C7790 Introduction to Molecular Modelling

TSM Modelling Molecular Structures

C9087 Computational Chemistry for Structural Biology

Lesson 2

Computational Chemistry vs Experiment

PS/2022 Present Form of Teaching: Rev6

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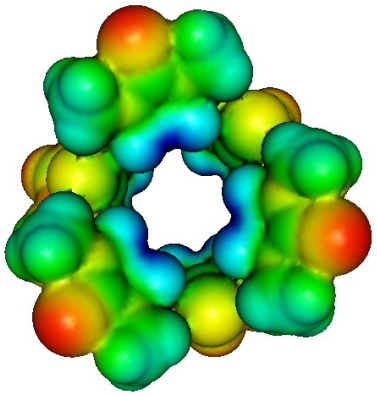
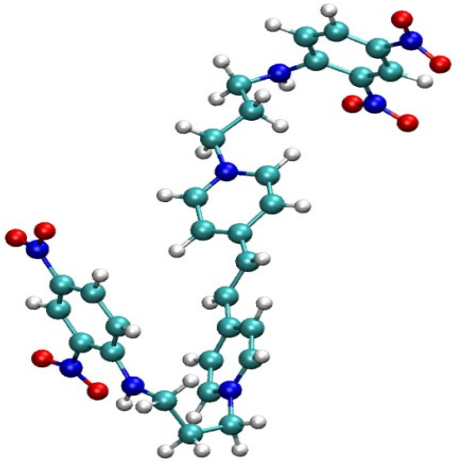
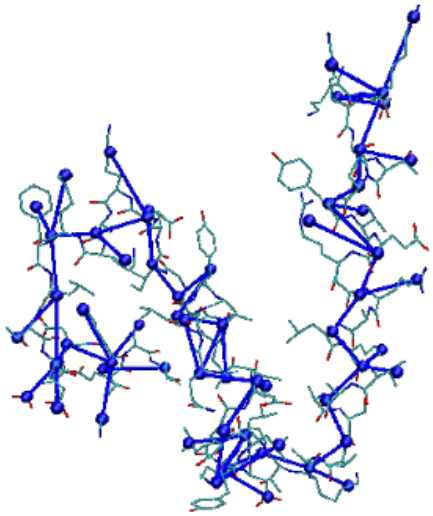
Method overview (model chemistry]

