Molecular Dynamics Simulations

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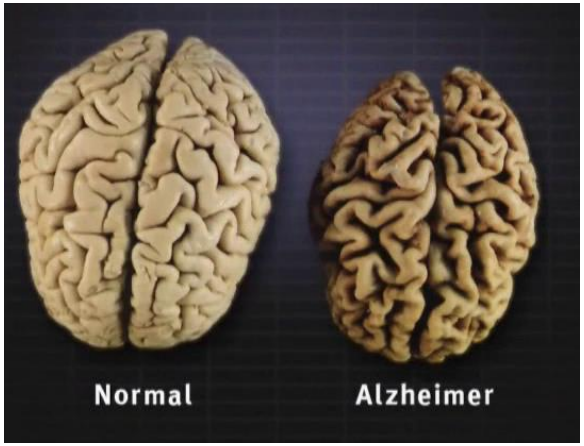
Structure-based drug design identifies polythiophenes as antiprion compounds

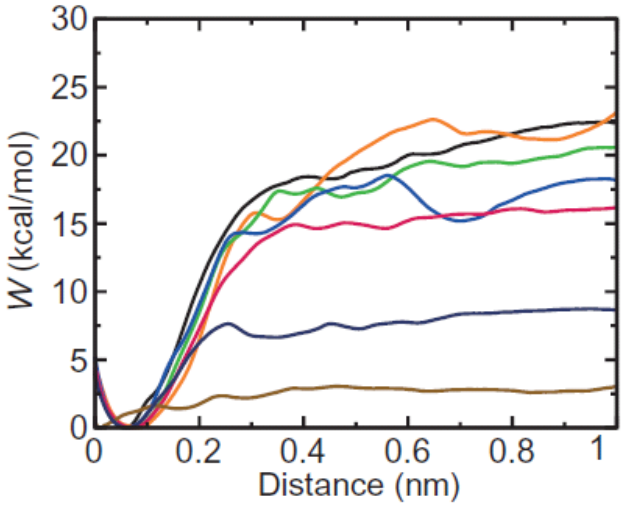
From *in silico* to .... *in vivo*



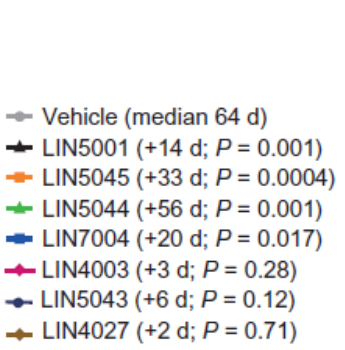
$$\vec{F}_i(t) = m_i \vec{a}_i(t) = m_i \frac{d^2 \vec{x}_i(t)}{dt^2}$$

Structure-based drug design identifies polythiophenes as antiprion compounds

From *in silico* to ……

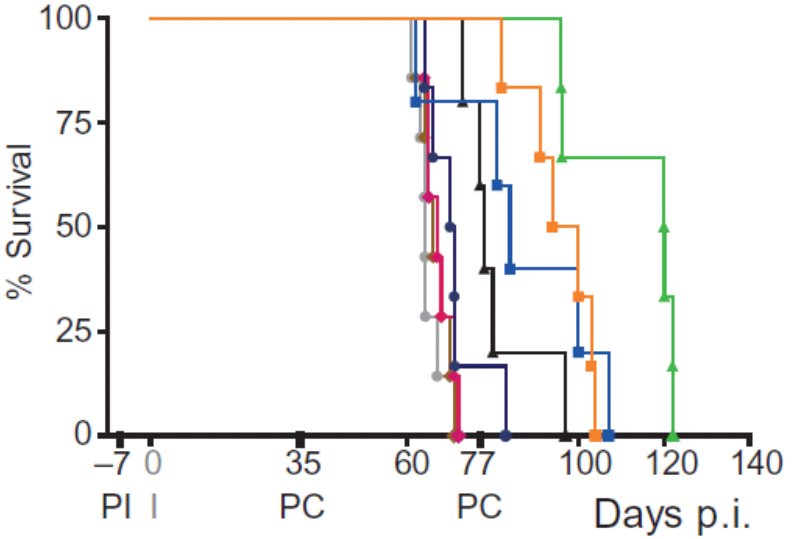


Free energy profile calculated by molecular dynamics (umbrella sampling)

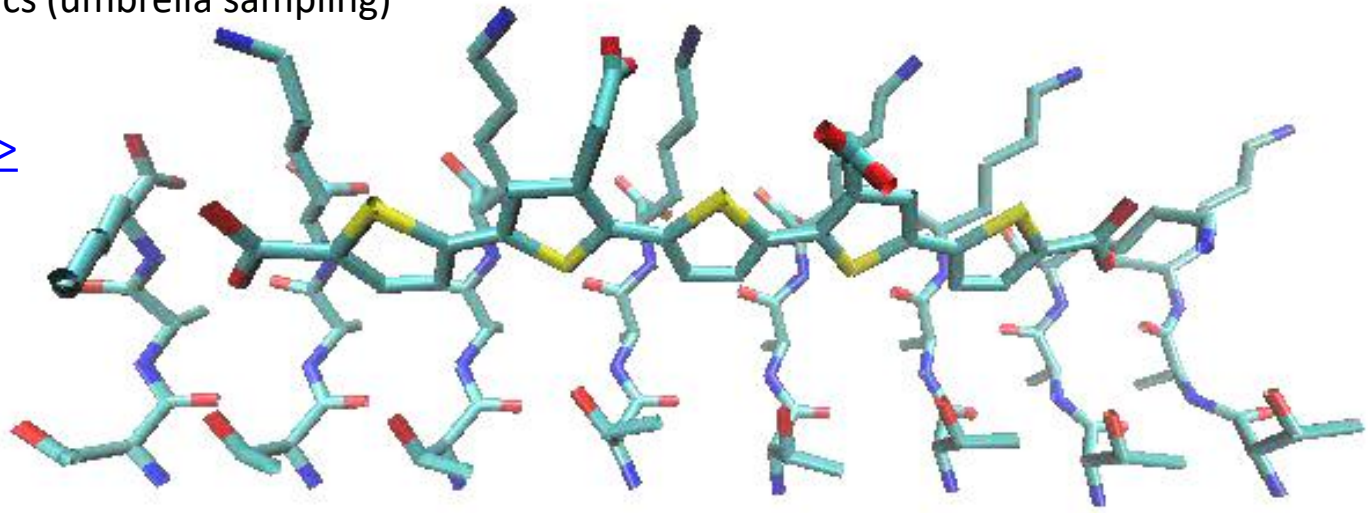


I: prion inoculation
PI: pump implantation
PC: pump change

….. *in vivo*



[Paper <click here>]



2362 Biophysical Journal Volume 108 May 2015 2362–2370

Article

Peptide Binding to a PDZ Domain by Electrostatic Steering via Nonnative Salt Bridges

Paper <click here>

Nicolas Blöchliger,[1] Min Xu,[1] and Amedeo Caflisch[1,*]
[1]Department of Biochemistry, University of Zurich, Zurich, Switzerland

ABSTRACT We have captured the binding of a peptide to a PDZ domain by unbiased molecular dynamics simulations. Analysis of the trajectories reveals on-pathway encounter complex formation, which is driven by electrostatic interactions between negatively charged carboxylate groups in the peptide and positively charged side chains surrounding the binding site. In contrast, the final stereospecific complex, which matches the crystal structure, features completely different interactions, namely the burial of the hydrophobic side chain of the peptide C-terminal residue and backbone hydrogen bonds. The simulations show that nonnative salt bridges stabilize kinetically the encounter complex during binding. Unbinding follows the inverse sequence of events with the same nonnative salt bridges in the encounter complex. Thus, in contrast to protein folding, which is driven by native interactions, the binding of charged peptides can be steered by nonnative interactions, which might be a general mechanism, e.g., in the recognition of histone tails by bromodomains.

$$\vec{F}_i(t) = m_i \vec{a}_i(t) = m_i \frac{d^2 \vec{x}_i(t)}{dt^2}$$

2013 Nobel Prize in Chemistry

Taking the Experiment to Cyberspace

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"*.

▶ Press release

Photo © Harvard University

Martin Karplus

Martin Karplus, U.S. and Austrian citizen. Born 1930 in Vienna, Austria. Ph.D. 1953 from California Institute of Technology, CA, USA. Professeur Conventionné, Université de Strasbourg, France and Theodore William Richards Professor of Chemistry, Emeritus, Harvard University, Cambridge, MA, USA.

Photo: S. Fisch

Michael Levitt

Michael Levitt, U.S., British and Israeli citizen. Born 1947 in Pretoria, South Africa. Ph.D. 1971 from University of Cambridge, UK. Robert W. and Vivian K. Cahill Professor in Cancer Research, Stanford University School of Medicine, Stanford, CA, USA.

▶ Have a look at Michael Levitt's

Photo: Wikimedia Commons

Arieh Warshel

Arieh Warshel, U.S. and Israeli citizen. Born 1940 in Kibbutz Sde-Nahum, Israel. Ph.D. 1969 from Weizmann Institute of Science, Rehovot, Israel. Distinguished Professor, University of Southern California, Los Angeles, CA, USA.

▶ Interviews with Chemistry

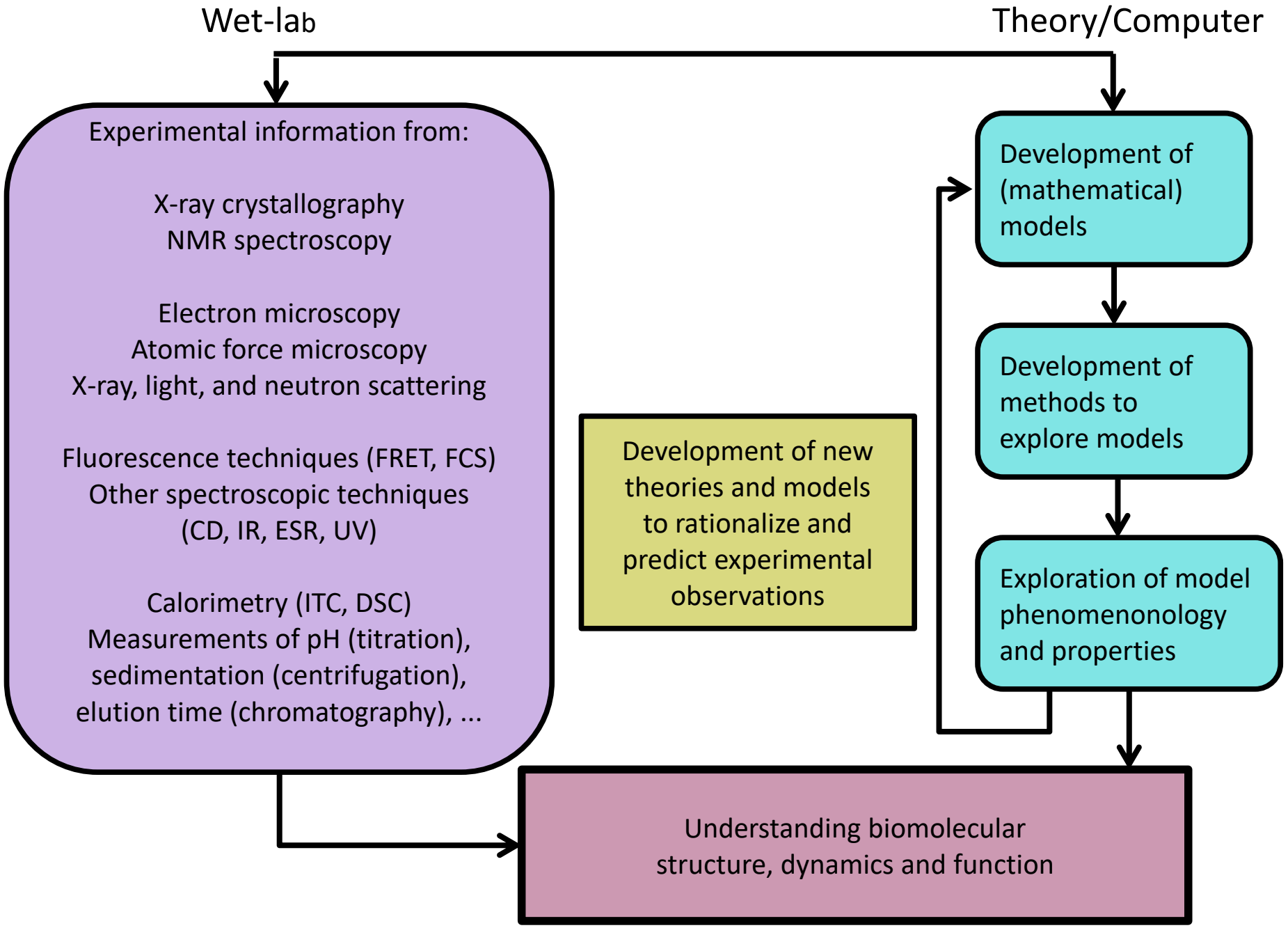
Introduction

To answer these questions (and many others) scientists use appropriate experimental techniques, e.g., single-molecule spectroscopy, NMR spectroscopy , site-directed mutagenesis etc.

