Biomolecular Modeling

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Biophysical Structures

Biomolecules: proteins, nucleic acids, lipids…

Aggregates of biomolecules: up to a cell ☺

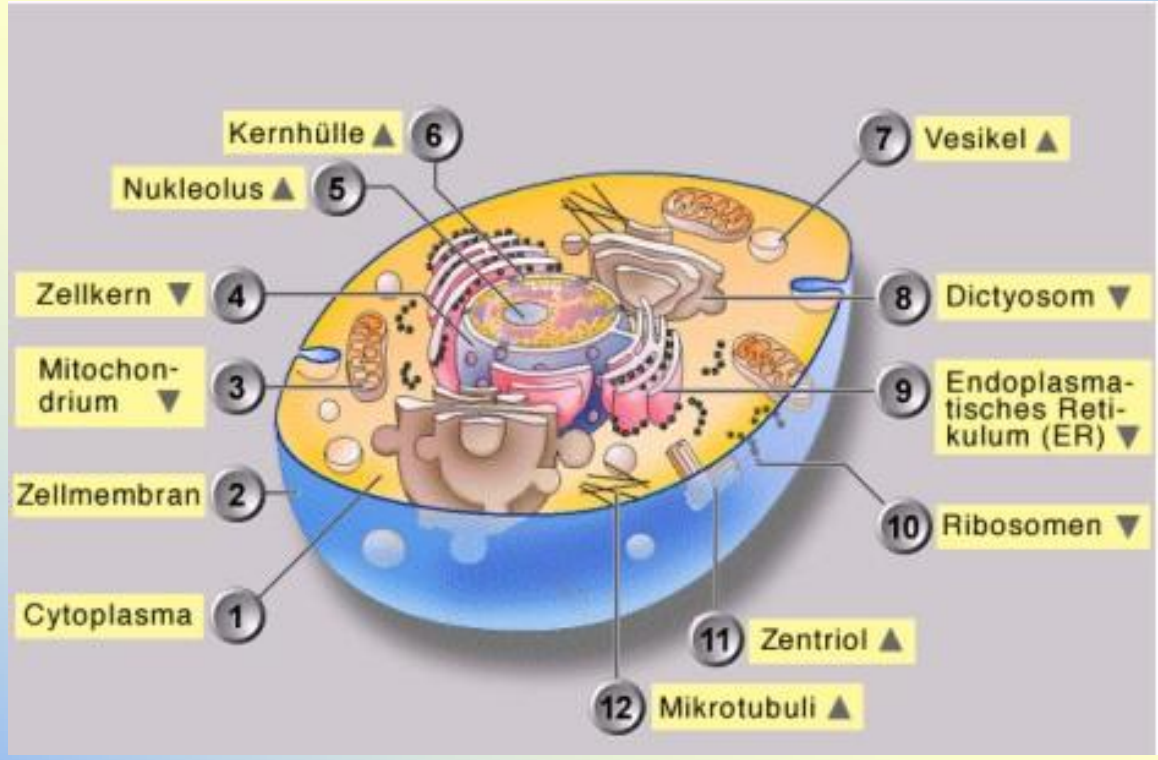
Biophysical Processes

Bioenergetics: receive and convert energy

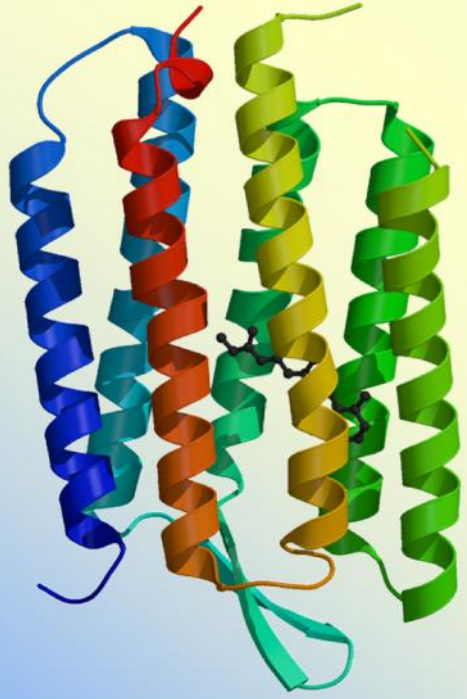
Catalysis: synthesis and decomposition of chemical substances

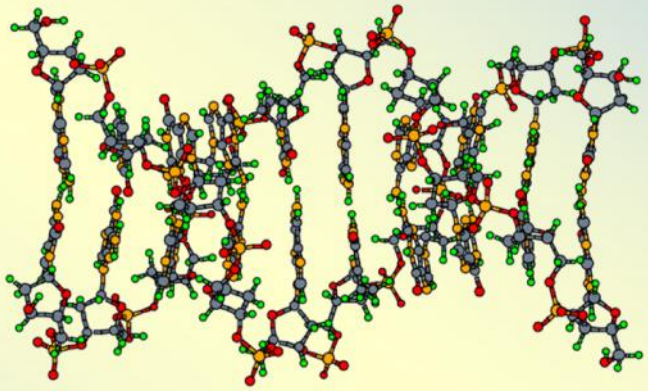
Transport: exchange of (ions, water…) with the surroundings