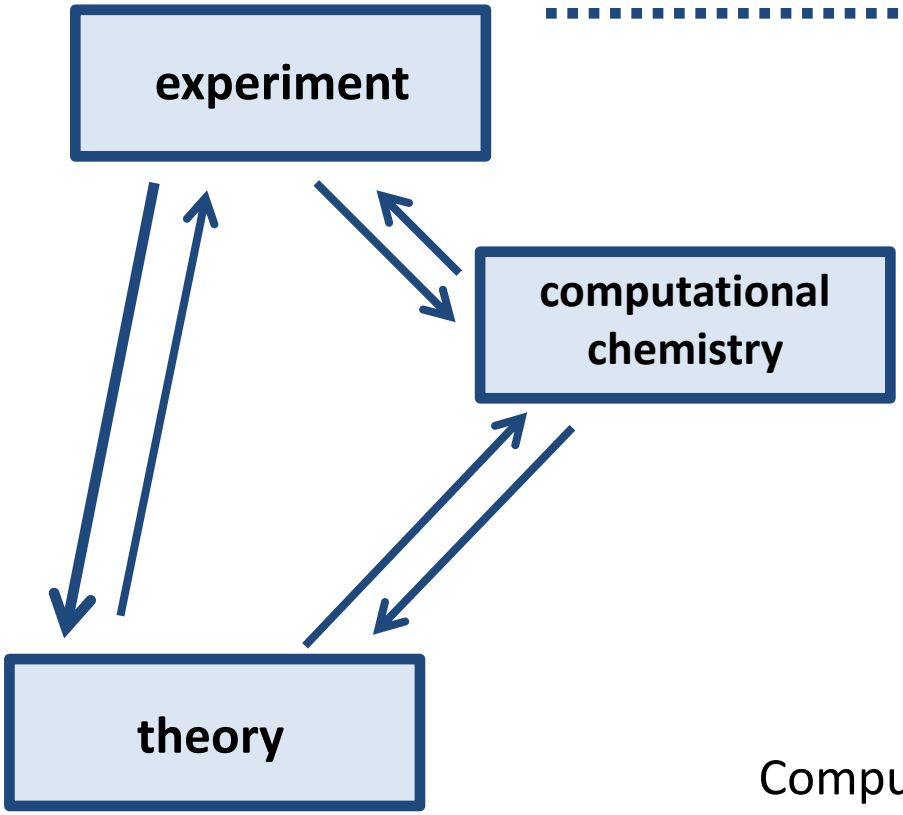


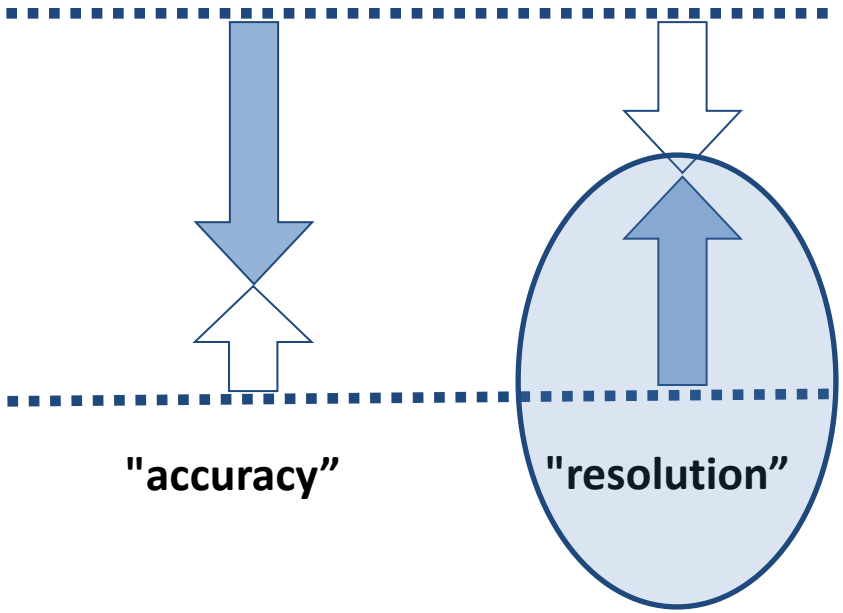




Quantum mechanics	Molecular mechanics	*Coarse-grained* mechanics
atomic resolution		bead resolution
reactivity	conformational movements	domain movement, folding
up to 1,000 atoms *	up to 1,000,000 atoms *	up to 1,000,000 beads *
up to 100 ps *	to 1 μs *	up to ms *

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**:

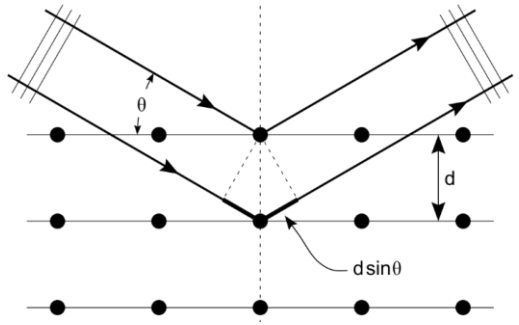
$$2d \sin\theta = n\lambda$$

X-rays diffracts on electrons from atoms.

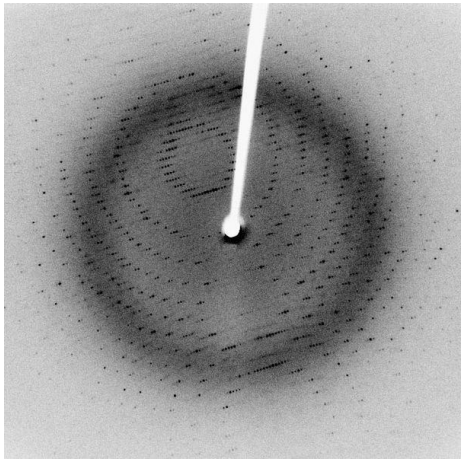
Disadvantages:

- 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.

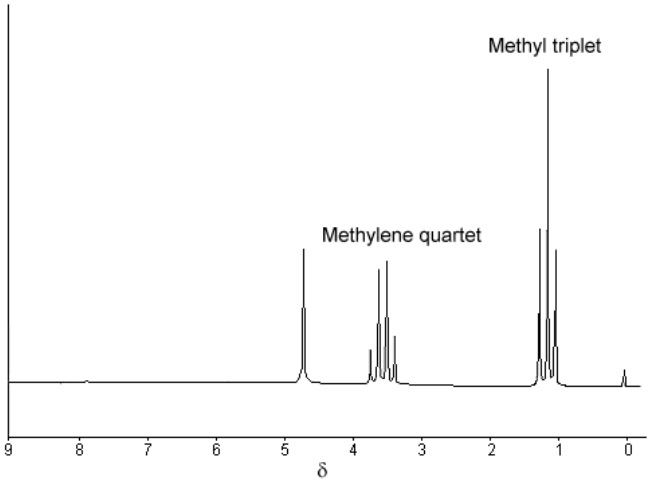
However, the positions of some atoms may not be determined in the case of low resolution or internal disorder. This usually happens for hydrogen atoms (weakly diffracting), side chains in biomolecules, or weakly bound substrates.

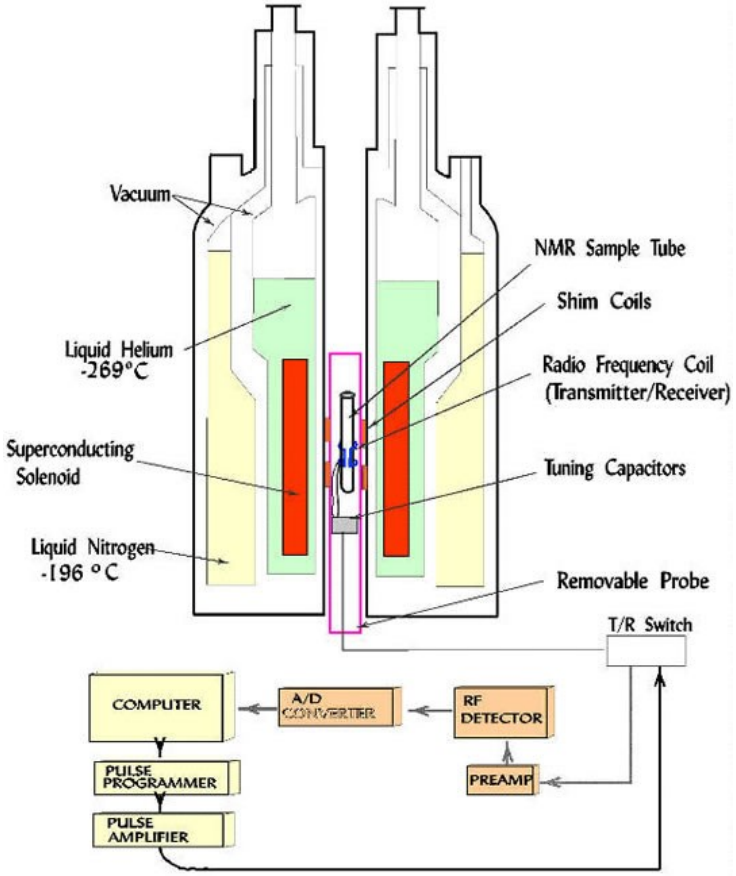
Diffraction on crystalls can be achieved with other sources of beams with suitable wavelengths:

- **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) difracts very well.
- **Electrons -** electron crystallography, availbale in modern electron microscopes

Nuclear Magnetic Resonance - NMR

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





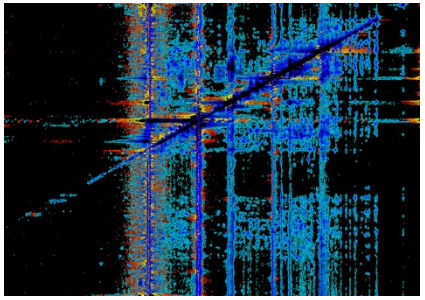
Advantages:

- sample in solution
- non-destructive

Disadvantages:

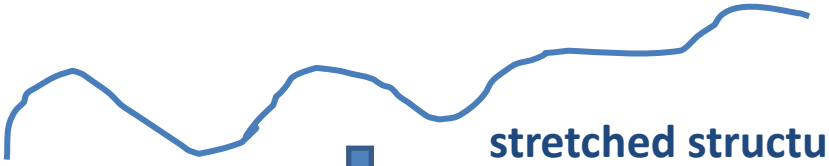
- isotope labeling
- not suitable for very large molecules

Nuclear Magnetic Resonance - NMR



NMR spectra

experimental data
providing some interatomic distances

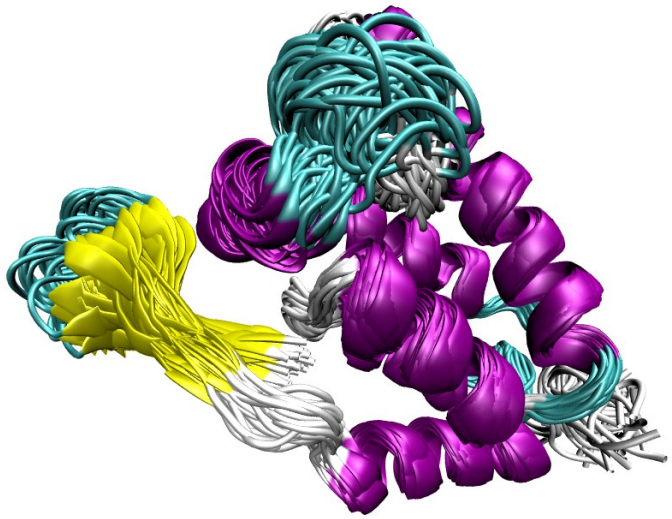


stretched structure

molecularly dynamic simulation

the resulting structure is represented by **several conformations**

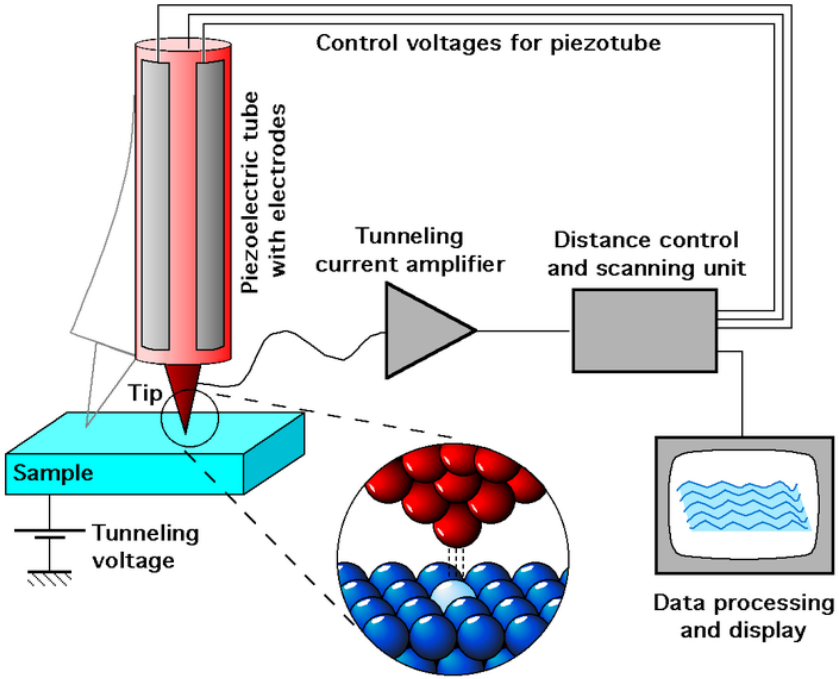
the structure contains hydrogen atoms, which are provided by used theoretical model (molecular mechanics)