In this lecture we will see how we can use a computer to analyze at atomic level of detail the structure, flexibility and function of biological (macro)molecules.

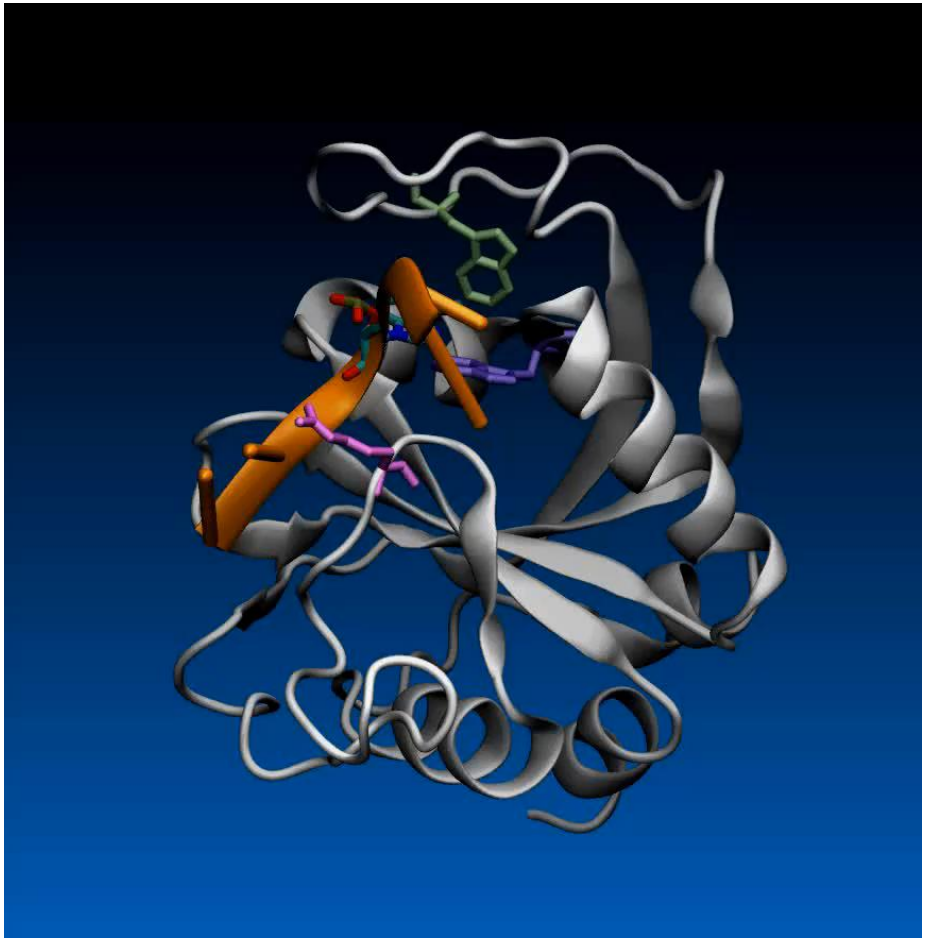
Introduction

- In Molecular Dynamics (MD) simulations the laws of classical physics are used to approximate the interactions and motion of (macro)molecules.
- MD simulations are a multidisciplinary field. The underlying laws and theories stem from mathematics, physics and chemistry; algorithms from various areas of applied mathematics and computer science are implemented in a wide variety of MD software packages.


Wet-lab
Theory/Computer
Experimental information from:
X-ray crystallography
NMR spectroscopy
Electron microscopy
Atomic force microscopy
X-ray, light, and neutron scattering
Fluorescence techniques (FRET, FCS)
Other spectroscopic techniques
(CD, IR, ESR, UV)
Calorimetry (ITC, DSC)
Measurements of pH (titration),
sedimentation (centrifugation),
elution time (chromatography), ...
Development of new
theories and models
to rationalize and
predict experimental
observations
Development of
(mathematical)
models
Development of
methods to
explore models
Exploration of model
phenomenonology
and properties
Understanding biomolecular
structure, dynamics and function

WHAT DO WE NEED?

- Molecule(s) of interest, e.g., protein, DNA, protein/RNA complex, protein/ligand complex, protein in a membrane
- Solvent (water, ions)
- Simulation box



Simulations of protein/RNA complex help to interpret experimental data. For the paper <click here>

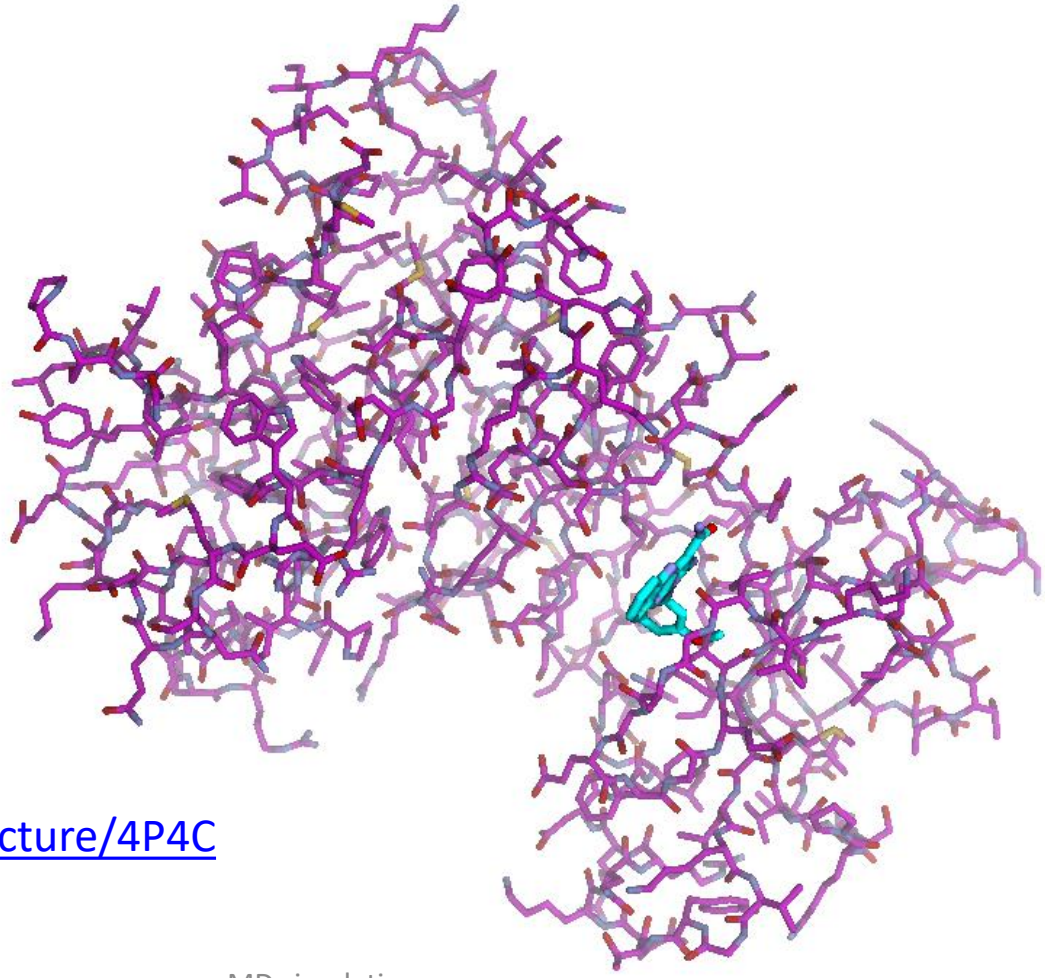
MOLECULE

- Instead of expressing and purifying the protein of interest ….. we supply the computer with the 3D coordinates of the desired protein(s).
- For proteins and small organic compounds the atomic coordinates can be downloaded from the PROTEIN DATA BANK (www.rcsb.org).
- In the following slides the molecule of interest will always be **protein**, keep in mind though that for other types of (macro)molecules everything works analogously.

An experiment on a computer

PROTEIN

An example of a set of atomic coordinates which can be used to run molecular dynamics simulations. Which protein/ligand complex is it?



http://www.rcsb.org/structure/4P4C

PROTEIN

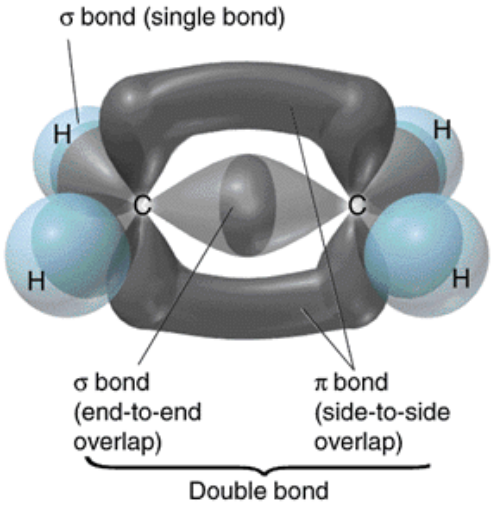
- Furthermore, we need a model to describe the geometry and the physical interactions of the atoms of our protein.
- There are two main approaches:
  - Molecular mechanics, where the atoms are rigid spheres connected by rigid and unbreakable bonds.
  - Quantum mechanics, where also the dynamical evolution of the electrons is taken into account.
- In this course we will discuss the model based on classical mechanics.

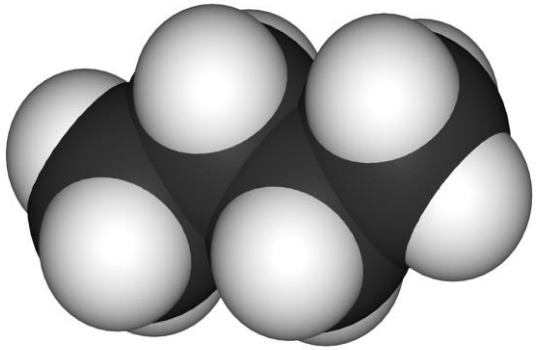
An experiment on a computer

MOLECULE

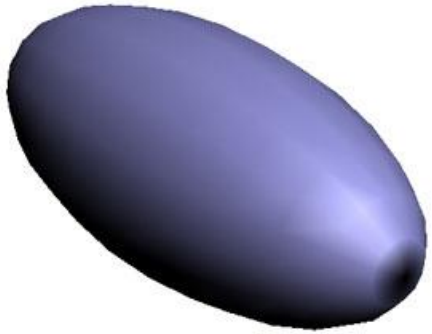
Structural Resolution in the Representation of Biomolecules

Ethene in electronic structure level representation (orbitals)



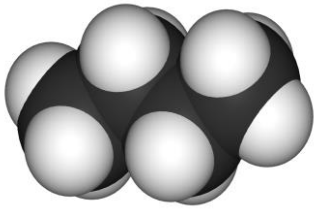


Short linear carbohydrate in coarse-grained representation (single ellipsoidal bead)

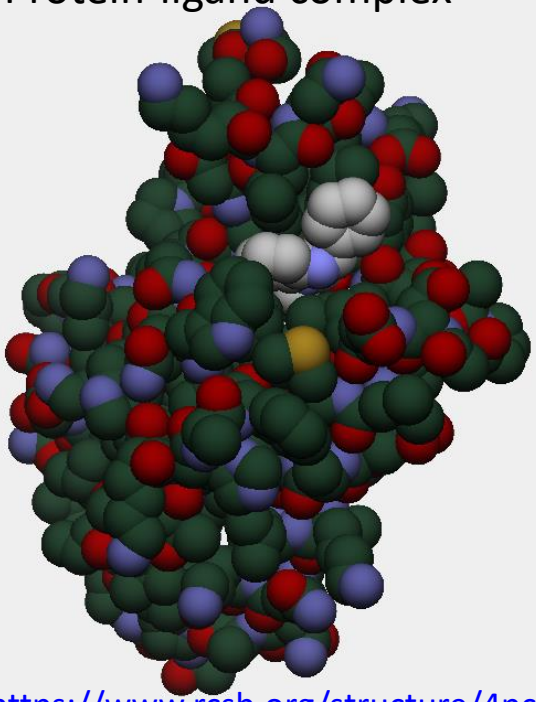


Butane in all-atom molecular mechanics representation (spheres)

Butane



Protein-ligand complex



https://www.rcsb.org/structure/4pci

Molecular Mechanics Representation

- Each atom is represented as a sphere.
- The biomolecular force field is what shapes the collection of spheres into things that look like molecules through so-called bonded interactions.
- The force field also describes the atom-atom interactions of distal parts within a flexible molecule as well as the interactions between molecules through nonbonded interactions.
- Sometimes all-atom representation is simplified to so-called united-atoms (e.g.: a methyl group is a single sphere).
- Electronic structure is in general coarse-grained out and expected to be captured by the force field.