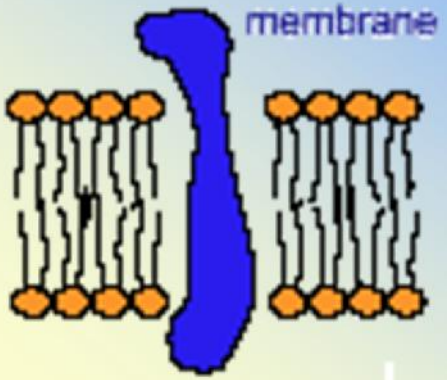
Biostructures

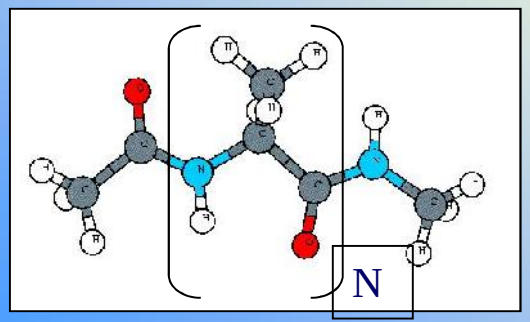


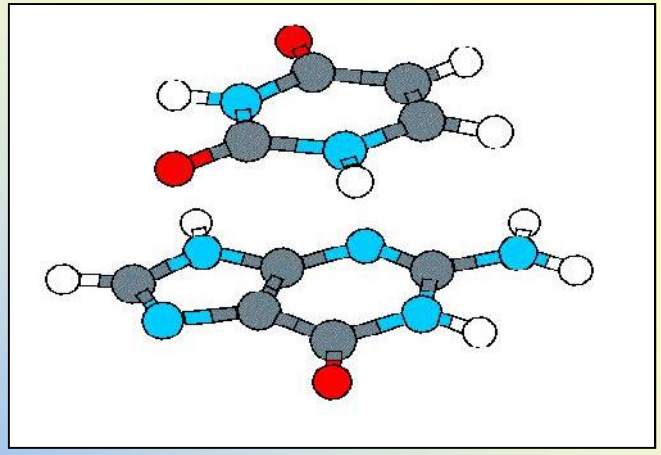
Proteins, Nucleic Acids, Lipids











Questions in the Theoretical Biophysics

I. Dynamics of complex structures

- Protein folding
- Molecular motors
- Protein-DNA complexes

II. Transport: water, ions, protons

