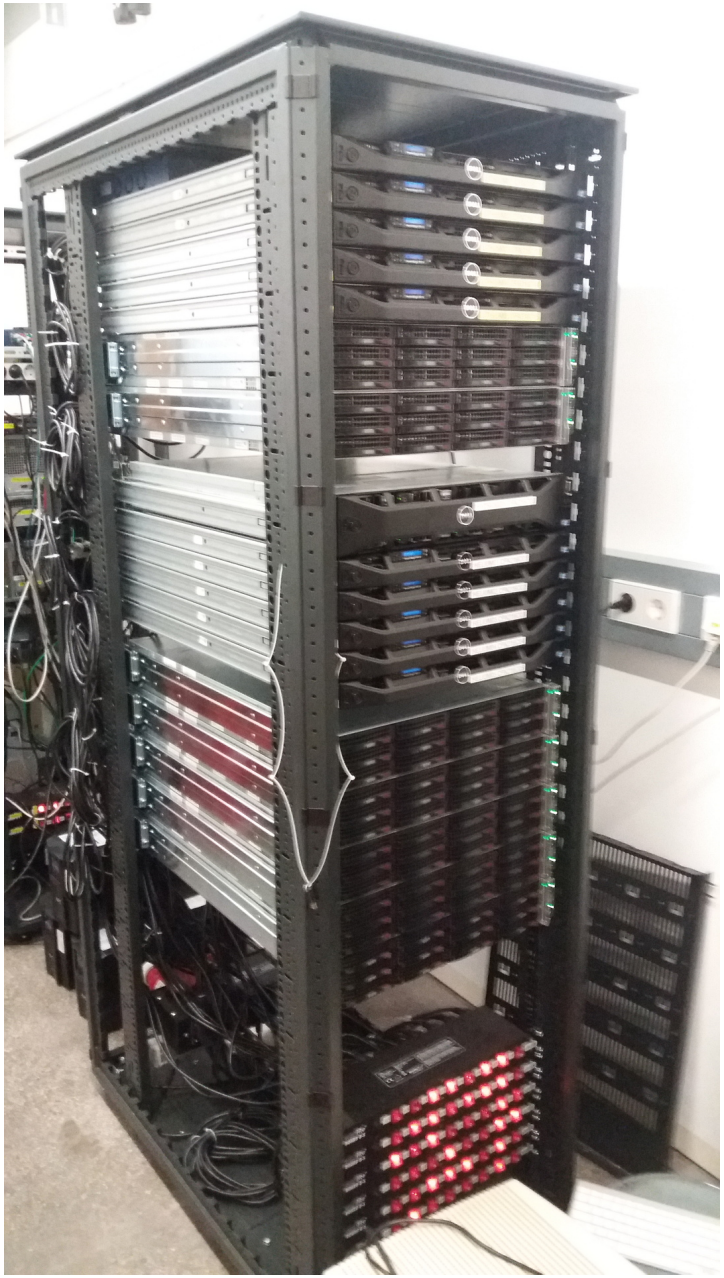
Structure $\rightarrow$ function

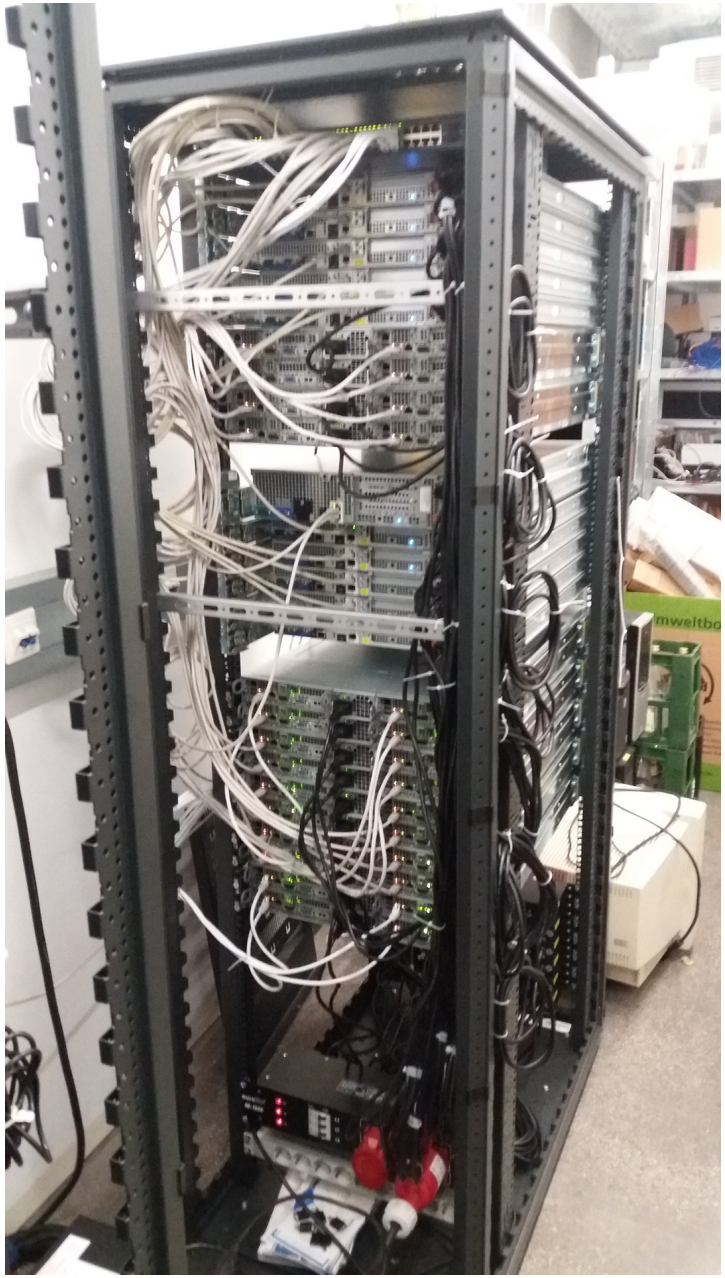
Combination of experiment and simulation – added value