An experiment on a computer

FORCE FIELD

- The force field is an analytical function of the spatial coordinates of the atomic nuclei.
- Several different force fields are commonly available (CHARMM, AMBER, OPLS) . The CHARMM paper contains detailed information

Abstract: CHARMM (Chemistry at HARvard Molecular Mechanics) is a highly versatile and widely used molecular simulation program. It has been developed over the last three decades with a primary focus on molecules of biological interest, including proteins, peptides, lipids, nucleic acids, carbohydrates, and small molecule ligands, as they occur in solution, crystals, and membrane environments. For the study of such systems, the program provides a large suite of computational tools that include numerous conformational and path sampling methods, free energy estimators, molecular minimization, dynamics, and analysis techniques, and model-building capabilities. The CHARMM program is applicable to problems involving a much broader class of many-particle systems. Calculations with CHARMM can be performed using a number of different energy functions and models, from mixed quantum mechanical-molecular mechanical force fields, to all-atom classical potential energy functions with explicit solvent and various boundary conditions, to implicit solvent and membrane models. The program has been ported to numerous platforms in both serial and parallel architectures. This article provides an overview of the program as it exists today with an emphasis on developments since the publication of the original CHARMM article in 1983.

J Comput Chem 30: 1545–1614, 2009

Key words: biomolecular simulation; CHARMM program; molecular mechanics; molecular dynamics; molecular modeling; biophysical computation; energy function

For the CHARMM paper <click here>

FORCE FIELD

- In modern force fields:

$$E = E_{Bonds} + E_{Angles} + E_{Dihedrals} + E_{Nonbonded}$$

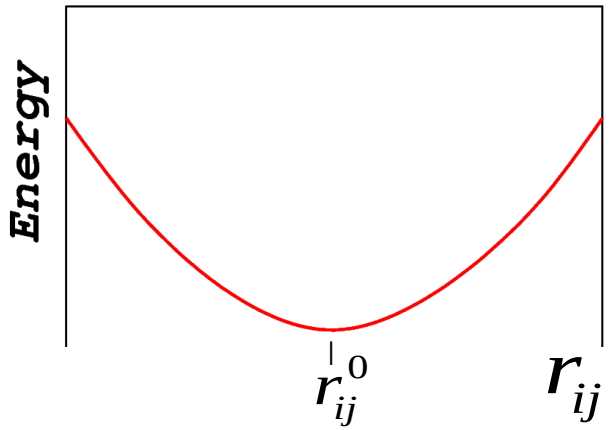
- Let's go through the single terms.

FORCE FIELD

- E_{Bonds} approximates the energy needed to stretch a covalent bond between two atoms by Hooke's law for the potential energy stored in a spring:

$$E_{Bonds}(r_{ij}) = k_{ij}^{B}(r_{ij} - r_{ij}^{0})^2$$

where i and j are two covalently connected atoms and r_{ij} is the distance between them. r_{ij}^{0} is the equilibrium bond length and k_{ij}^{B} is a constant representing the stiffness of the bond.

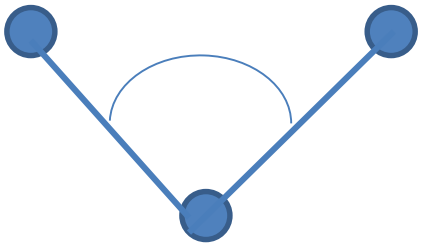


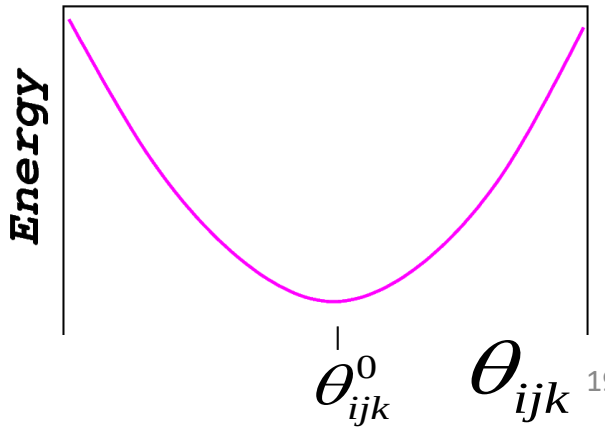
FORCE FIELD

- E_{Angles} models the energy needed to bend the angle formed by two covalent bonds. This term is represented by the following formula:

$$E_{Angles}(\theta_{ijk}) = k_{ijk}^{\Theta}(\theta_{ijk} - \theta_{ijk}^{0})^2$$

where i, j and k are three covalently connected atoms and θ_{ijk} is the angle between them. θ_{ijk}^{0} is the equilibrium angle width and k_{ijk}^{Θ} represents the rigidity of the angle.



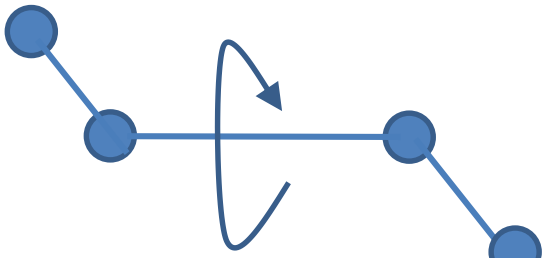


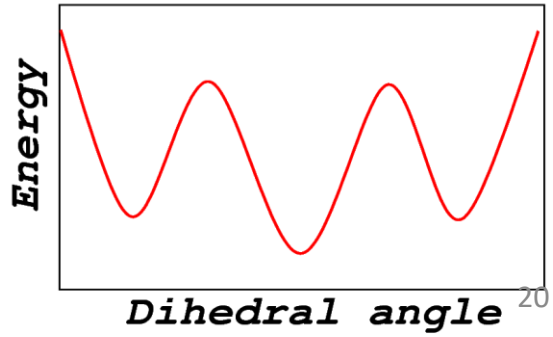
FORCE FIELD

- $E_{Dihedrals}$ models the energy needed to bend the dihedral angle formed by three covalent bonds. This term is represented by the following formula:

$$E_{Dihedrals}(\varphi_{ijkl}) = k_{ijkl}^{\Phi}[1+\cos(n\varphi_{ijkl}-\delta)]$$

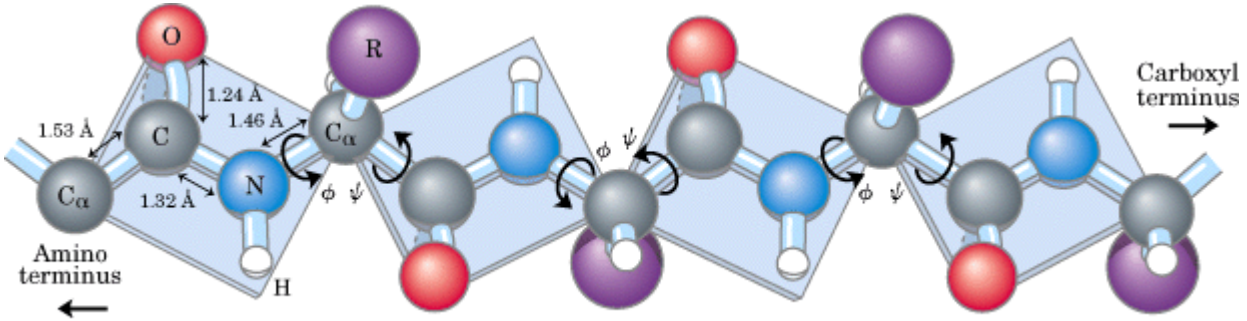
where *i*, *j*, *k* and *l* are four covalently connected atoms and φ_{ijkl} is the dihedral angle between them.





FORCE FIELD

- In $E_{Dihedrals}$, the k_{ijkl}^{Φ} parameter stands for the rigidity of the dihedral, while the parameters n and δ determine the value(s) where the energy has a minimum. For example for the ω dihedral angle of the protein backbone the two minima should always be close to 180° or 0°.



FORCE FIELD

- So far we have treated covalently bonded atoms. What about the interactions between non covalently bonded atoms, i.e., pairs of atoms that are separated by more than two covalent bonds in the same protein or pairs of atoms indifferent proteins?
- In the classical force field representation, these interactions are **pairwise** and modeled with the following formula:

$$E_{Nonbonded} = E_{vdW} + E_{electrostatic}$$

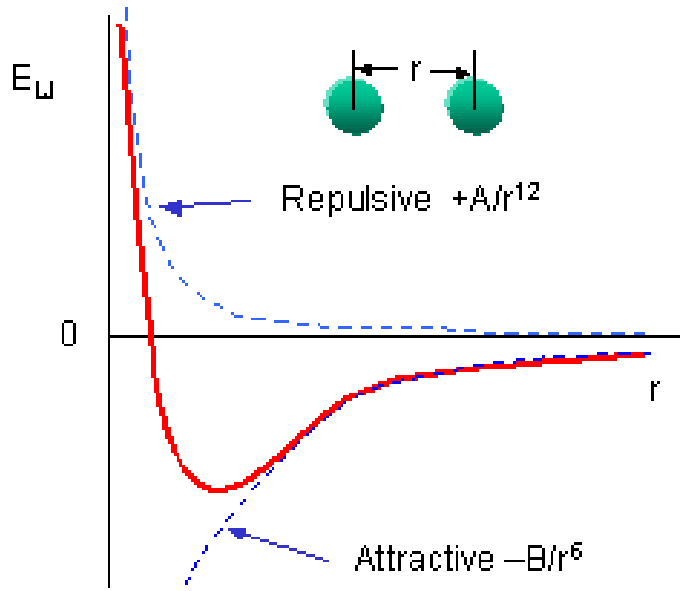
- In principle, $E_{Nonbonded}$ should be calculated for every pair of atoms in the system. In practice, a distance threshold is used, i.e., nonbonding interactions are actually calculated only for atom pairs whose distance is smaller than a threshold (usually about 1.2 nm).

VAN DER WAALS

- E_{vdW} is modeled by the following energy function:

$$E_{vdW}(r_{ij}) = E_{\min_{ij}} \left[\left(\frac{r_{\min}^{ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{r_{\min}^{ij}}{r_{ij}} \right)^{6} \right]$$

- The repulsive term at short distances stems from the energy arising from the Pauli repulsion of overlapping electronic orbitals of different atoms;
- The attractive term at longer distances describes the attractive dispersion interactions.



COULOMBIC

- $E_{electrostatic}$ models the coulombic interactions between partial charges:

$$E_{electrostatic}(r_{ij}) = \frac{q_i q_j}{4\pi\varepsilon r_{ij}}$$

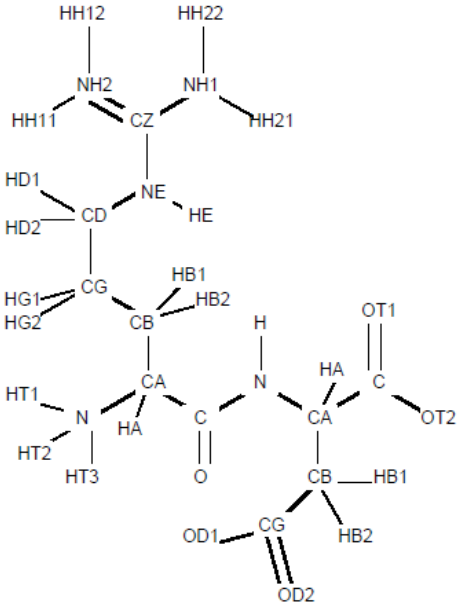
where ε is the dielectric constant of the surrounding medium.

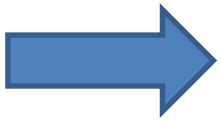
- What are q_i and q_j ?

