

C7790 Introduction to Molecular Modelling

TSM Modelling Molecular Structures

C9087 Computational Chemistry for Structural Biology

Lesson 2

Computational Chemistry vs Experiment

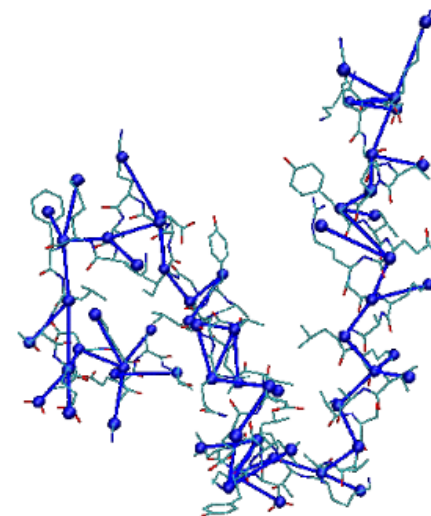
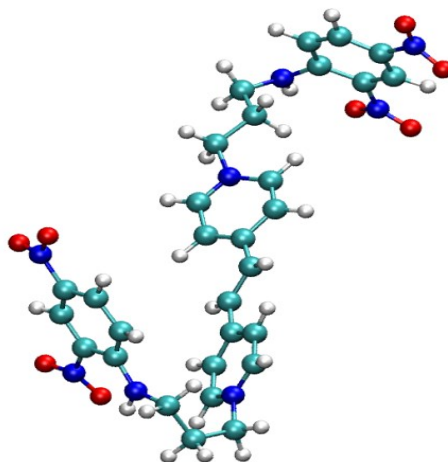
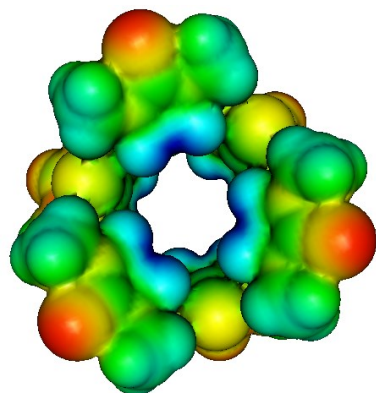
JS/2022 Present Form of Teaching: Rev5

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Method overview (model chemistry)