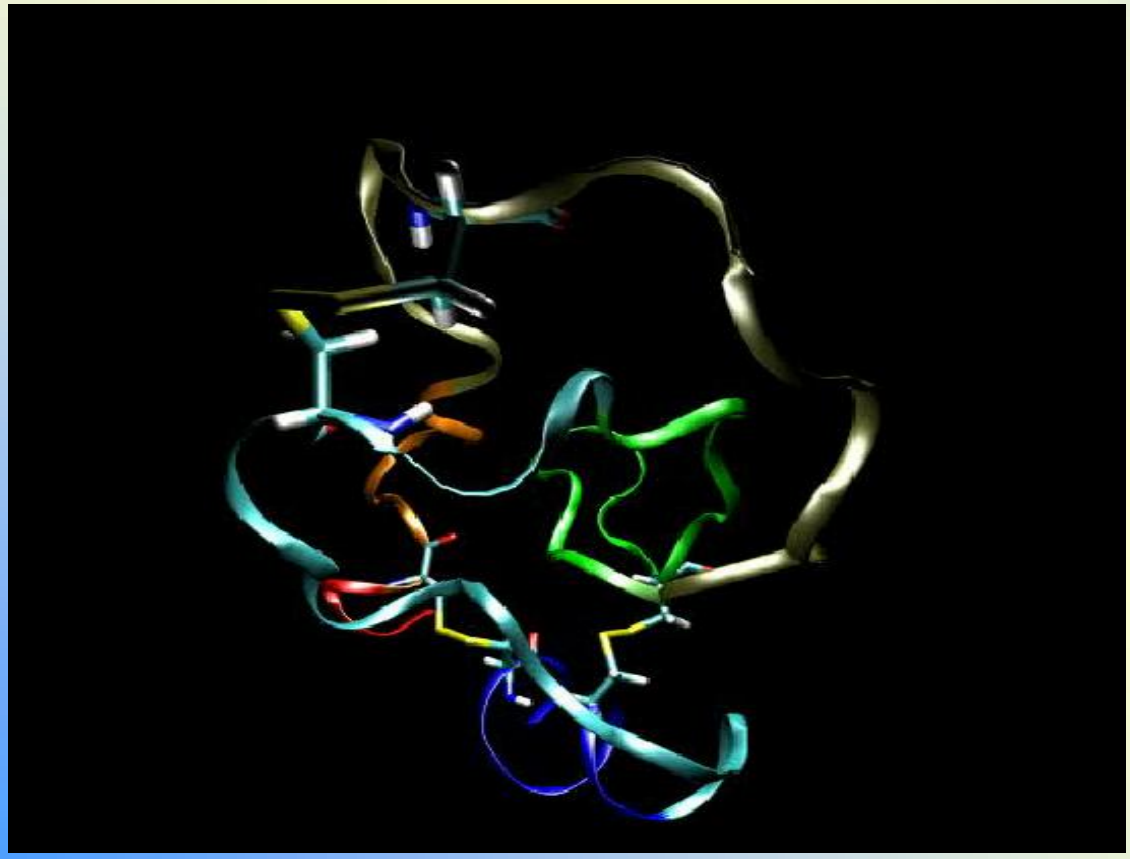
III. Electron transfer

IV. Enzymes: why are they so efficient?

- Chemical reactions - catalysis
- Photochemistry: light -> chemical energy

First Simulation of Protein Dynamics: 9.2 ps

McCammon, Gelin & Karplus, Nature 267, **1977**



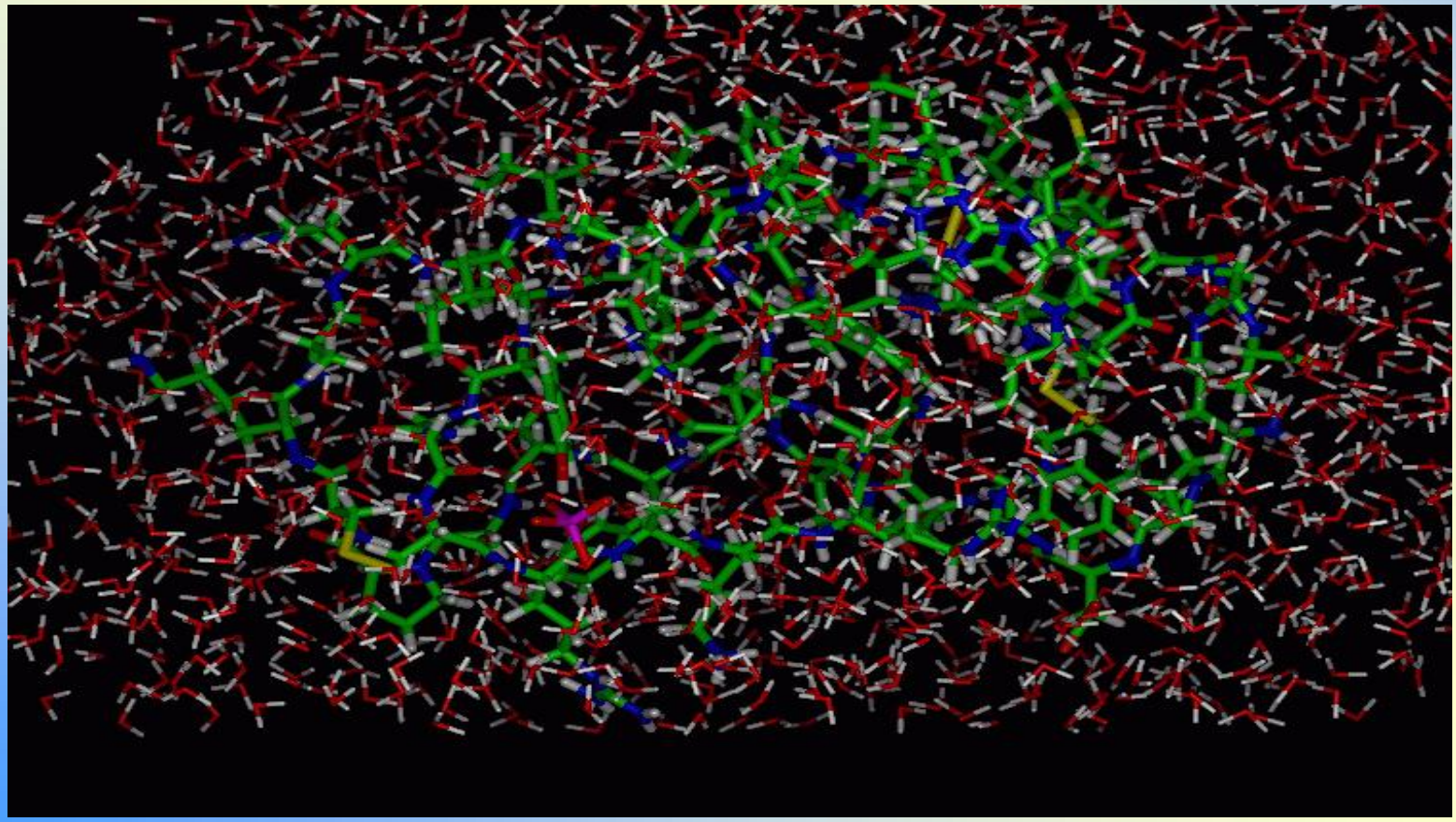
BPTI

(bovine pancreatic trypsin inhibitor)