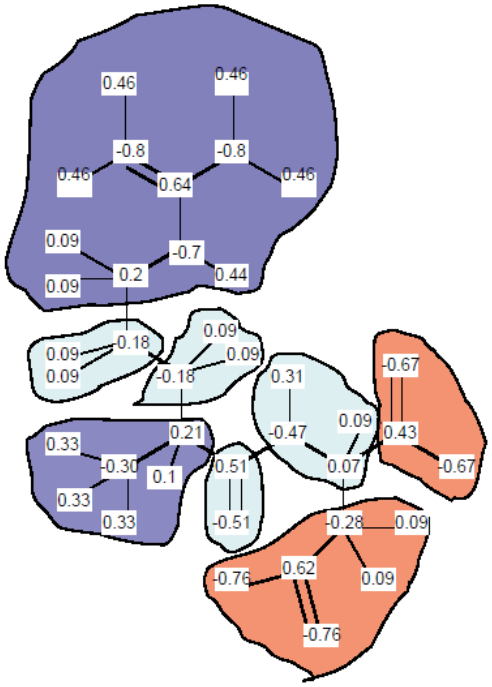
An experiment on a computer

COULOMBIC

- From chemistry we know that the electrons do not evenly distribute along a covalent bond (cfr. electronegativity values).
- In order to reproduce the polarization of a covalent bond, which leads for example to the hydrogen-bonding, a partial charge is assigned to each atom of our protein, depending on the bond partners.







FORCE FIELD

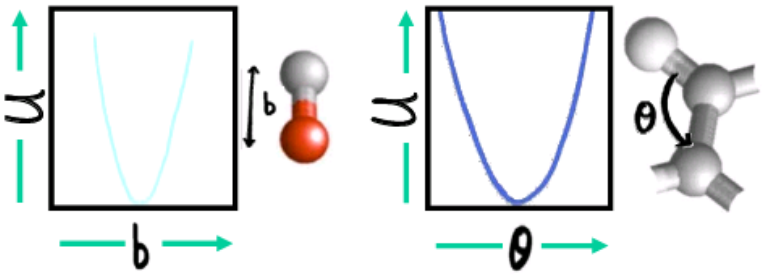
- The parameters of the force field, e.g., the equilibrium values and the spring constants in E_{Bond} or the values of $r_{\min}^{ij}$ and $E_{\min_{ij}}$ in E_{vdW}, have to be calibrated for each desired molecule.
- The parameters are derived form experimental data (e.g., force constants from vibration spectroscopy) and quantum mechanical calculations (e.g., partial charges).

An experiment on a computer

$$E = E_{Bonds} + E_{Angles} + E_{Dihedrals} + E_{Nonbonded}$$

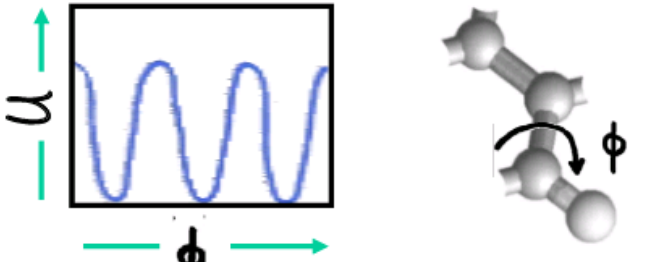
$$E = \sum \tfrac{1}{2} K_b (b - b_0)^2 + \sum \tfrac{1}{2} K_\theta (\theta - \theta_0)^2$$

All Bonds — Hooke 1635 — All Angles



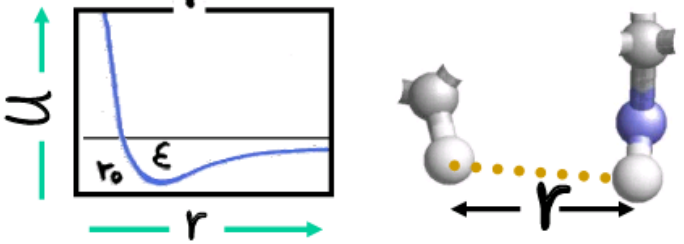
$$+ \sum K_\phi [1 - \cos(n\phi + \delta)]$$

All Torsion Angles — Fourier 1768



$$+ \sum \varepsilon \left[\left(r_0/r\right)^{12} - 2\left(r_0/r\right)^{6} \right]$$

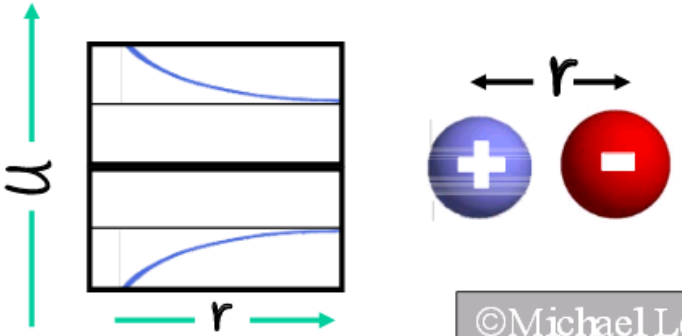
All Nonbonded pairs — Van der Waals 1837



$$+ \sum 332 q_i q_j / r$$

All partial charges — Coulomb 1736

Simple sum over many terms



Cautionary Notes

- "*Everything should be made as simple as it can be but not simpler*" (A. Einstein).
- A force field (model) is never perfect. A model that is not quantitatively fully accurate does not preclude one from formulating hypothesis to guide experiments.
- One of the major sources of systematic error in classical force fields is the lack of polarization. Partial charges are assigned at the beginning of the calculation (minimization or dynamics) and kept constant.
- It is important to compare simulation results to all available experimental data.

SOLVENT

- Most of the experiments in biochemistry are performed in aqueous solvent. Therefore we need to model the interactions of our protein with the aqueous environment.
- There are two different ways to model the protein/solvent interactions:
    - Explicit solvent representation:
      Water molecules and ions are modeled considering all of their nuclei as interaction centers and degrees of freedom.
    - Implicit solvent representation:
      The interactions of the examined protein with the surrounding solvent are described by a mean field framework.

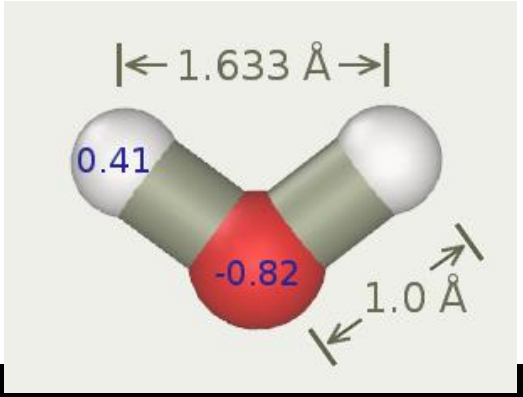
Explicit Water Representation

- The description of the water molecules is based on the same principles aforementioned for the protein.
- Water molecule's geometry is described with spheres connected by rigid and unbreakable bonds.
- The interactions of the water molecules with each other and with the examined protein are given by the following term of the force field:

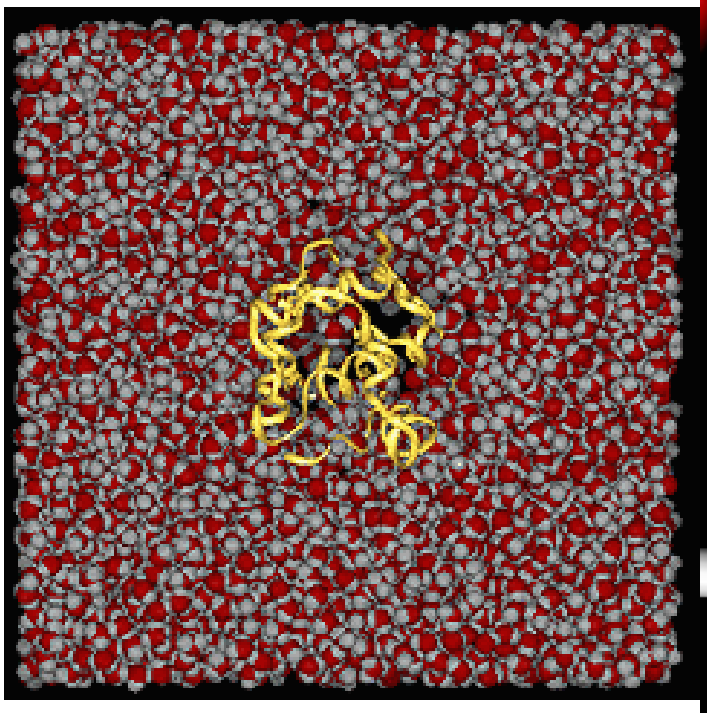
$$E_{Nonbonded} = E_{vdW} + E_{electrostatic}$$