Quantum mechanics

Molecular mechanics

***Coarse-grained* mechanics**

atomic resolution

bead resolution

reactivity

conformational movements

domain movement, folding

up to 1,000 atoms *

up to 1,000,000 atoms *

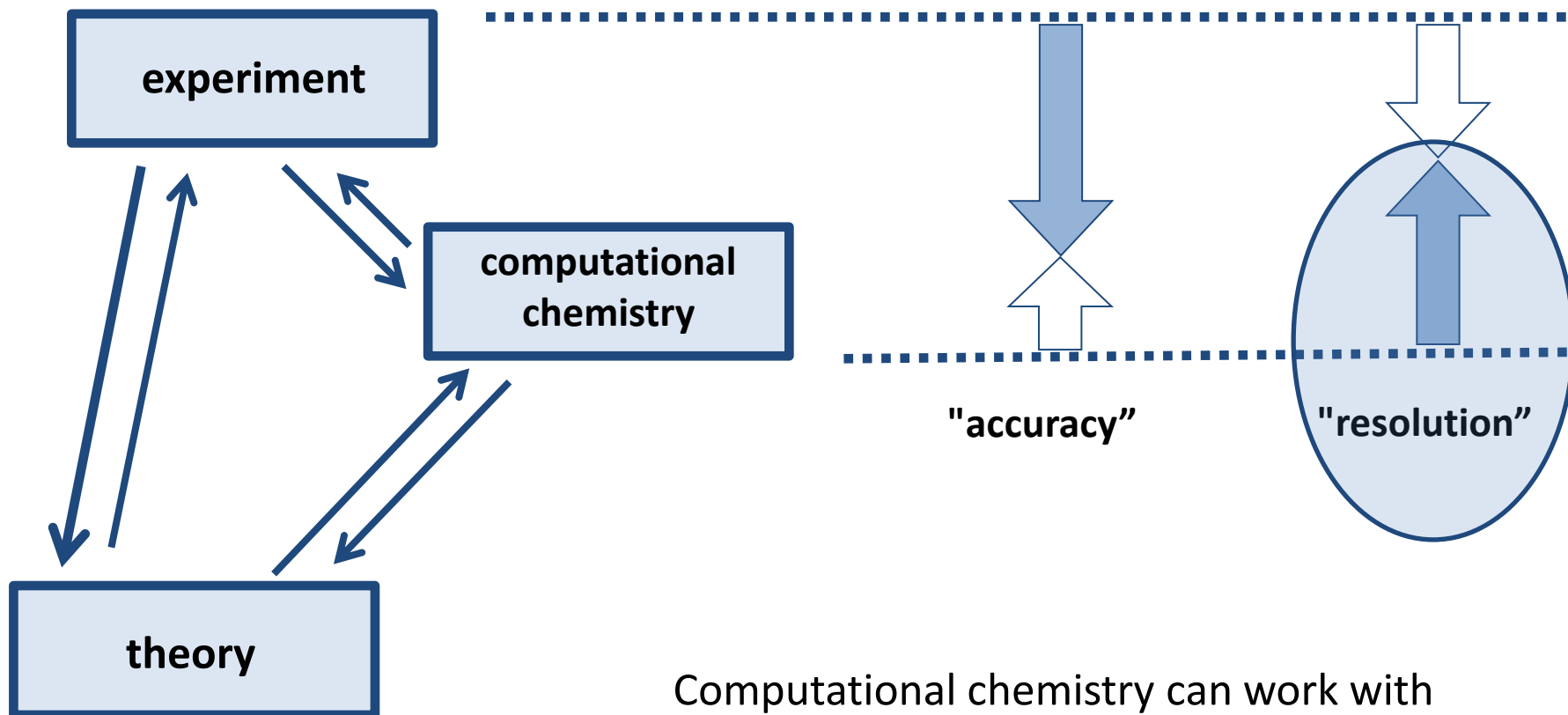
up to 1,000,000 beads *

up to 100 ps *

to 1 μ s *

up to ms *

Importance of computational chemistry



Computational chemistry can work with **single atom resolution**.

Atomic resolution

computational chemistry

atomic resolution since the introduction of quantum theory (1925)

- it refines models
- it improves calculation procedures
- it achieves more accurate results in less computational time

Historical development



experiment

atomic resolution since the introduction of X-ray crystallography (1923)

- it refines techniques
- it improves the resolution

Experiments with single atom or molecule resolution.
(Single Molecule Experiments)

Atomic Resolution Experiments

X-ray Crystallography

X-ray striking an electron produces secondary spherical waves emanating from the electron. This phenomenon is known as **elastic scattering**, and the electron is known as the scatterer.

A **regular array** of scatterers produces a regular array of spherical waves.

Although these waves cancel one another out in most directions through **destructive interference**, they add **constructively** in a few specific directions, determined by **Bragg's law**:

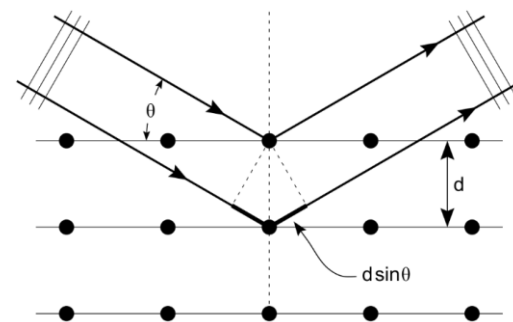
$$2d \sin \theta = n\lambda$$

X-rays diffract on electrons from atoms.

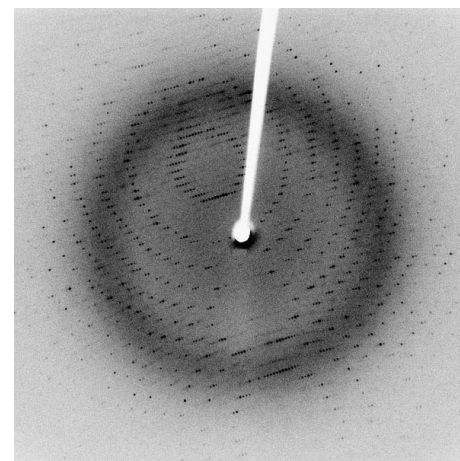
Disadvantages:

- the sample must be a monocrystal
- radiation damage

Diffraction (schematic model)



Diffraction pattern (enzyme crystal)



<http://www.wikipedia.org>

X-ray Crystallography

X-ray crystallography method determines the position of individual atoms in the unit cell of crystal.

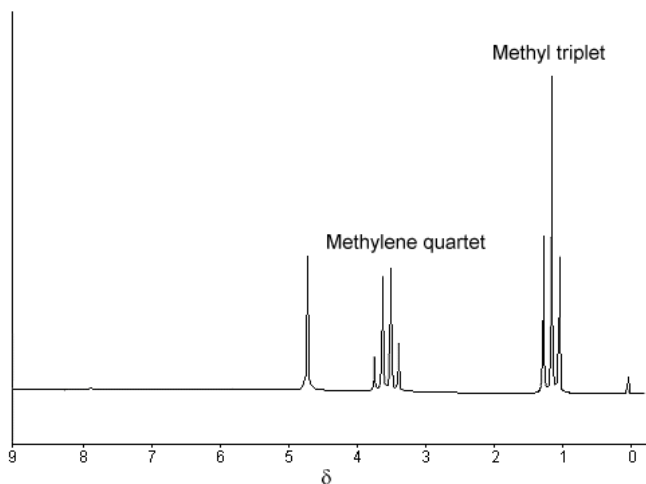
However, the positions of some atoms may not be determined in the case of low resolution or internal disorder. This usually happens for hydrogen atoms (weakly diffracting), side chains in biomolecules, or weakly bound substrates.

Diffraction on crystals can be achieved with other sources of beams with suitable wavelengths:

- **Neutrons** - Benefit of **neutron diffraction** is that the diffraction occurs at the nuclei of individual atoms. This method can determine hydrogen atom positions, because protons (hydrogen atom nuclei) diffracts very well.
- **Electrons** - electron crystallography, available in modern electron microscopes

Nuclear Magnetic Resonance - NMR

- chemical shift
- J-coupling
- NOE (Nuclear Overhauser Effect) - proportional to the distance
- and more