58 AAs

BPTI + water: 210 ps

Levitt & Sharon, PNAS 85, **1988.**



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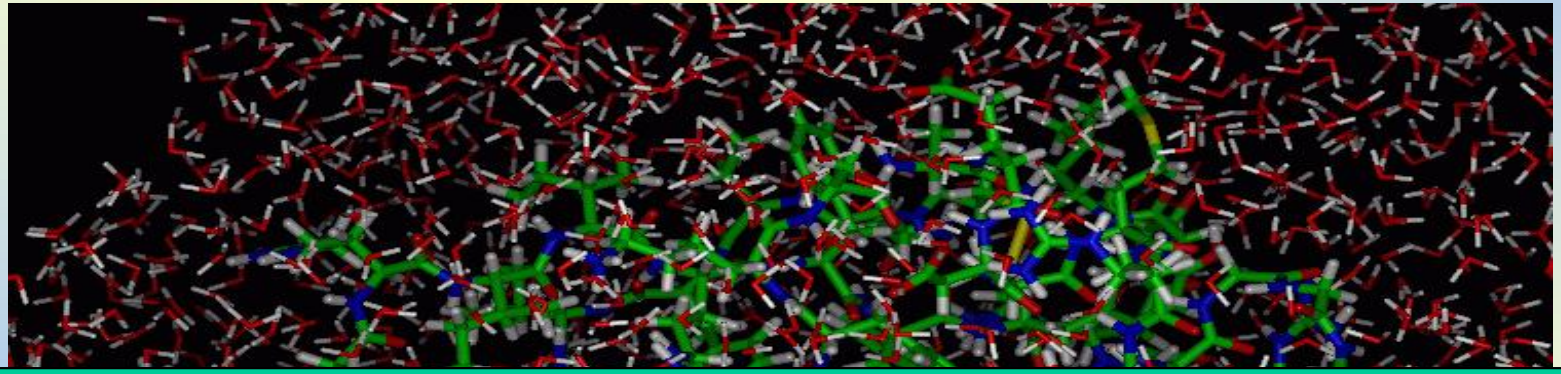

today: ~ 100,000 atoms
~ 100 ns

Timeline

1687 – Newton, equations of motion

similar – Hooke, harmonic spring

...

1946 – molecular mechanics

1950‘s – useful computers

1959 – Alder & Wainwright, MD of a fluid

1975 – **MD of a protein** – Levitt & Warshel, Gelint & Karplus

1976 – QM/MM proposed, Levitt & Warshel

1990 – significant QM/MM work, Karplus

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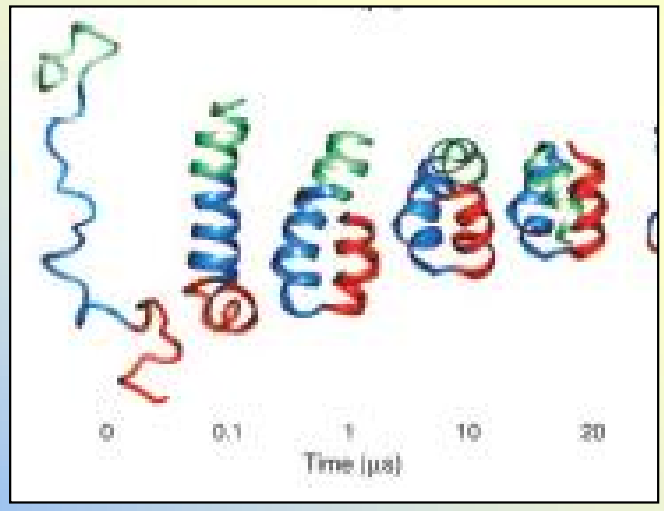
Protein Folding:
How does a protein find its native structure?



Karplus & Kuriyan, PNAS 2005

Problems:

- long times scales > μs
- accuracy of MM
- large molecular systems (solvent effects)