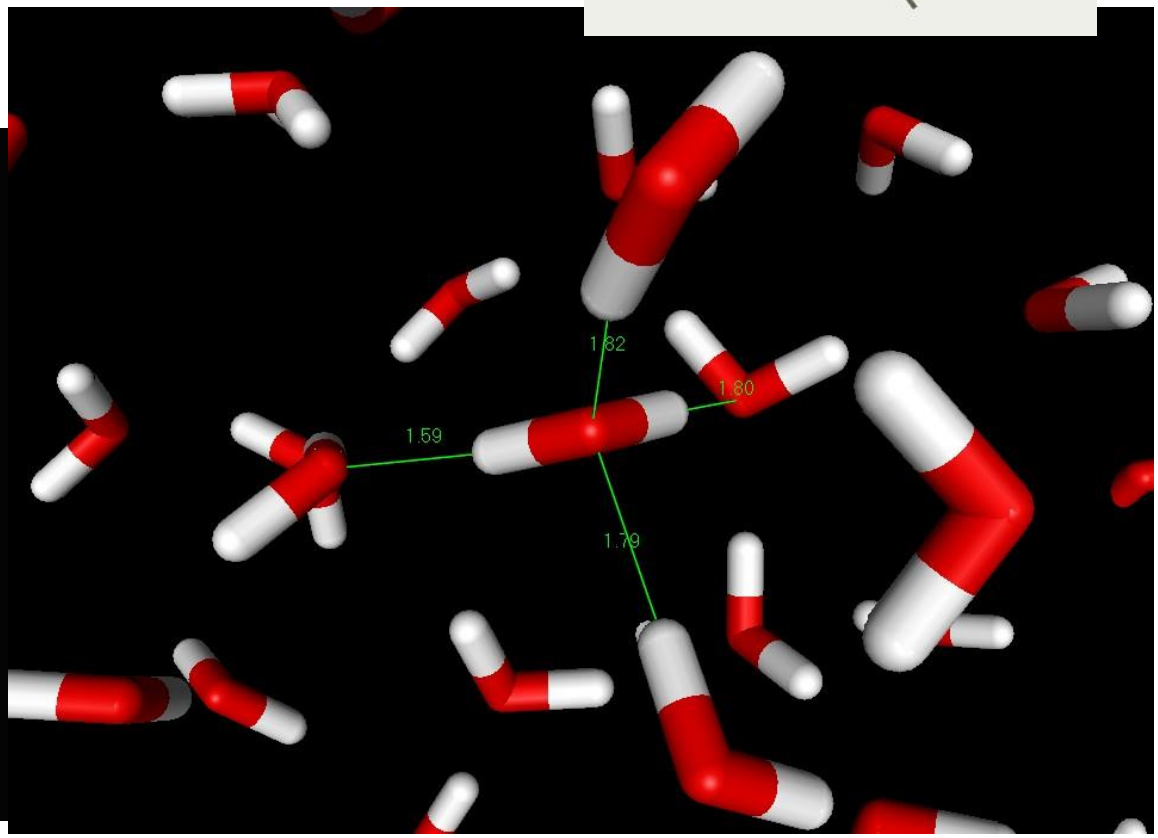
An experiment on a computer

SOLVENT



Explicit Water Representation





An experiment on a computer

SOLVENT

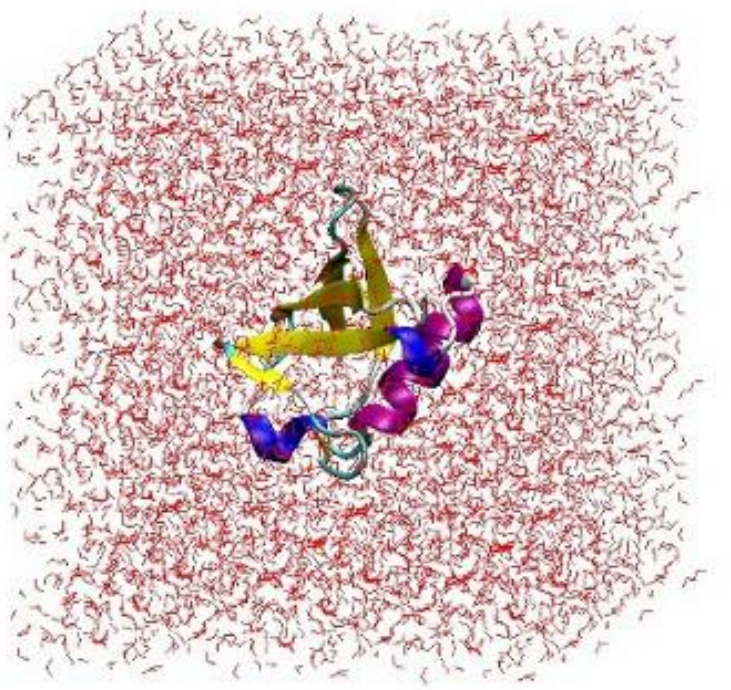
Implicit Water Representation

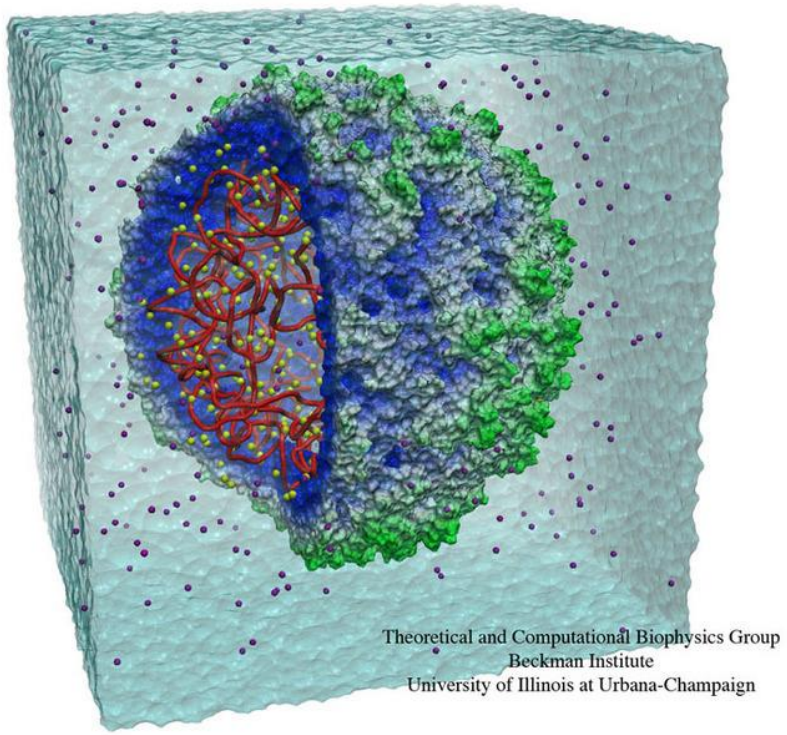
- From the pictures in the previous slide it stands out that usually the protein is much “bigger” than a water molecule.
- Consider a boat on the Lake of Zurich: in order to study the motion of the boat on the water we do not need to consider the interactions of it with all the single water molecules surrounding it.
- Analogously, we can avoid representing each water molecule in our simulation, given that we have a function that models the mean interaction of the aqueous solvent with the examined protein. This is what is meant by Implicit Water Representation

An experiment on a computer

SIMULATION BOX

- We have seen how to model the protein and the solvent, now we have to “place” them somewhere.
- Where in experiments you would use a cuvette, in simulation we use a virtual box of a given geometry (cubic, orthorombic, truncated octahedron, etc.)

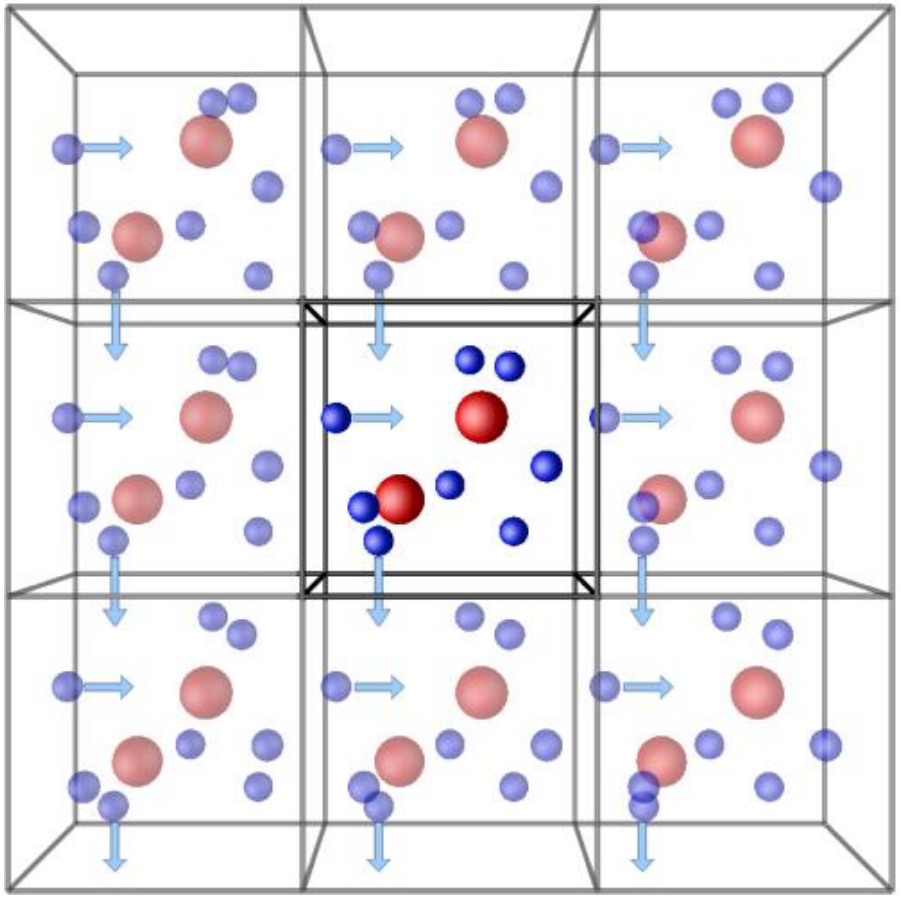




An experiment on a computer

SIMULATION BOX

- To avoid finite-size effects and prevent molecules from leaving the box, Periodic Boundary Conditions (PBC) are usually applied.
- The actual simulation box is replicated so that it is fully surrounded by “image” boxes.
- Special algorithms deal with the interactions between the “real” molecules and their images.



- Once we have our protein properly solvated in a simulation box, we can start our simulation(s).
- In our approximation, the evolution in time of our system will be governed by **Newton**'s equation of motion

$$\vec{F}_i(t) = m_i \vec{a}_i(t) = m_i \frac{d^2 \vec{x}_i(t)}{dt^2}$$

where for atom *i*, $\vec{F}_i(t)$ is the force acting on it, m_i its mass, $\vec{a}_i(t)$ the acceleration, and $\vec{x}_i(t)$ is the position at time *t*.

- At t = 0, the positions of each atom are given from the PDB structure.
- An initial velocity, taken from a Gaussian distribution, is assigned to each atom.
- The force acting on each atom i at a certain time t is the gradient of the energy, i.e., the vector of first derivatives of the force field:

$$-\frac{\partial E(t)}{\partial \vec{x}_i} = \vec{F}_i(t) = m_i \vec{a}_i(t)$$

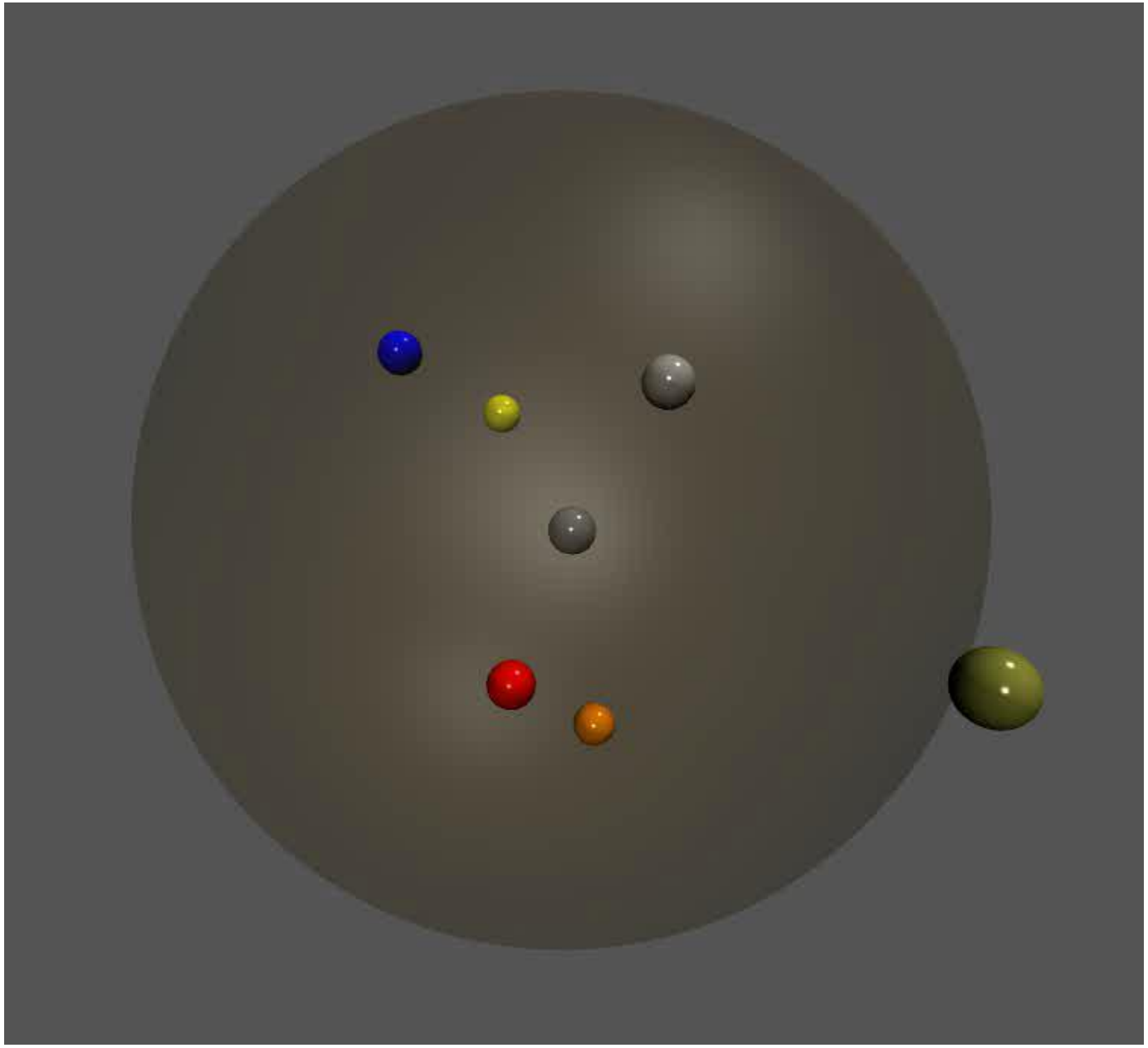
- Knowing the acceleration, the velocity and the position at time *t* for all the atoms, we can calculate the positions at time (*t* + Δ*t*):

$$\vec{x}_i(t+\Delta t) = \vec{x}_i(t) + \vec{v}_i(t)\Delta t + \frac{1}{2}\vec{a}_i(t)\Delta t^2$$

while the velocities are given by the equation:

$$\vec{v}_i(t+\Delta t) = \vec{v}_i(t) + \vec{a}_i(t)\Delta t$$

Usually, the time step is chosen to be Δ*t* = 2 fs.