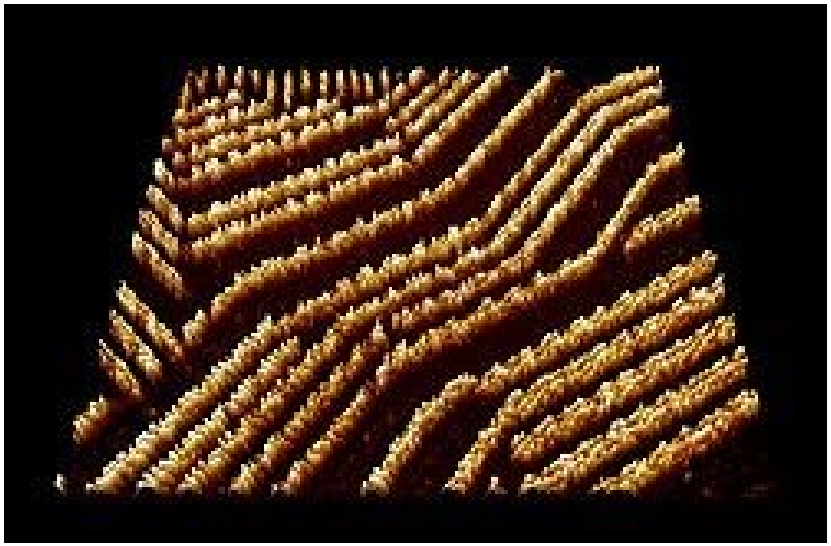
Macek, P .; Hops, J .; Cross, I .; Savoy cabbage, P .; Padrta, P .; Žídek, L .; Wild, M .; Hadravová, R .; Chaloupková, R .; Pichová, I .; et al. NMR Structure of the N-Terminal Domain ofCapsid Protein from the Mason – Pfizer Monkey Virus. *Journal of Molecular Biology* **2009**, *392*, 100–114.

Scanning Tunneling Microscopy STM

Principle:



Result:



Disadvantages:

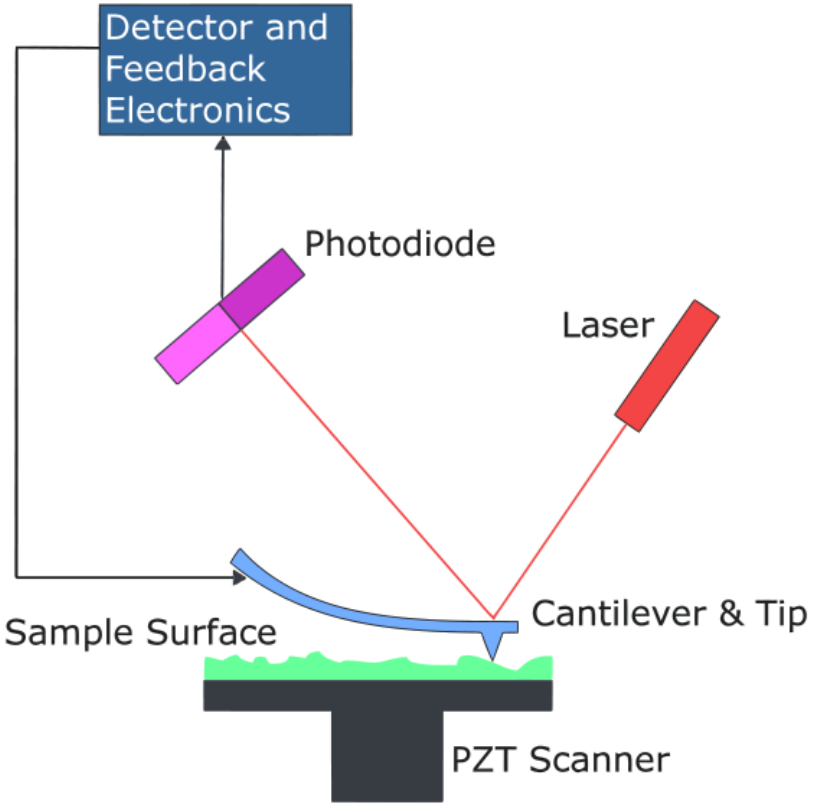
- electroconductive materials

http://www.wikipedia.org

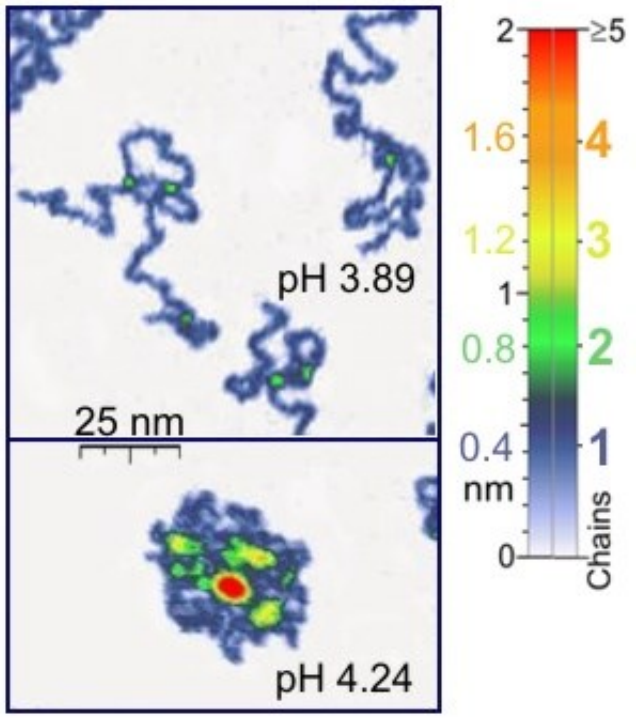
Single Molecule Experiments

Atomic Force Microscopy - AFM

Principle:



Result:

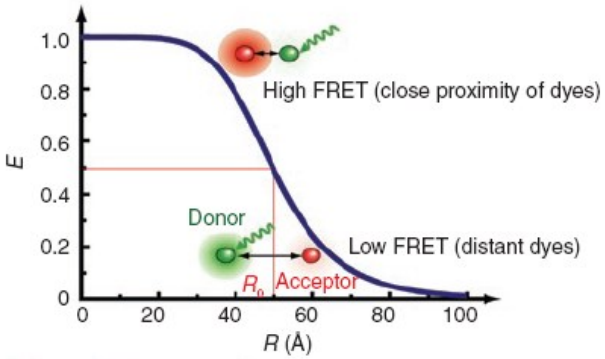


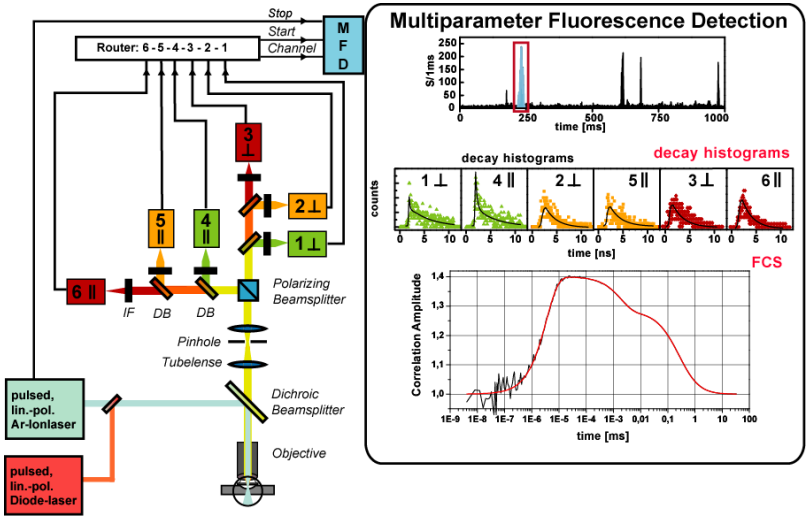
http://www.wikipedia.org

FRET Experiments

FRET: Fluorescent Resonance Energy Transfer

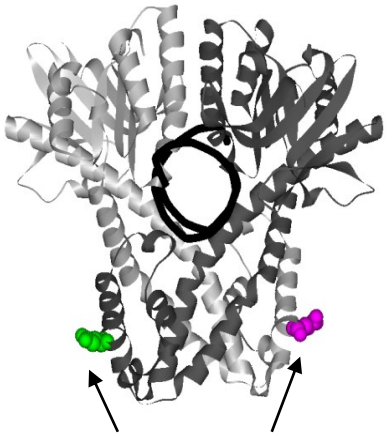
Principle:





Result:

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



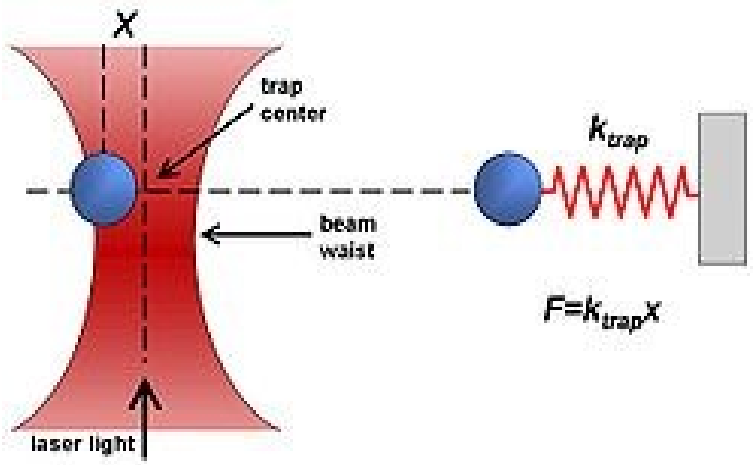
two chromophores
we can determine the distance

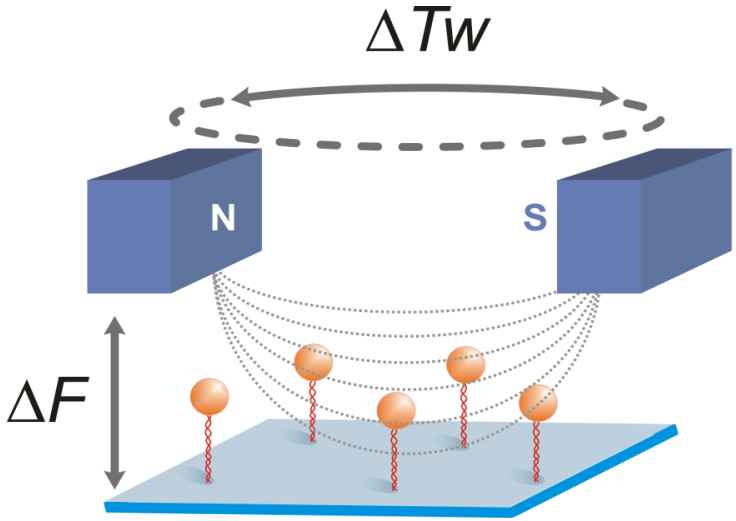
BsoBI

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

Magnetic and Optical Tweezers

Principle:



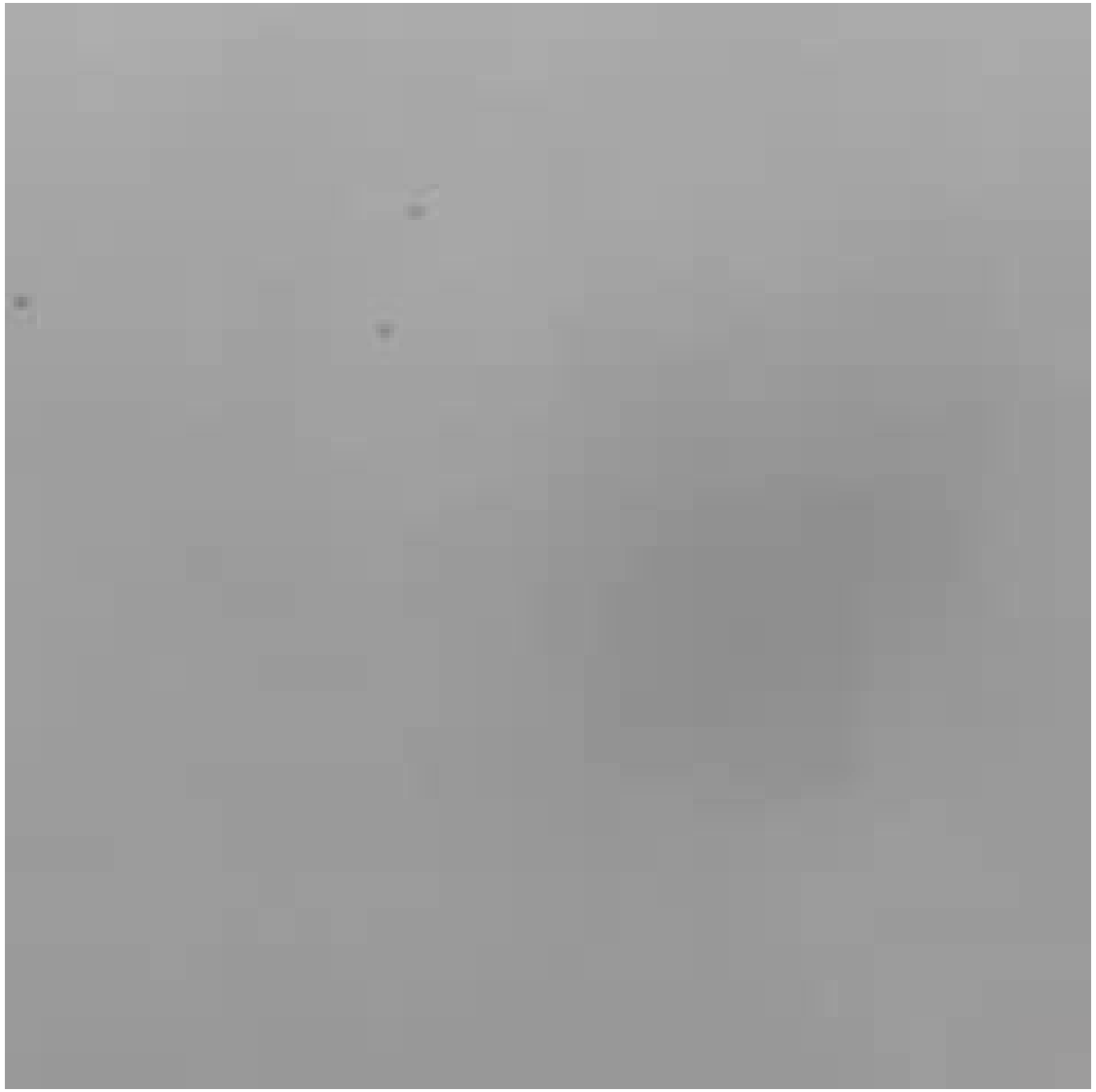


Suitable for:

- Active/Binding site location
- Kinetics measurements

http://www.wikipedia.org

Optical tweezers - use



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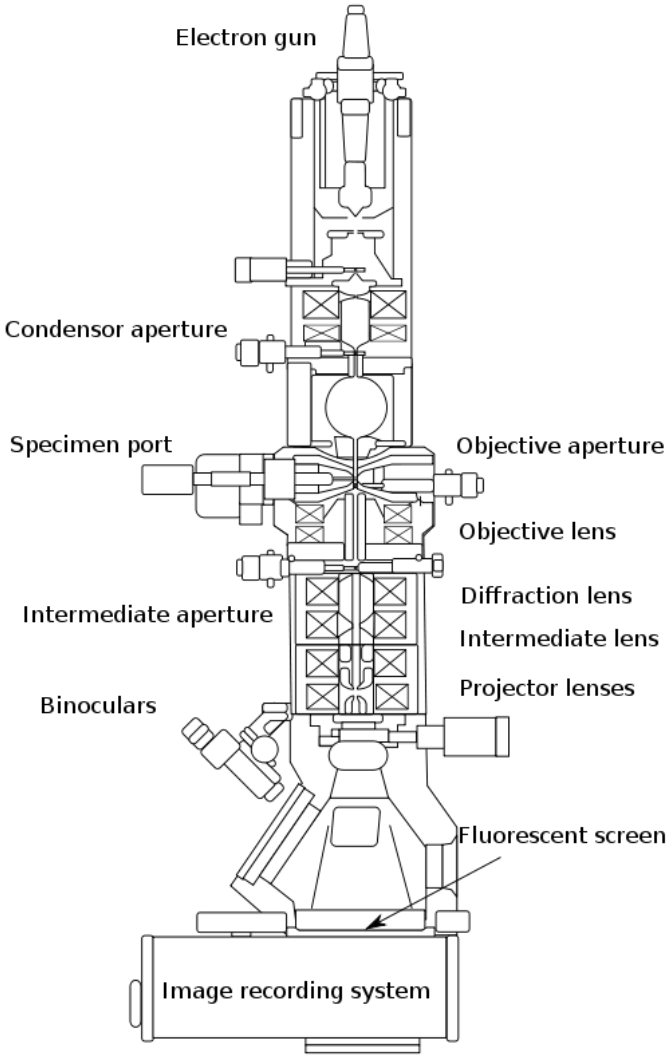
Electron cryomicroscopy - cryoEM

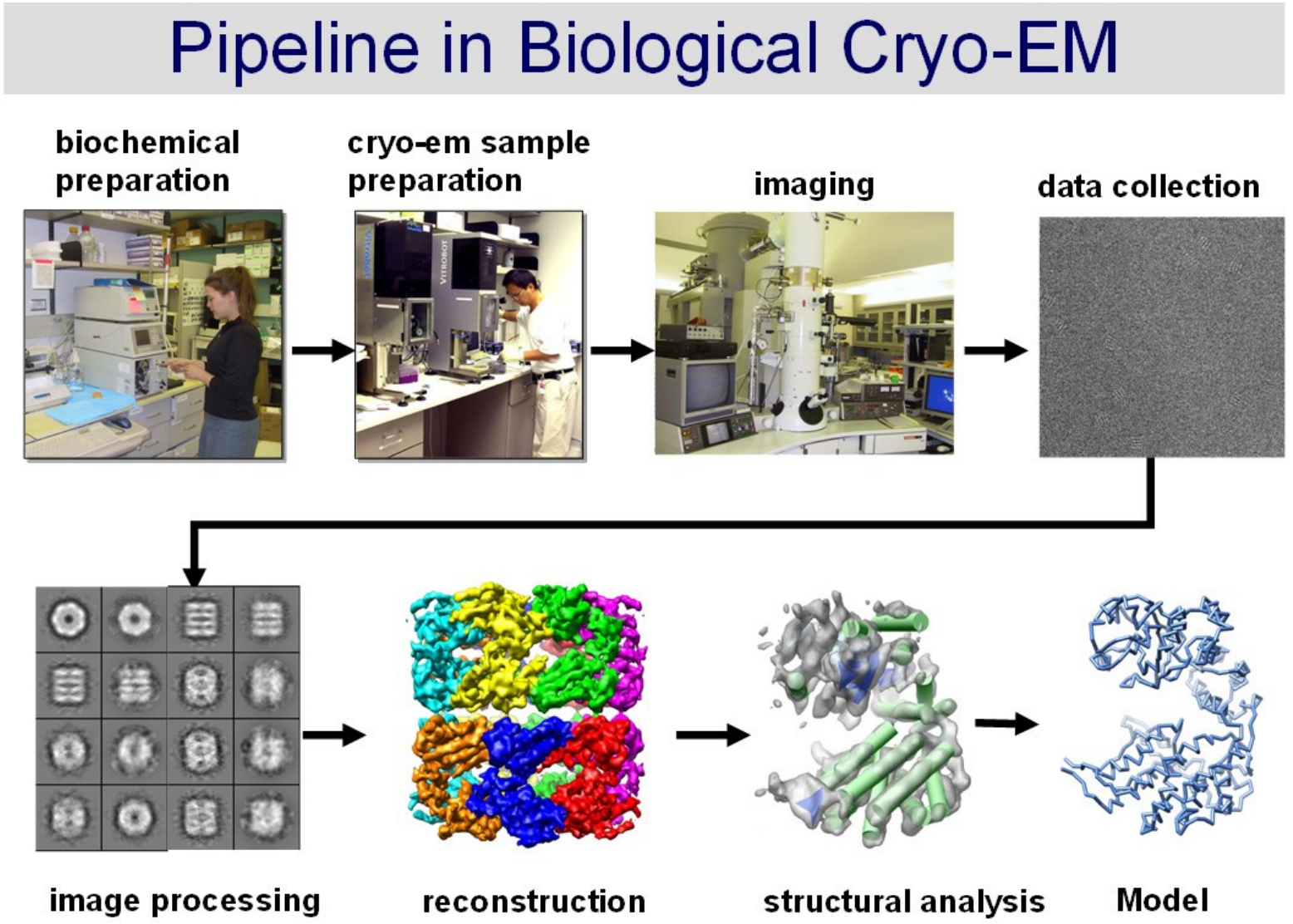
Electron microscopy is a form of transmission electron microscopy where a sample is studied at low temperatures (typically liquid nitrogen temperature). The technique is used in structural biology.