Typical hardware

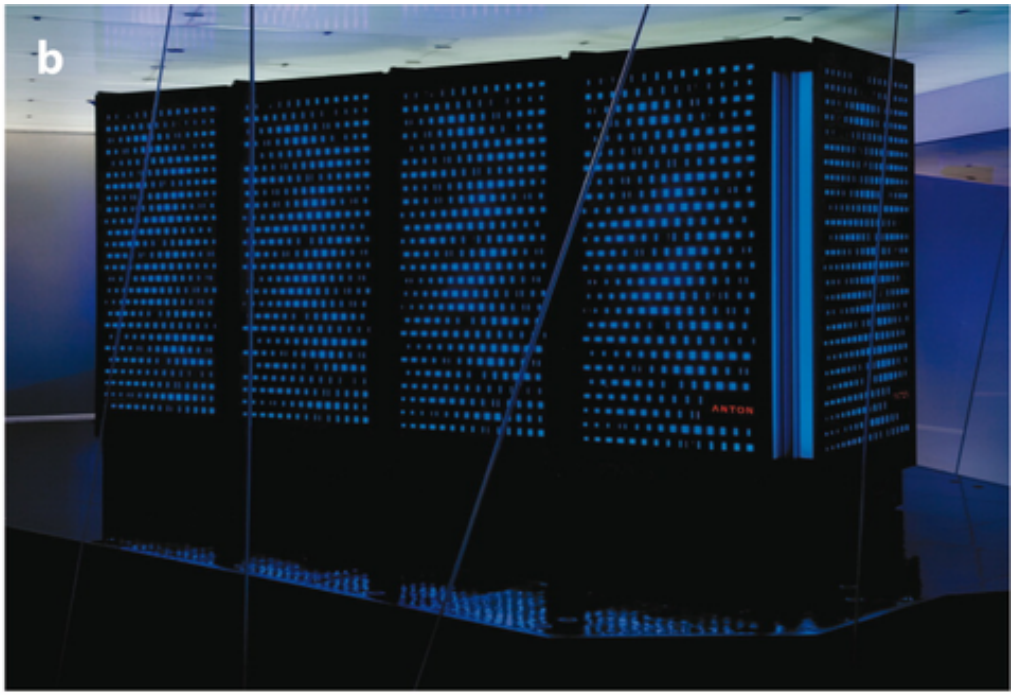


Typical hardware





Cutting-edge hardware



Dror RO, et al. 2012.
Annu. Rev. Biophys. 41:429–52