Changing the ensemble

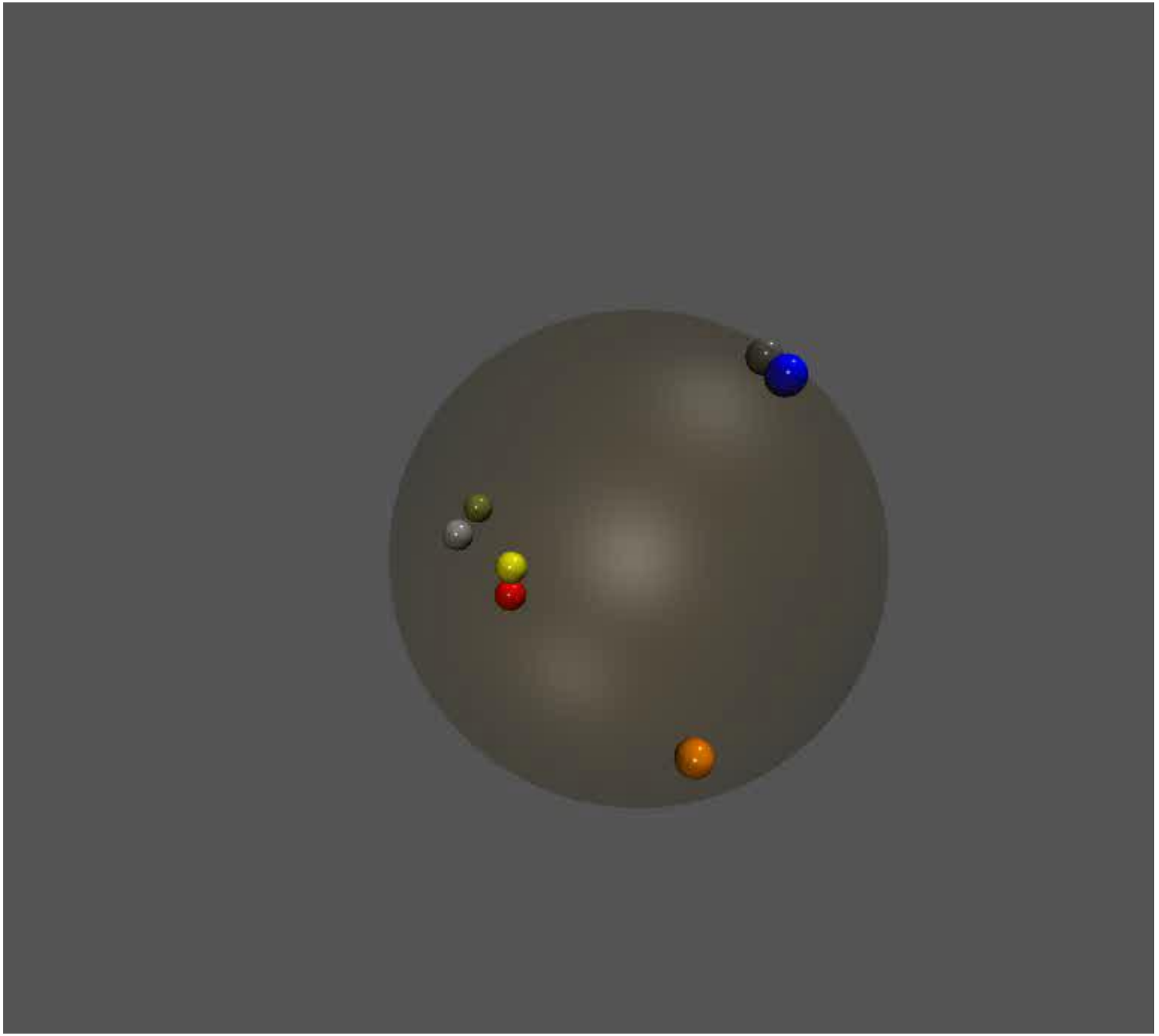
- The system we have put together has constant number of particles, constant volume and constant energy. The simulation samples then what in statistical mechanics is called a microcanonical ensemble (NVE).
- Often, it will be necessary to match the conditions of a simulation to that of an experiment or to something that is physically more suitable to the problem.
- **NVE → NVT**: Add a thermostat; in essence an auxiliary process that modifies particle velocities (common: Berendsen, Nose-Hoover, Andersen, Bussi-Parrinello)
- **NVE → NPT**: Add a manostat and a thermostat; in essence, a manostat is an auxiliary process that rescales the volume of the system in response to the difference between internal and external pressure (common: Berendsen, Parrinello-Rahman, Langevin piston)
- **NVE → μ_mVT**: Add a thermostat and a chemostat (particle bath); in essence, a chemostat is a reservoir of "bath" particles that allows the concentration of particles in the explicitly represented volume to fluctuate (remember aquaporins).

Langevin's Equation of Motion

- Alternatevely to Newton's equation, **Langevin**'s equation of motion can be used to reproduce the time evolution of our system. For each (classical) atom, we have a modified differential equation:

$$m_i\vec{a_i}(t) = \vec{F_i}(t) + \sqrt{2\gamma_i k_B T m_i}\,\vec{R}(t) - m_i\gamma_i\vec{v_i}(t)$$

- Newton's equation is "extended" by two terms: a random force relying on a stationary and normalized random (Wiener) process, and a friction term that is velocity-dependent.
- The rate of kinetic energy dissipation (friction) and the magnitude of the random force resulting from equilibrium fluctuations are fundamentally linked because they are caused by the same underlying process: assumed collisions with "bath" particles.
- Because the system is coupled explicitly to an (assumed) bath, energy is not conserved and one naturally obtains a canonical ensemble (**NVT**) when using Langevin's equations of motion to propagate a dynamical system.

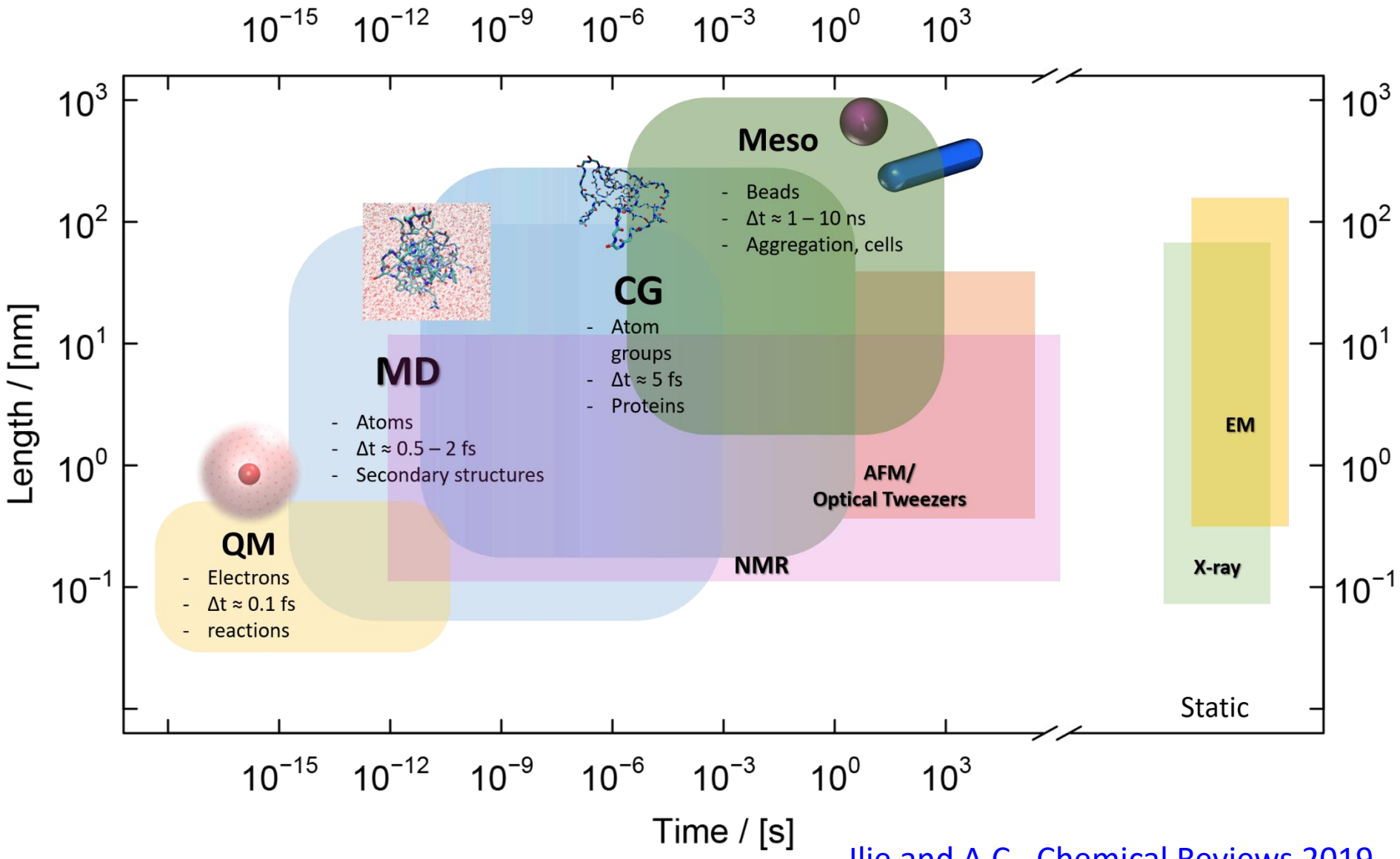


- Since modelling all atoms explicitly is computationally expensive, representations with lower resolution (coarse graining) have been developed to simulate processes that take place on longer time scales.
- Coarse graining can reduce the statistical error (i.e., can reach longer time scales because of less degrees of freedom and longer time step) but increases the systematic error.

System	Time scale
Ligand unbinding of a weak binder from the binding pocket on a protein	~ 10 ns
Structural rearrangements of a domain of ~ 100 a.a. in the native state in explicit water	~ns to µs
Reversible folding of a miniprotein ~ 20 a.a. in implicit water	~µs
Aggregation of a model peptide in coarse-grained representation	~10 µs

An experiment on a computer

DYNAMICS



Ilie and A.C., Chemical Reviews 2019

ANALYSIS

- The simulation packages produce an output file called *trajectory*, that contains the coordinates of all the atoms at specific time intervals, e.g. every 2-20 ps depending on the type of simulation and on the studied system.
- From the trajectory, we can calculate time evolution or averages over time of quantities like radius of gyration, internal energy, secondary structure propensity, interaction energy, root mean square deviation (RMSD) of the protein(s).

ANALYSIS

Simulations of PDZ3 of PSD-95/SAP90 in native state:

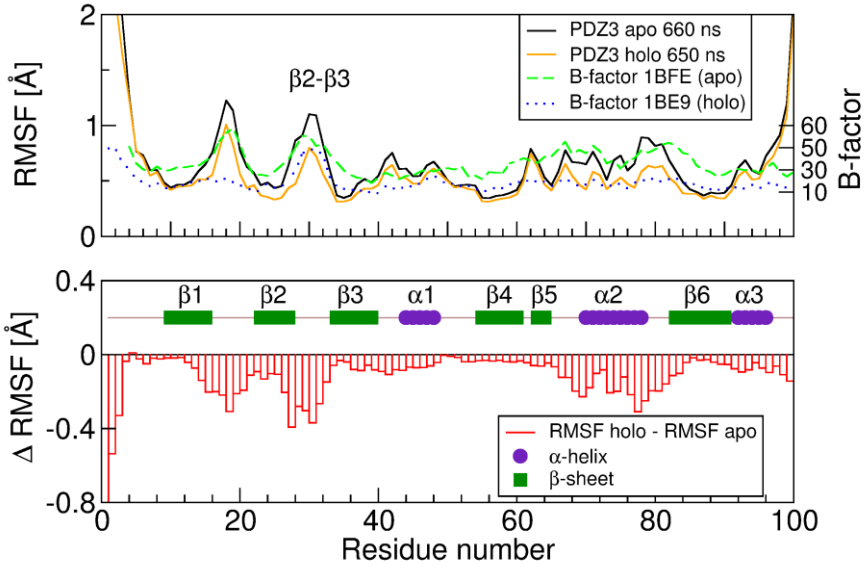
Over the complete MD trajectory we can compute the root mean square fluctuations (RMSF) for specific atoms.

The formula for the RMSF of an atom i is the following :

$$RMSF = \sqrt{\frac{1}{T}\sum_{t_j=1}^{T}(x_i(t_j) - \tilde{x}_i)^2}$$

where T is the time over which one wants to average, $x_i(t_j)$ is the position of atom *i* at time t_j and $\tilde{x}_i$ is its reference position (usually its average position over a time interval of 1 ns to 5 ns).

The plot of RMSF of the Cα's of each residue of PDZ3 shows that loop regions fluctuate much more than secondary structure elements. The profile of RMSF along the sequence can be compared with the crystallographic B-factors.