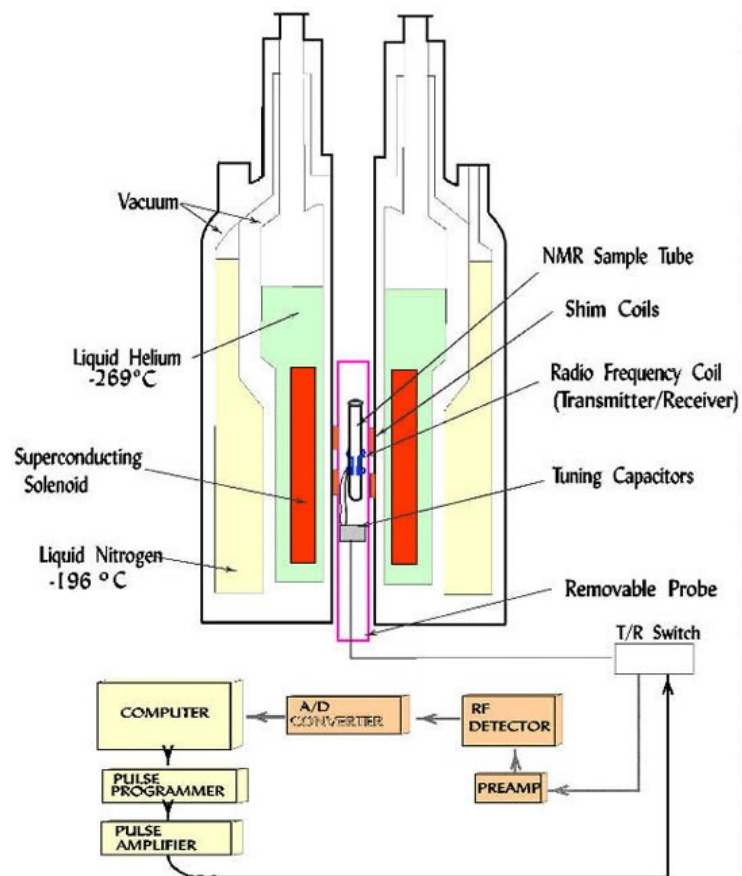


Advantages:

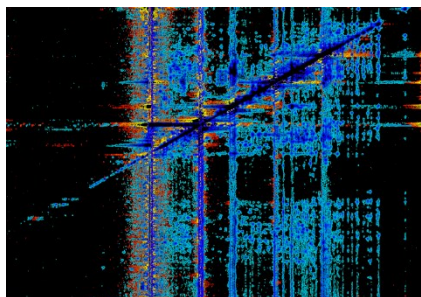
- sample in solution
- non-destructive

Disadvantages:

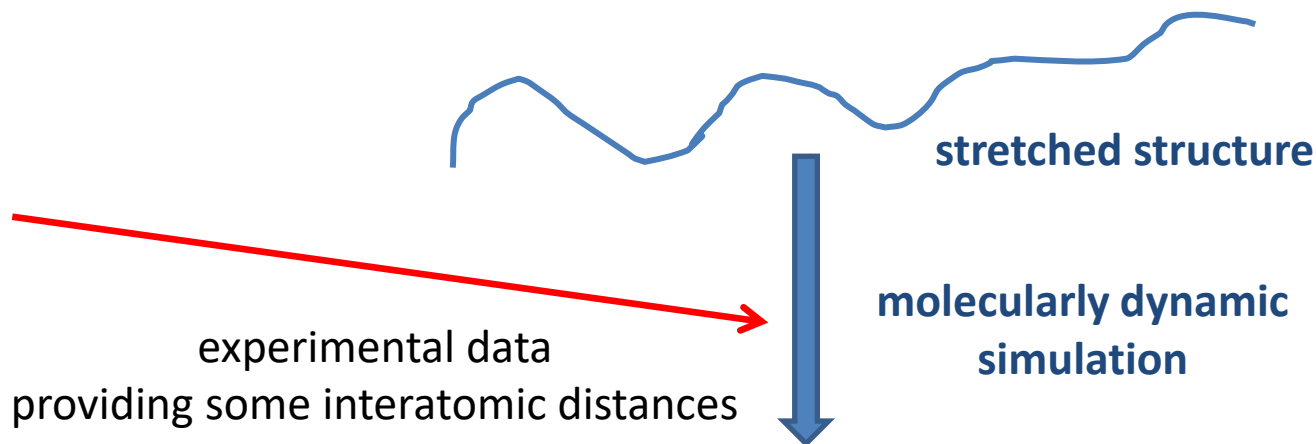
- isotope labeling
- not suitable for very large molecules