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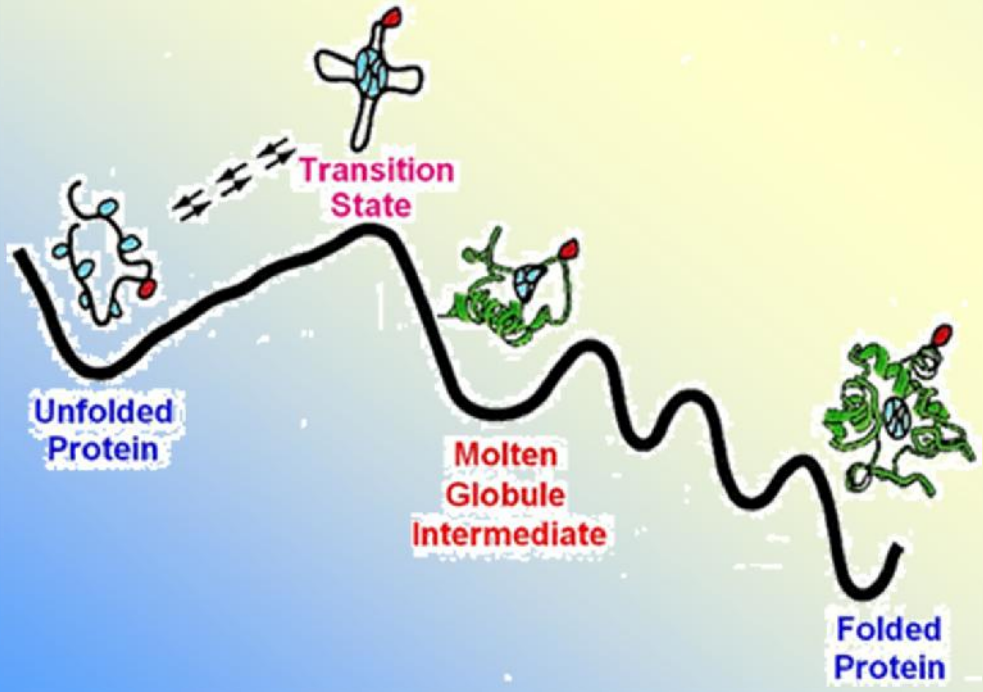
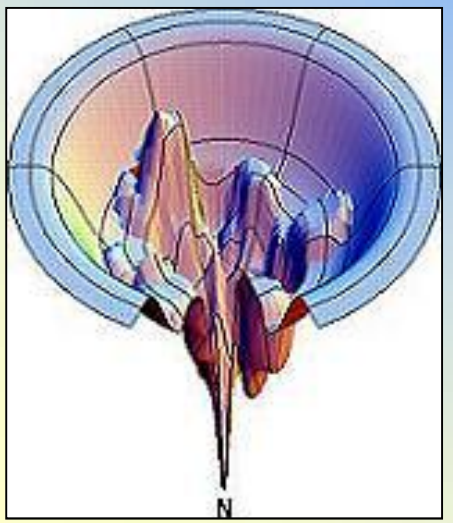
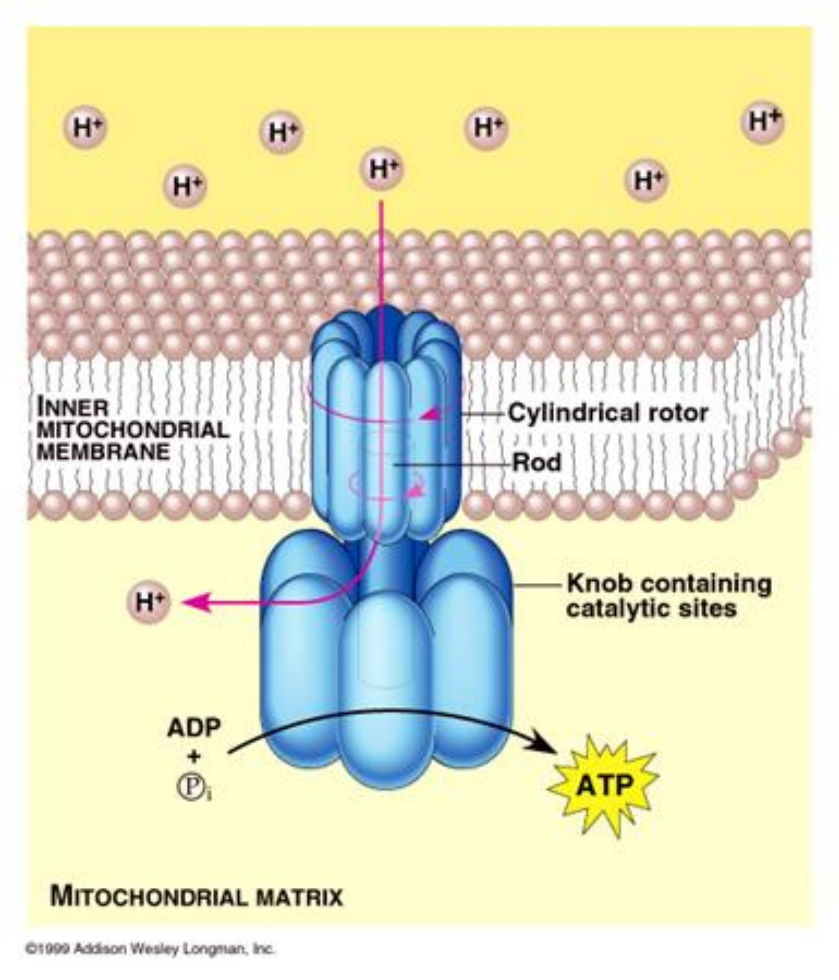
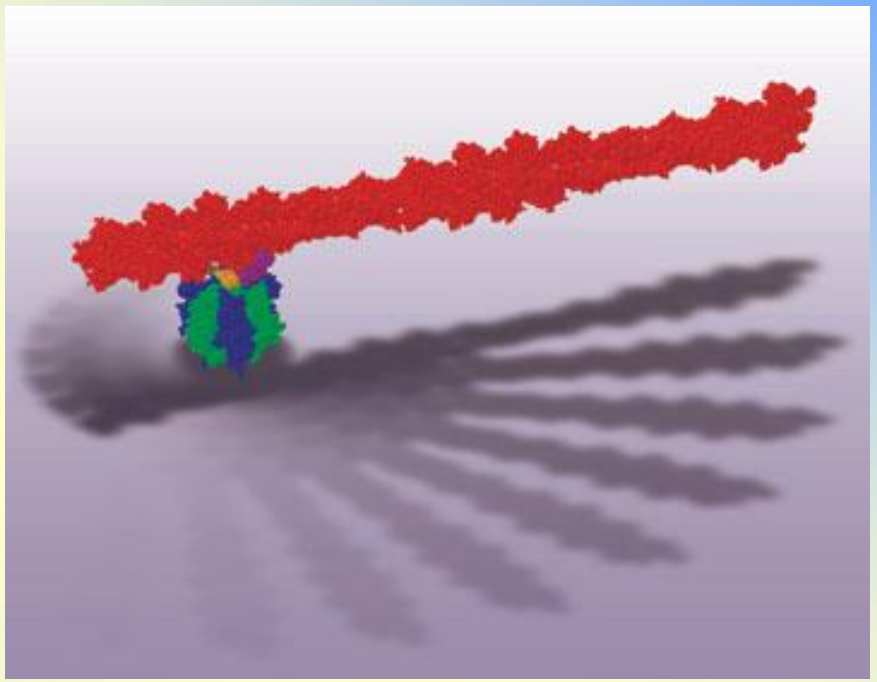