From: [Steiner & Caflisch, Proteins. 80(11): 2562-72 (2012)]

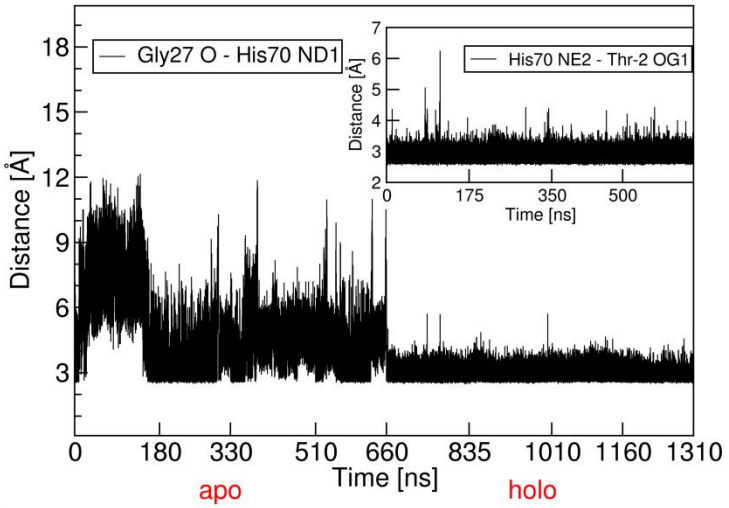
An experiment on a computer

ANALYSIS

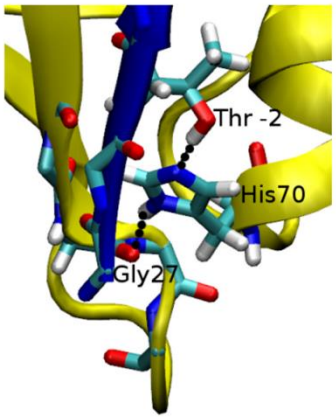
Since the MD trajectory allow us to follow the position of every single atom over time, we can also monitor individual interactions over time.

The distance of the donor and acceptor atoms involved in a hydrogen bond reports on the stability of that interaction
(for the time series in panel **A**, note that the optimal hydrogen bond distance is around 3 Å).

A



B

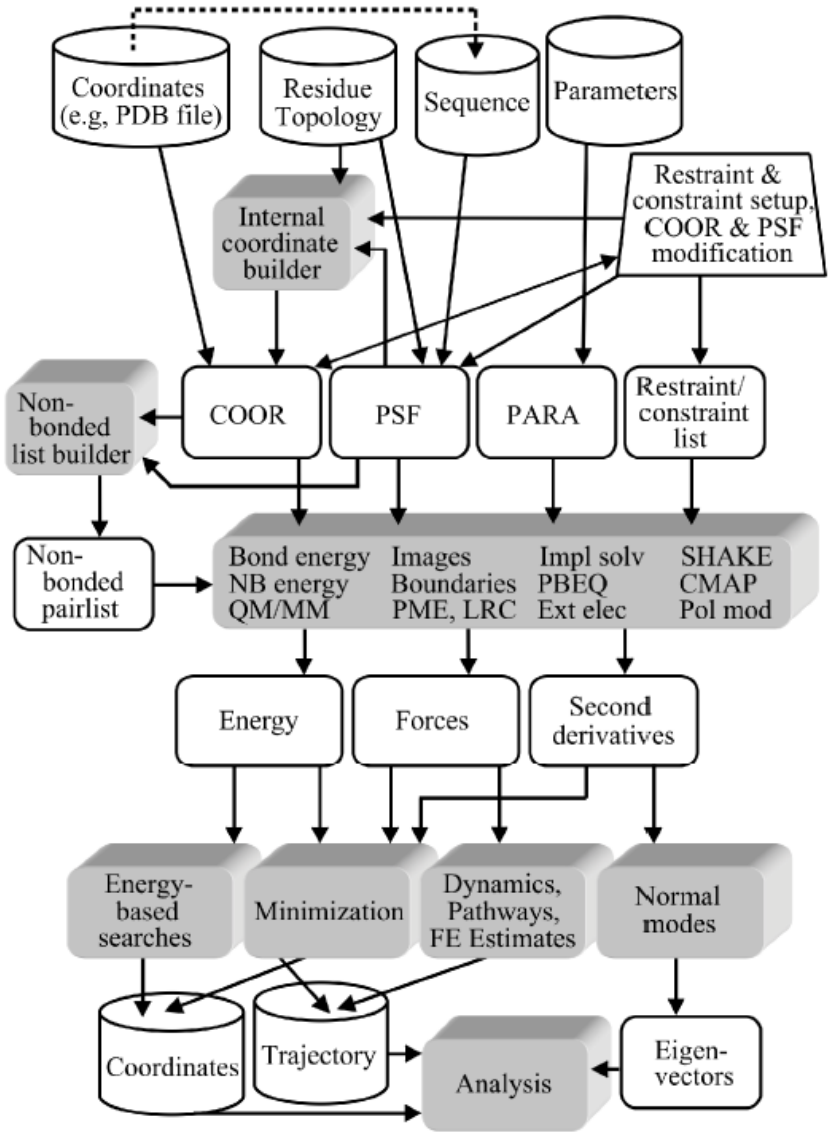


From: [Steiner & Caflisch, Proteins. 80(11): 2562-72 (2012)]

An experiment on a computer

Software Packages for MD

SOFTWARE



From: Brooks *et al.*, J. Comp. Chem. **30**, 1545-1614 (**2009**)

[For the CHARMM paper <click here>]

Input files (force field, molecular topologies, coordinates)

Software setup of structural representation

Setup and use of force field

Implementation of sampling algorithms

Simulation data and their analysis

An experiment on a computer

SOFTWARE

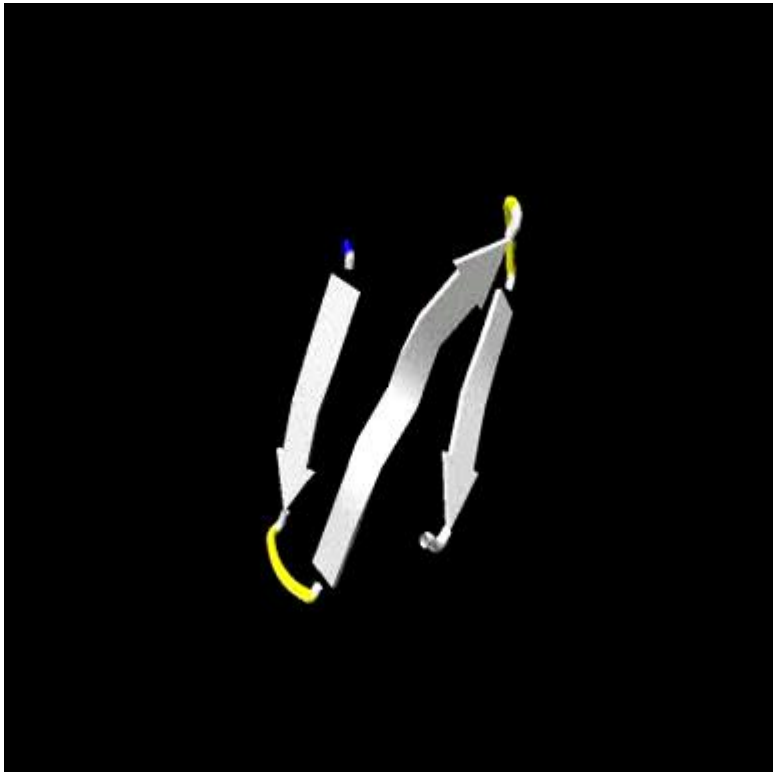
Dynamics Software Packages

- CHARMM (co-development of ~20 research groups around the world over past few decades, originated at Harvard under Martin Karplus, 2013 Nobel laureate in Chemistry)
  - Developed over the last three decades with a primary focus on molecules of biological interest, including proteins, peptides, lipids, nucleic acids, carbohydrates and small molecule ligands.
  - Solution, crystals, and membrane environments.
  - Energy minimization, normal mode analysis, molecular dynamics, Monte Carlo sampling, umbrella sampling, free energy perturbation, large set of analysis techniques, and model-building capabilities.
  - Different energy functions and models including classical potential energy (force field), mixed quantum mechanical-molecular mechanical approach, and interface to ab initio quantum chemistry.
  - Explicit solvent and various boundary conditions, several implicit solvent models (surface based, generalized Born, finite-difference Poisson).
- AMBER (originated at UCSF)
- GROMACS (originated at University of Groningen)
- NAMD, DESMOND, and many more ...

An experiment on a computer

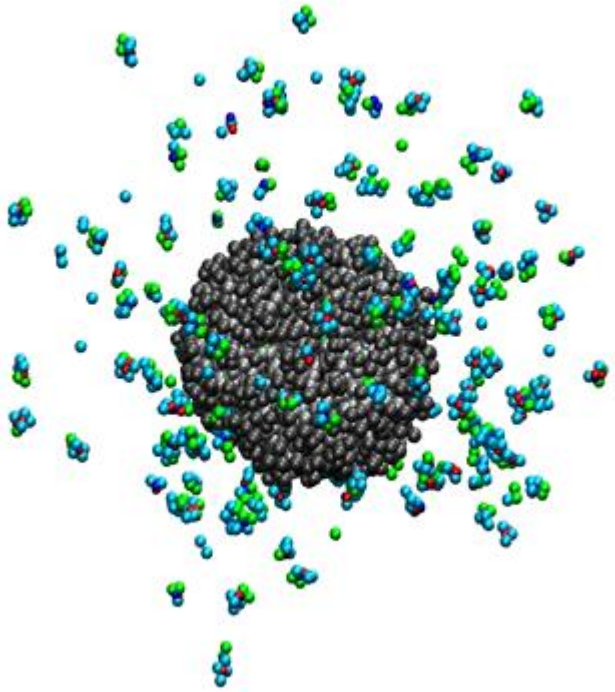
RESULTS

- Typical applications:
  - Reversible **folding** of a miniprotein in implicit water



www.biochem-caflisch.uzh.ch/movies/0001/

- Amyloid **aggregation** on the surface of a lipid vesicle



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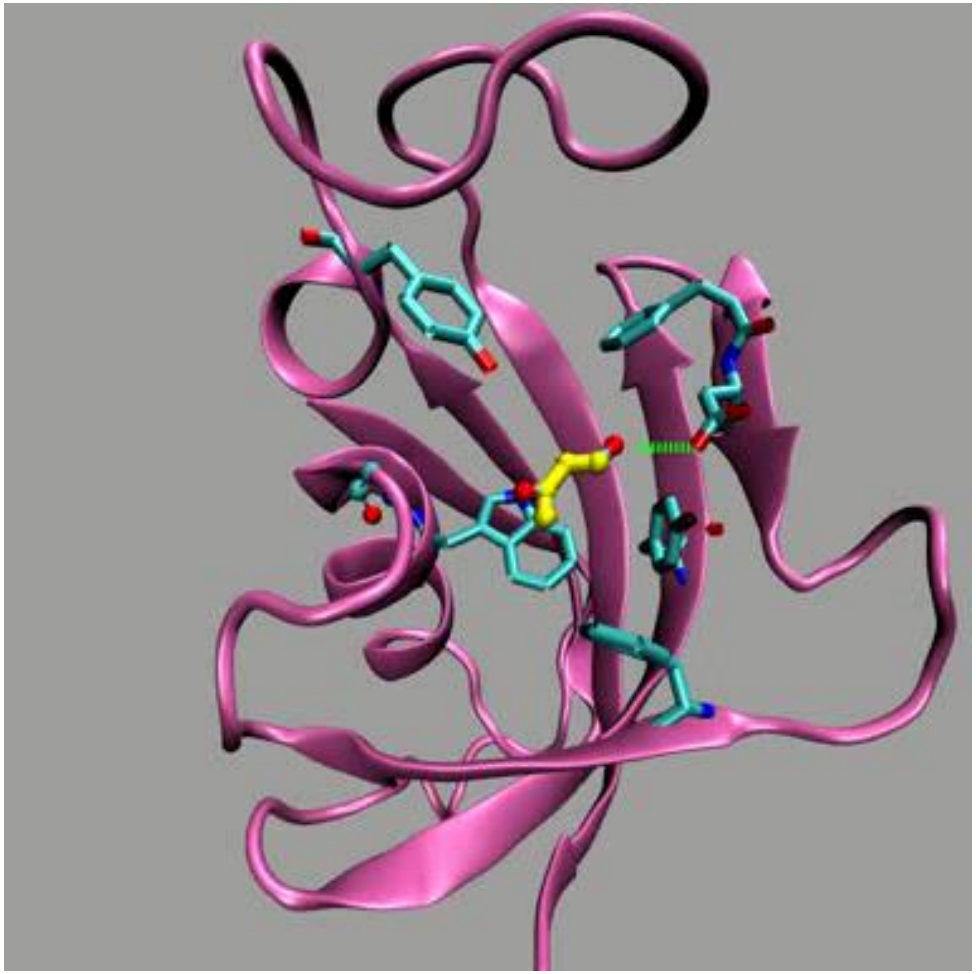
RESULTS

- Typical applications:
  - Small molecule **unbinding**

Experimental approaches to the study of fragment binding to proteins have limitations in resolution. Molecular dynamics simulations of small molecule binding and unbinding provide femtosecond temporal resolution and full spatial resolution.