Nuclear Magnetic Resonance - NMR

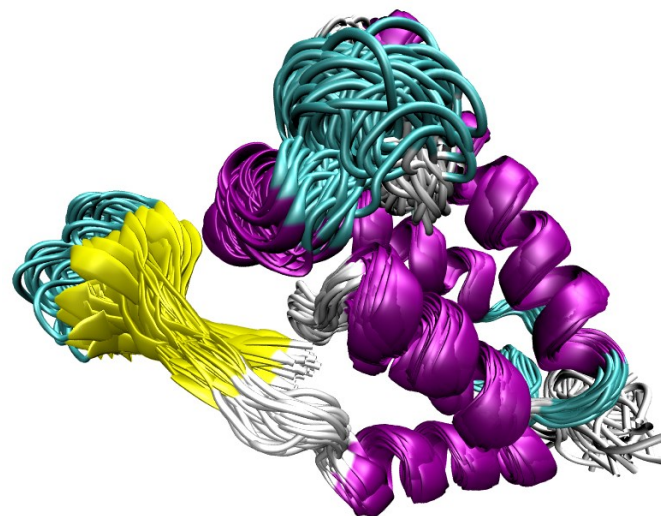


NMR spectra



the resulting structure is represented by
several conformations

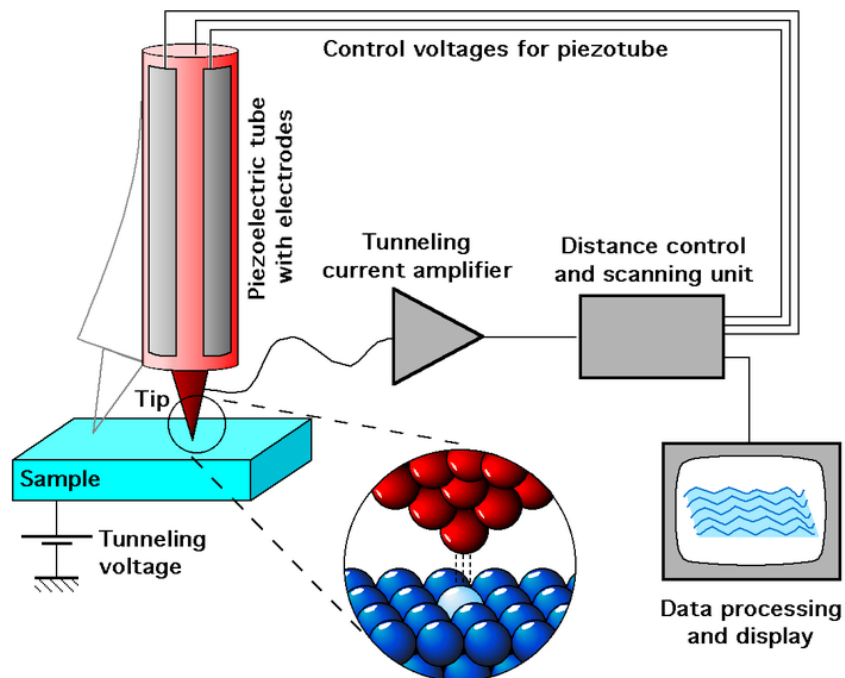
the structure contains hydrogen atoms, which
are provided by used theoretical model
(molecular mechanics)



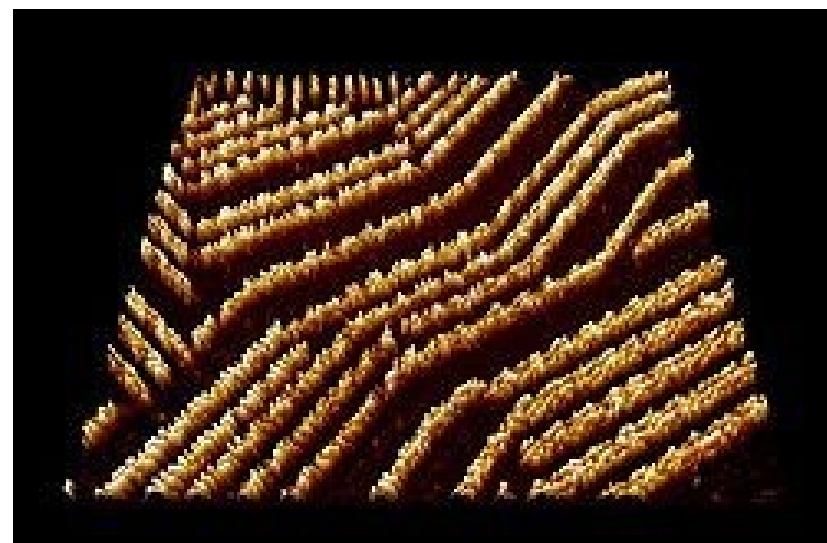
Macek, P .; Hops, J .; Cross, I .; Savoy cabbage, P .; Padrta, P .; Žídek, L .; Wild, M .; Hadravová, R .; Chaloupková, R .; Pichová, I .; et al. NMR Structure of the N-Terminal Domain of Capsid Protein from the Mason – Pfizer Monkey Virus. *Journal of Molecular Biology* **2009**, 392, 100–114.

Scanning Tunneling Microscopy STM

Principle:



Result:



Disadvantages:

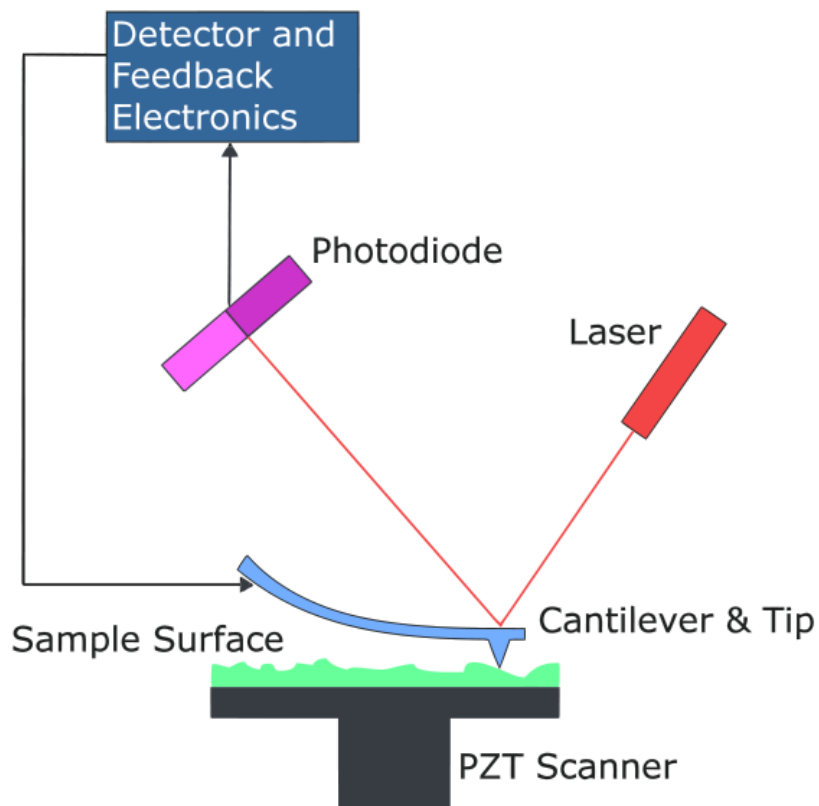
- electroconductive materials

<http://www.wikipedia.org>

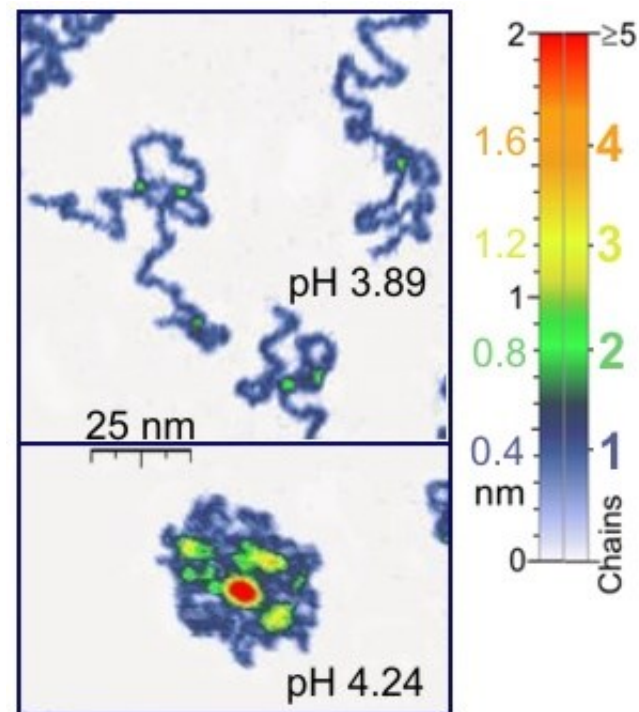
Single Molecule Experiments

Atomic Force Microscopy - AFM

Principle:



Result:

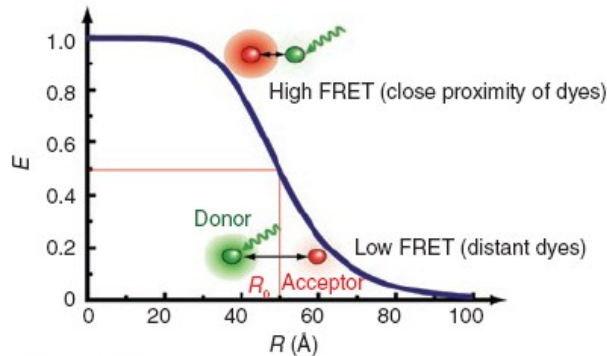


<http://www.wikipedia.org>

FRET Experiments

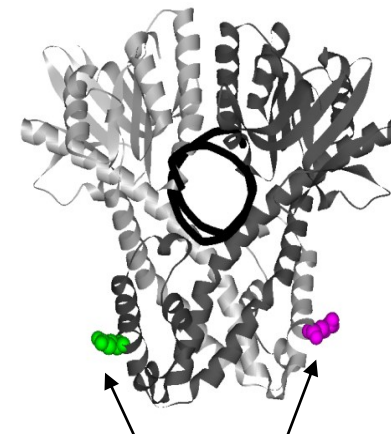
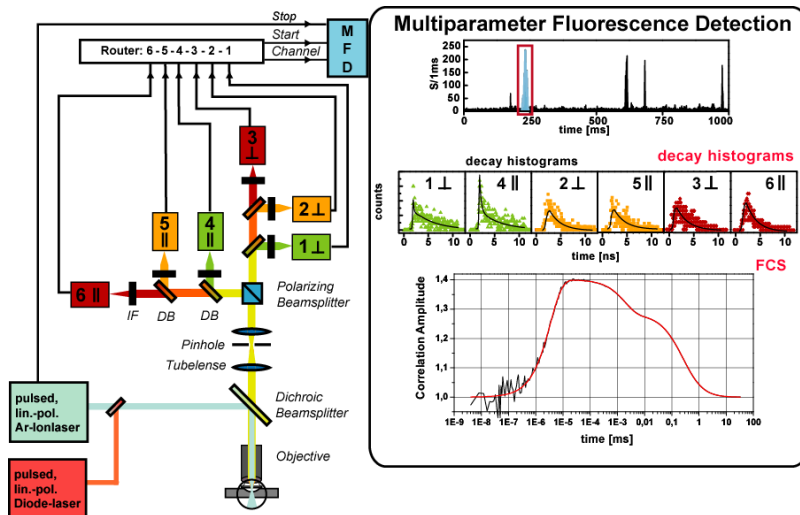
FRET: Fluorescent Resonance Energy Transfer

Principle:



Result:

$$E = \frac{1}{1 + (R / R_0)^6}$$



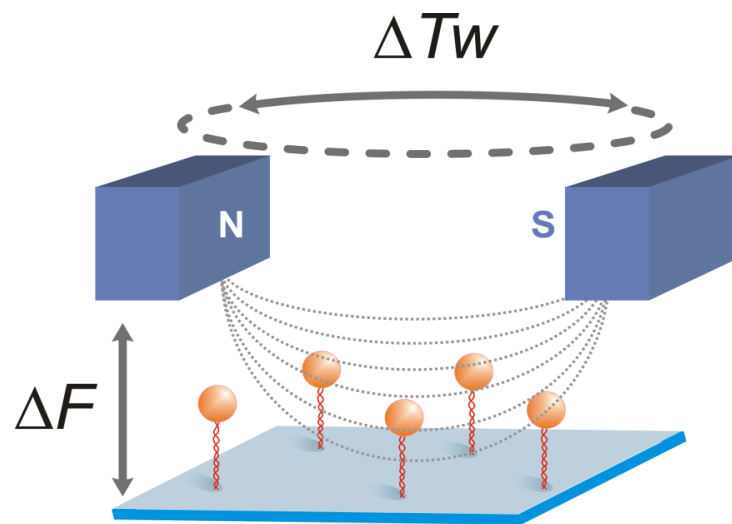
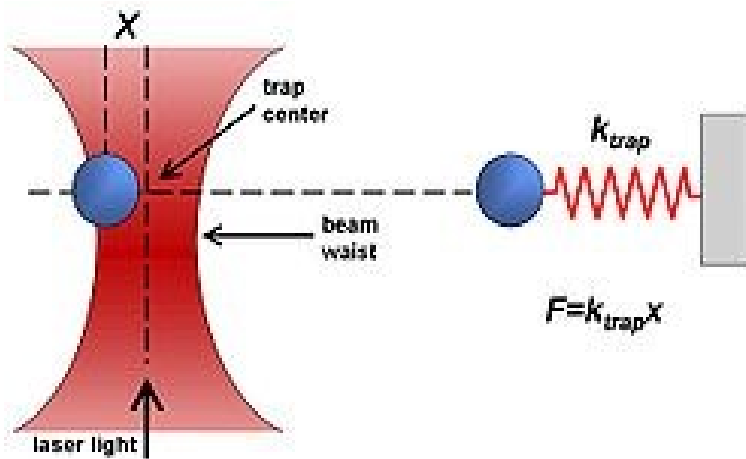
two chromophores
we can determine the distance

BsoBI

Q: Is it opened during DNA binding and if so, on which side?

Magnetic and Optical Tweezers

Principle:



Suitable for:

- Active/Binding site location
- Kinetics measurements

<http://www.wikipedia.org>

Optical tweezers - use

VU University, Amsterdam



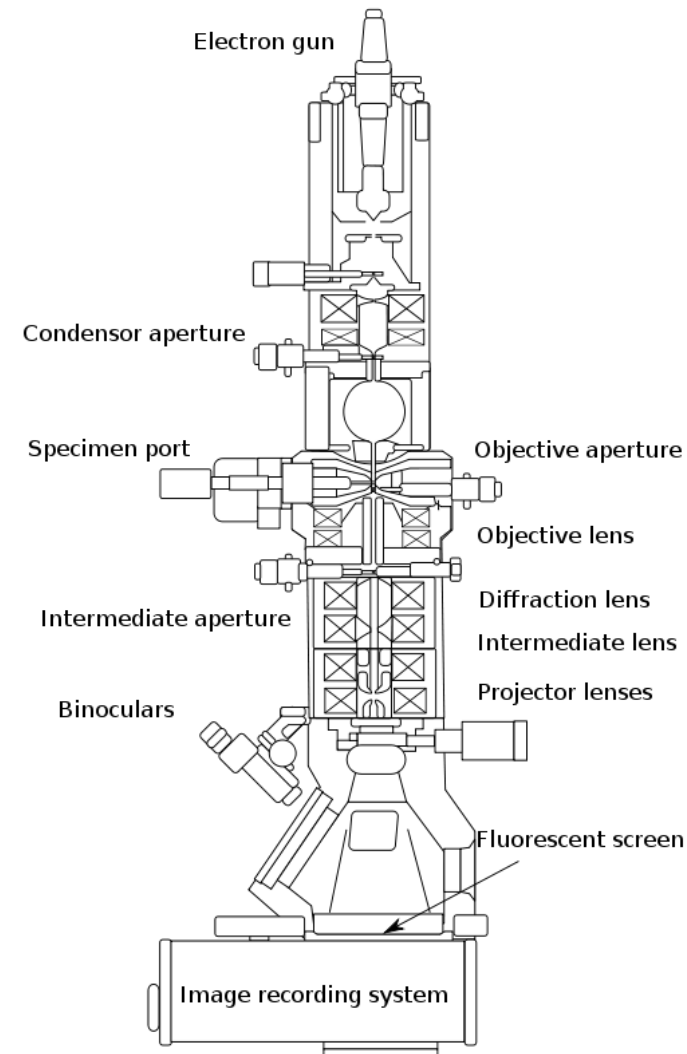
Electron cryomicroscopy - cryoEM

Electron microscopy is a form of transmission electron microscopy where a sample is studied at low temperatures (typically liquid nitrogen temperature). The technique is used in structural biology.