ATPase:
Conversion of chemical energy into mechanical





Rotation of the F1 subunit visualized via an actin filament

Rotation: μs–ms

Problem: Large Systems and Long Time Scales

- systems with >100,000 atoms
- duration of relevant processes > μs

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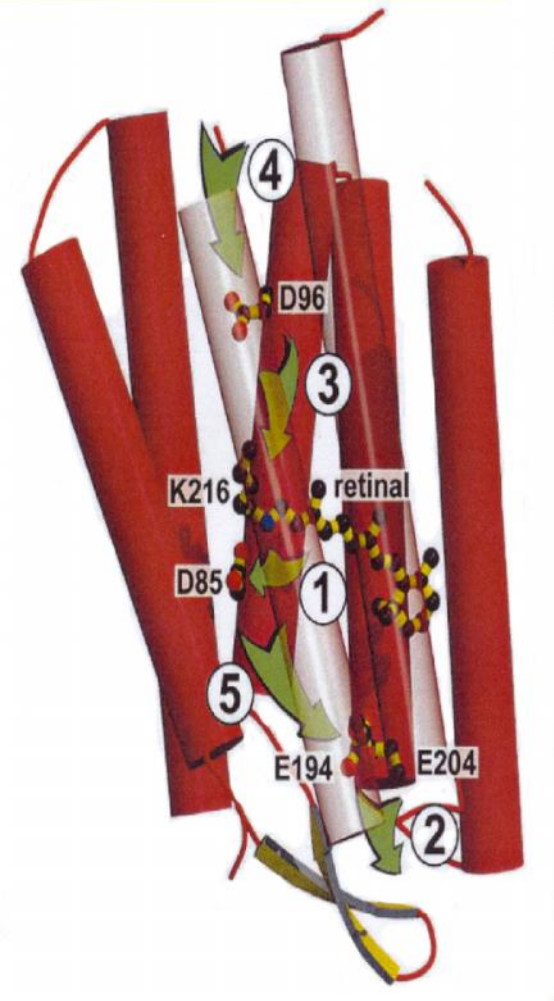
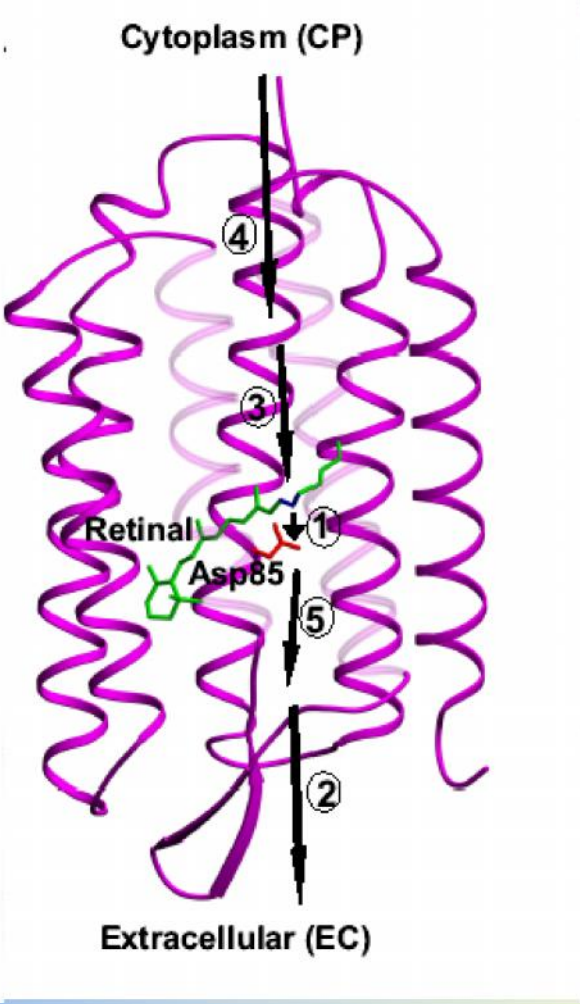
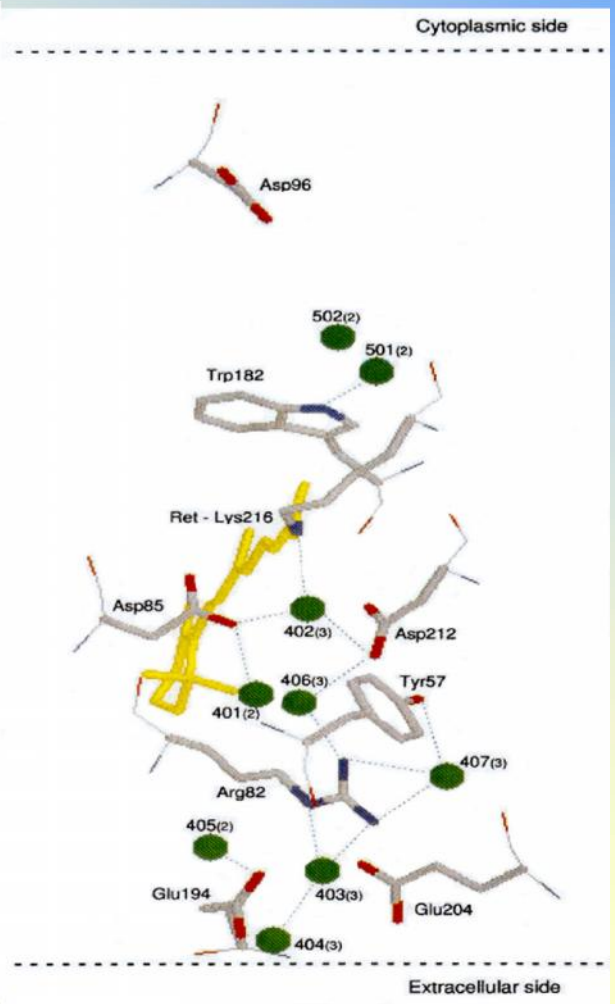
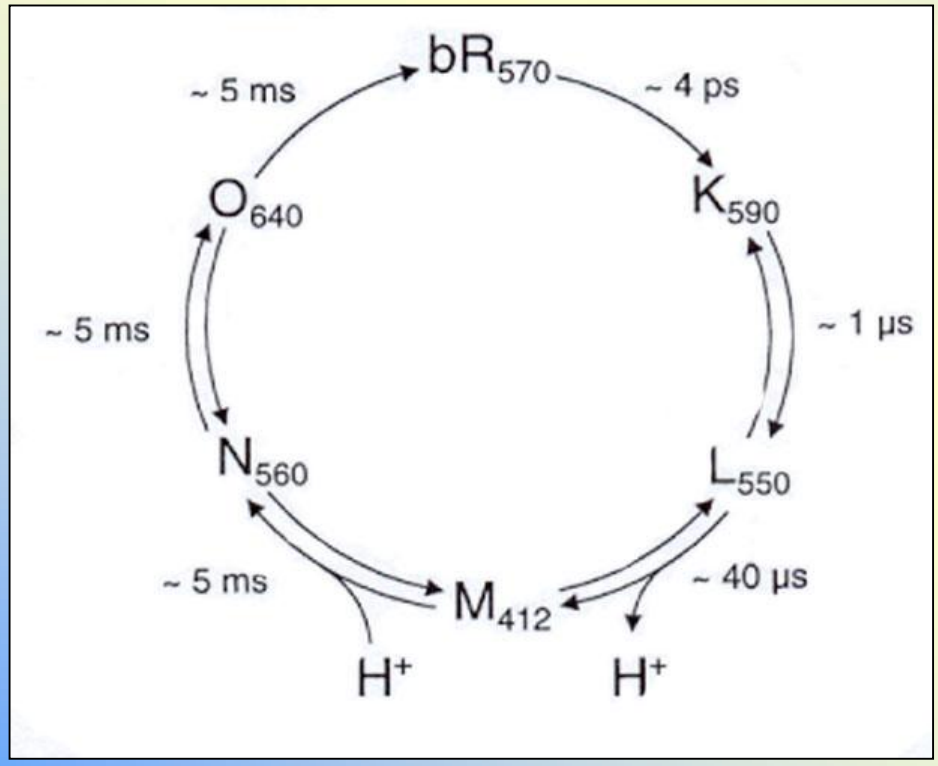
Proton transfer