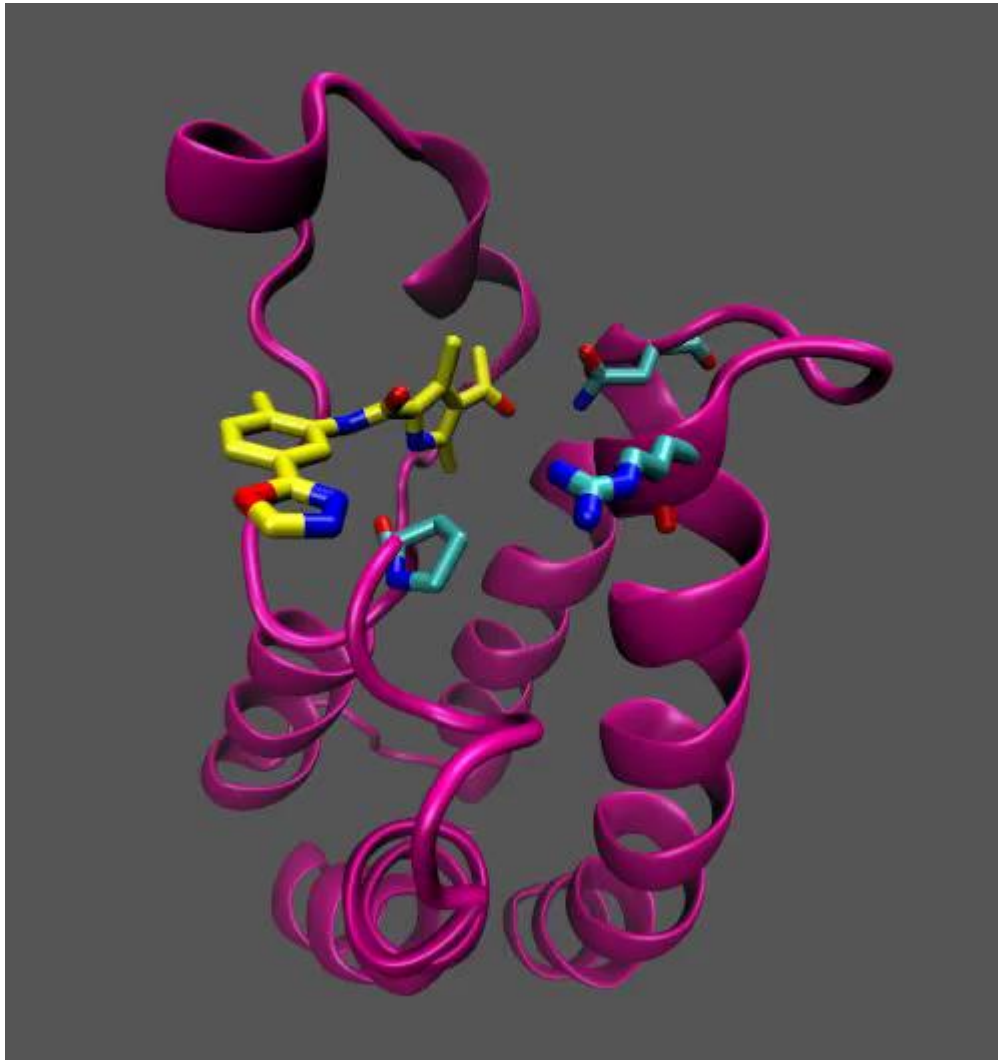


http://www.biochem-caflisch.uzh.ch/movies/0012/

RESULTS

- Typical applications:
  - Ligand **optimization**

Molecular dynamics simulations can be used to guide the optimization of hit compounds by medicinal chemistry.
For the link to the paper <click here>



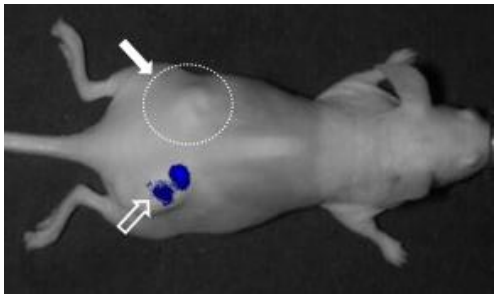
Example of a movie

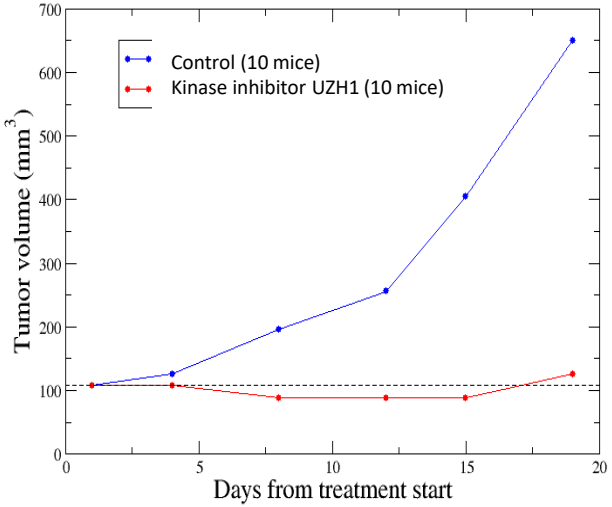
http://www.biochem-caflisch.uzh.ch/movies/0028/

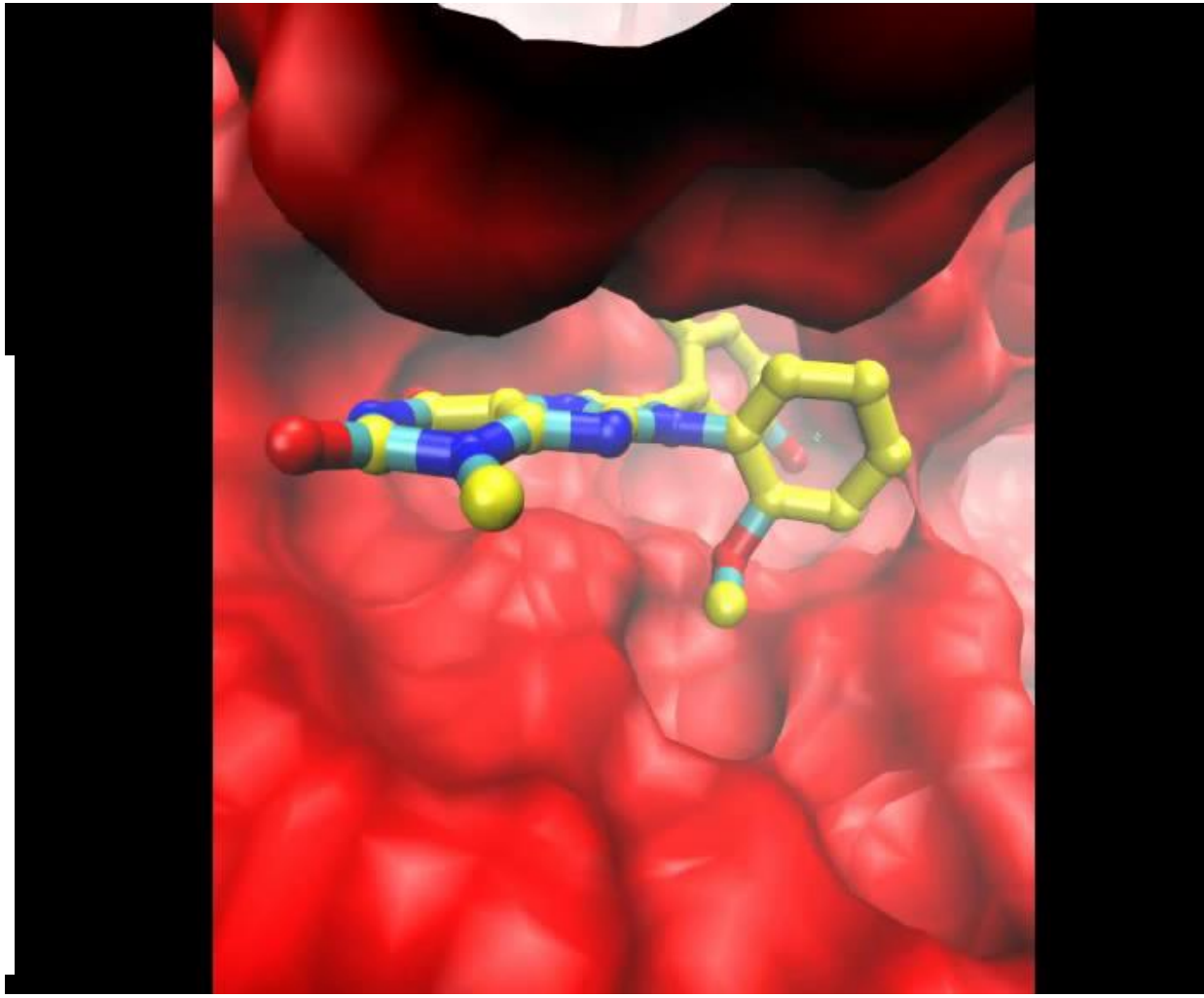
An experiment on a computer

RESULTS

- Drug design:







Unzue et al., J. Med. Chem. 2014, 57, 6834−6844

http://www.biochem-caflisch.uzh.ch/movies/0010/

An experiment on a computer

Movies ….

EXAMPLES

http://www.biochem-caflisch.uzh.ch/movies/

Kinetic response of a photoperturbed allosteric protein

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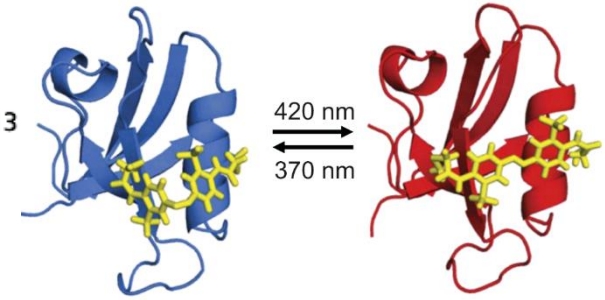
Departments of [a]Chemistry and [b]Biochemistry, University of Zurich, CH-8057 Zurich, Switzerland

Edited by Hans Frauenfelder, Los Alamos National Laboratory, Los Alamos, NM, and approved June 3, 2013



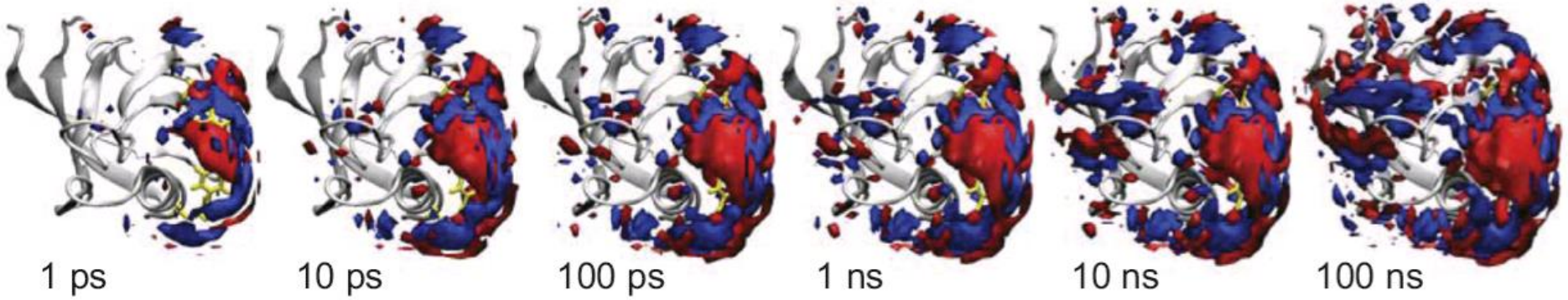


Fig. 5. Change of water density as a function of simulation time, compared with that just before switching. Red depicts increased density and blue decreased density. The contour surfaces correspond to changes of ±0.01 water/Å^3 (for comparison, the bulk water density is ~0.033 water/Å^3). The protein is shown as a gray ribbon and the photoswitch (visible only in part) is shown in yellow. See also Movie S1.

Interested in a position?

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