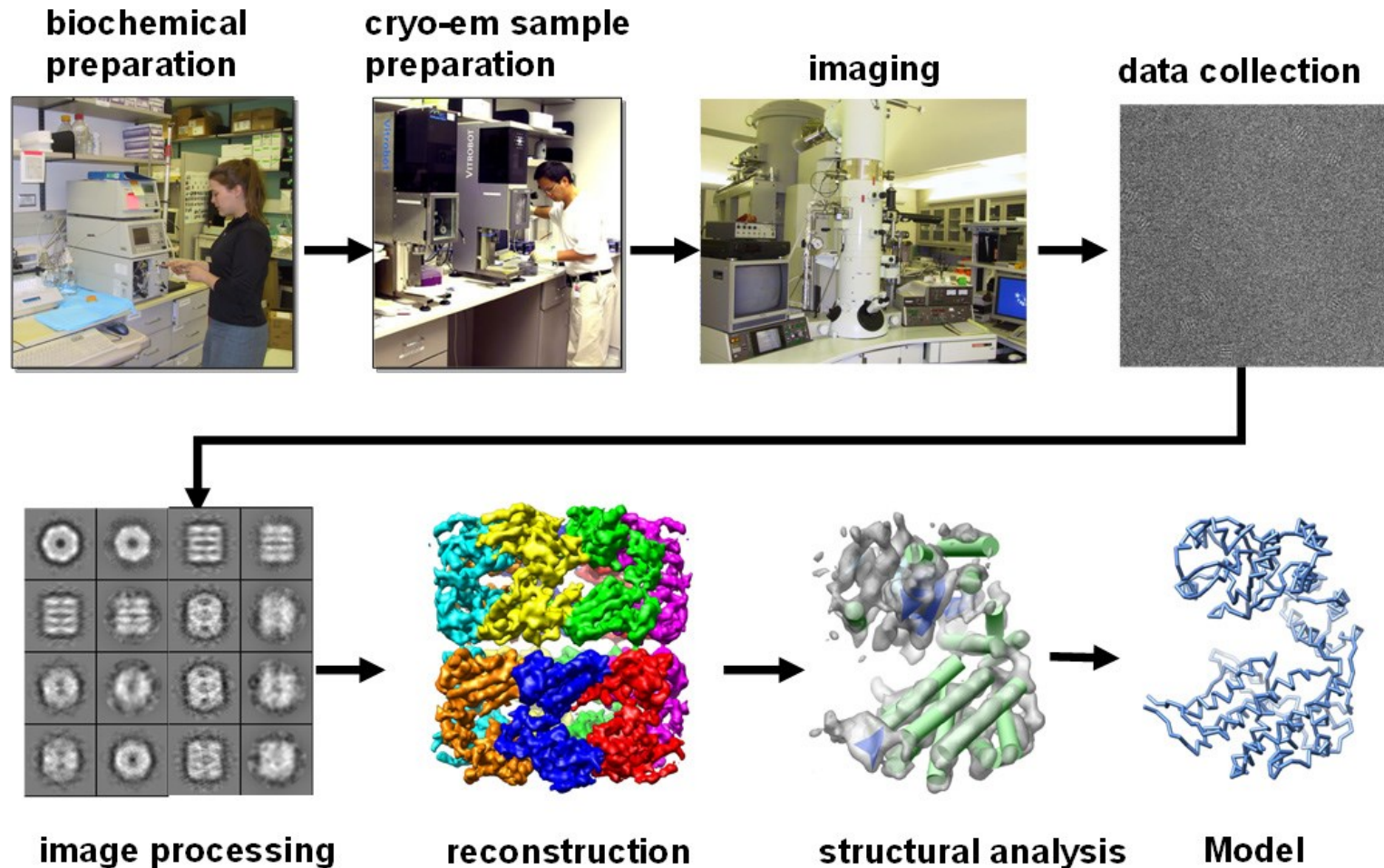
Acceleration voltage: 300 kV

Building E35/ CEITEC



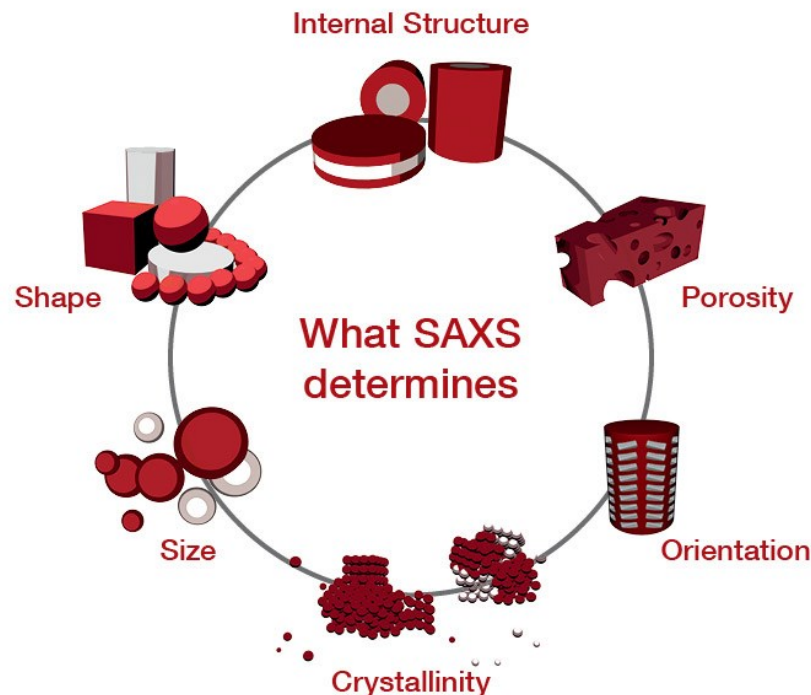
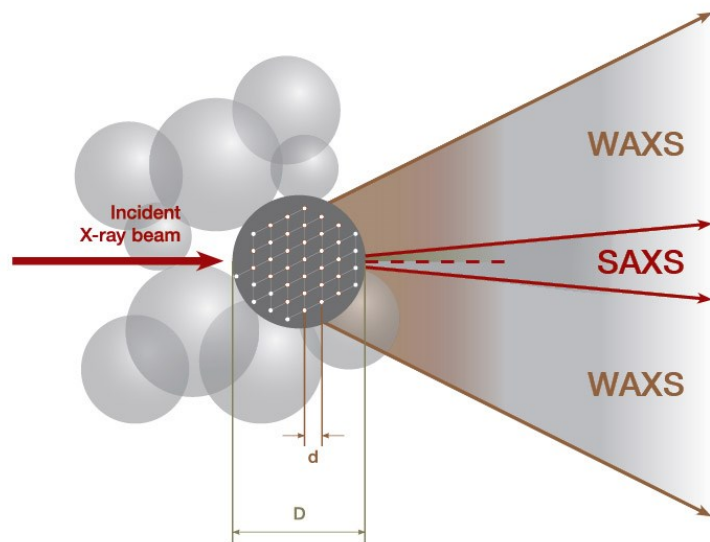
Electron cryomicroscopy - cryoEM