Acceleration voltage: 300 kV

Building E35/ CEITEC

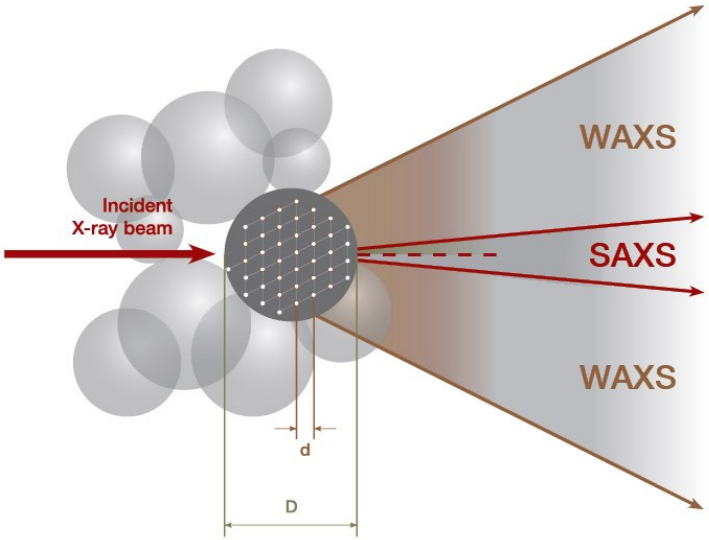


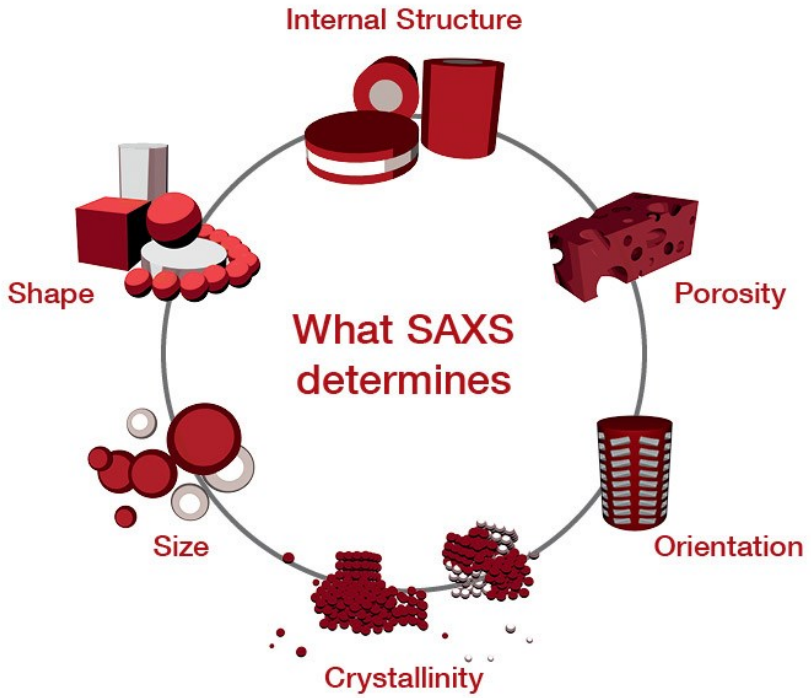
Electron cryomicroscopy - cryoEM



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

Small-angle X-ray scattering SAXS





Small-angle X-ray scattering (SAXS) is 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

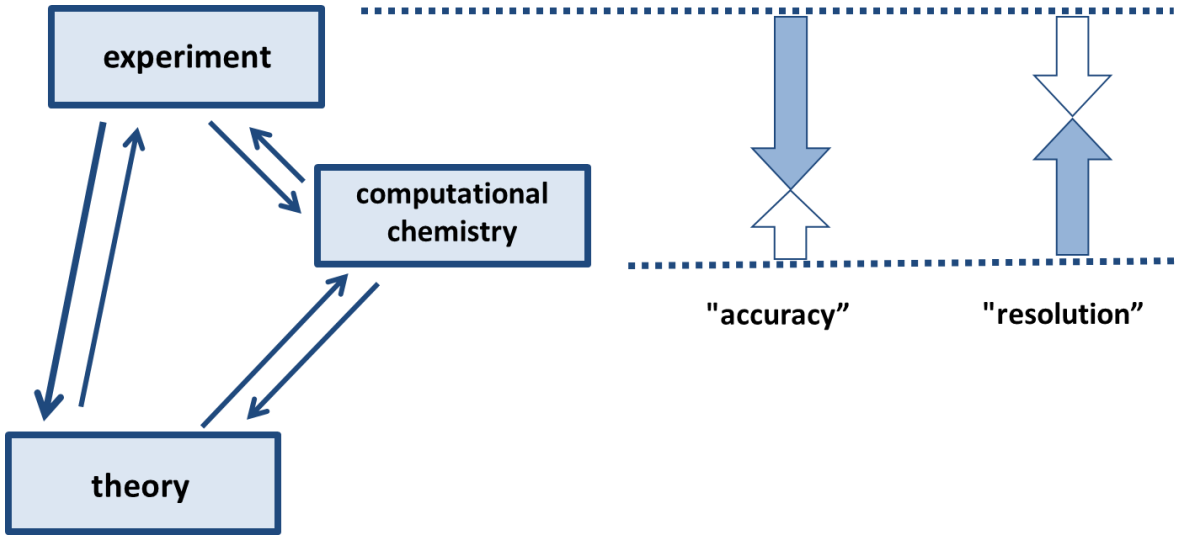
It contains about 94 thousand structures of biomolecular systems determined mainly by X-ray structural analysis.

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?