Pipeline in Biological Cryo-EM



<http://proj.ncku.edu.tw/research/commentary/e/20080919/2.html>

Small-angle X-ray scattering SAXS



Small-angle X-ray scattering (SAXS) is a technique by which nanoscale density differences in a sample can be quantified.

It can determine nanoparticle size distributions, resolve the size and shape of (monodisperse) macromolecules, determine pore sizes, characteristic distances of partially ordered materials, and much more.

<https://wiki.anton-paar.com>

Structure Databases

Cambridge Structural Database (CSD)

<http://www.ccdc.cam.ac.uk/Solutions/CSDSystem/Pages/CSD.aspx>

It contains about half a million structures of small molecules determined by X-ray and neutron diffraction. Suitable software: Mercury

<http://www.ccdc.cam.ac.uk/Solutions/CSDSystem/Pages/Mercury.aspx>

Protein Data Bank (PDB)

<http://www.pdb.org>

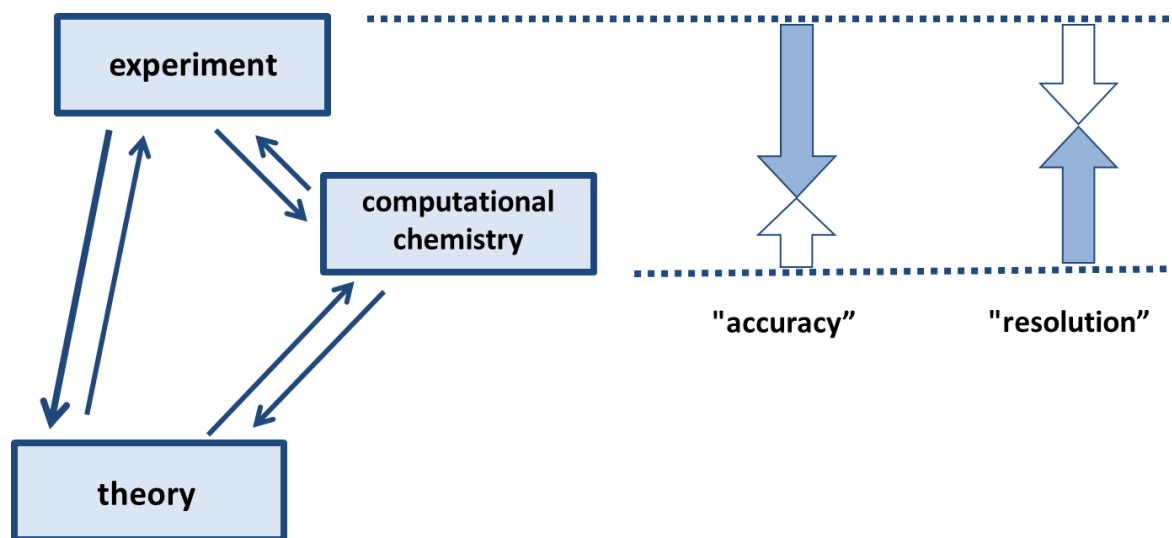
It contains about 94 thousand structures of biomolecular systems determined mainly by X-ray structural analysis.

| Experimental method | Proteins (P) | Nucleic acids (NA) | P / NA complexes | Other | Overall |
|---------------------|--------------|--------------------|------------------|-------|---------|
| X ray | 77445 | 1481 | 4069 | 3 | 82998 |
| NMR | 8851 | 1046 | 193 | 7 | 10097 |
| electron microscopy | 469 | 45 | 129 | 0 | 643 |

status in September 2013

Summary

- Use molecular modelling for problems that cannot be solved by experimental techniques
- Use molecular modelling to complement experimental data
 - NMR, FRET, cryoEM, SAXS, etc.



Homework



Homework

1. What is the typical wavelength of radiation used in X-ray structural analysis?
2. What is the de Broglie wavelength of electrons in electron microscopy for an accelerating voltage of 300 kV?
3. How is the fluorescently labeled enzyme BsoBI prepared (page 13)?
4. How many structures determined by electron microscopy are currently stored in the PDB database?