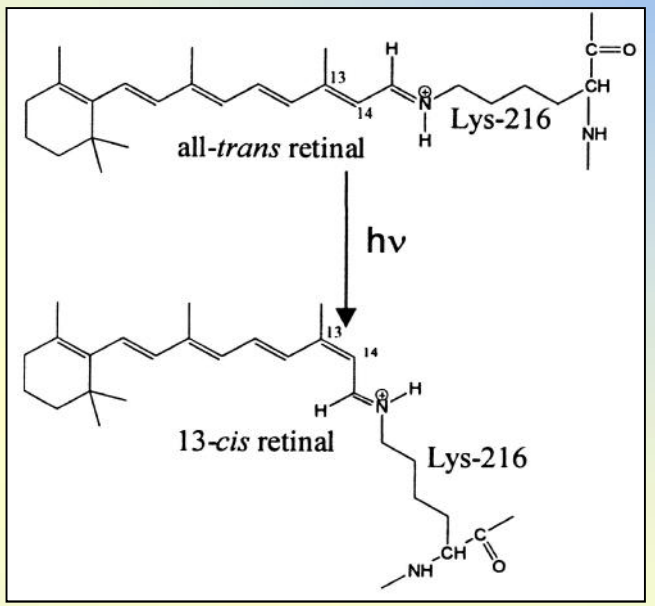






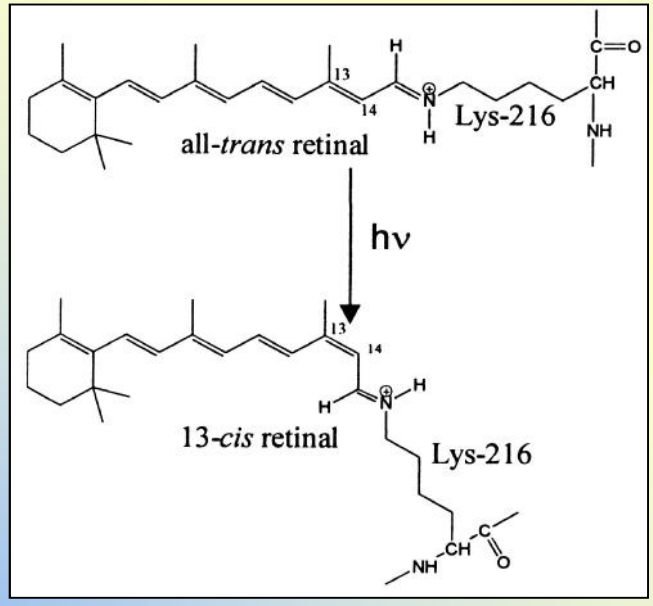
First Step: Photoisomerization

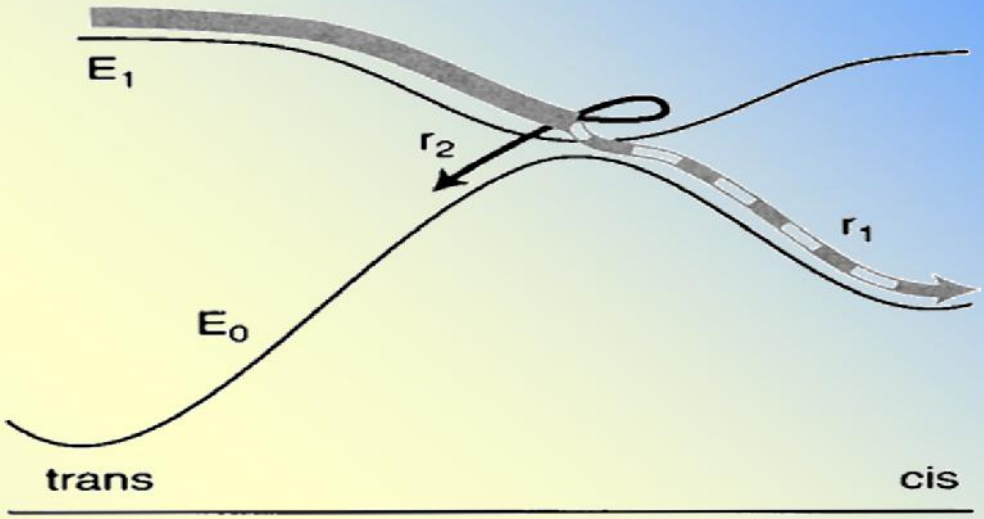




Retinal proteins:

Dynamics of an electronically excited state





- MD in an excited state
- QM/MM
- Semi-empirical treatment

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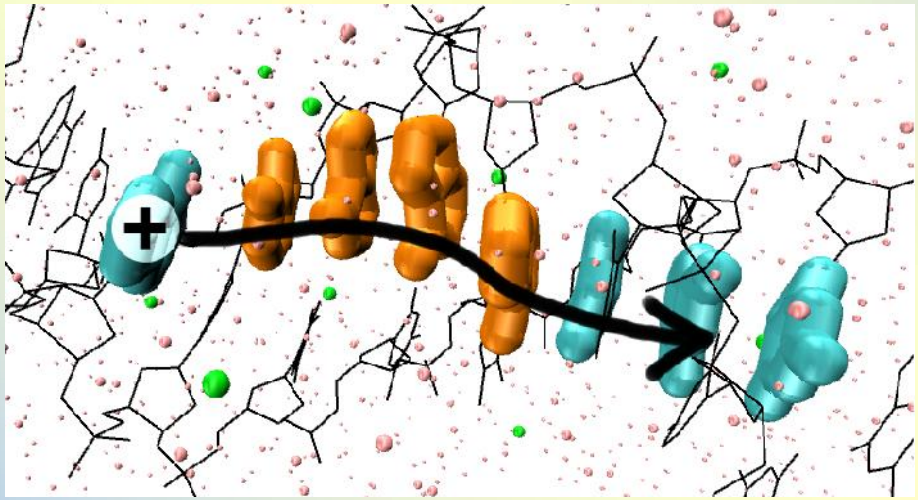
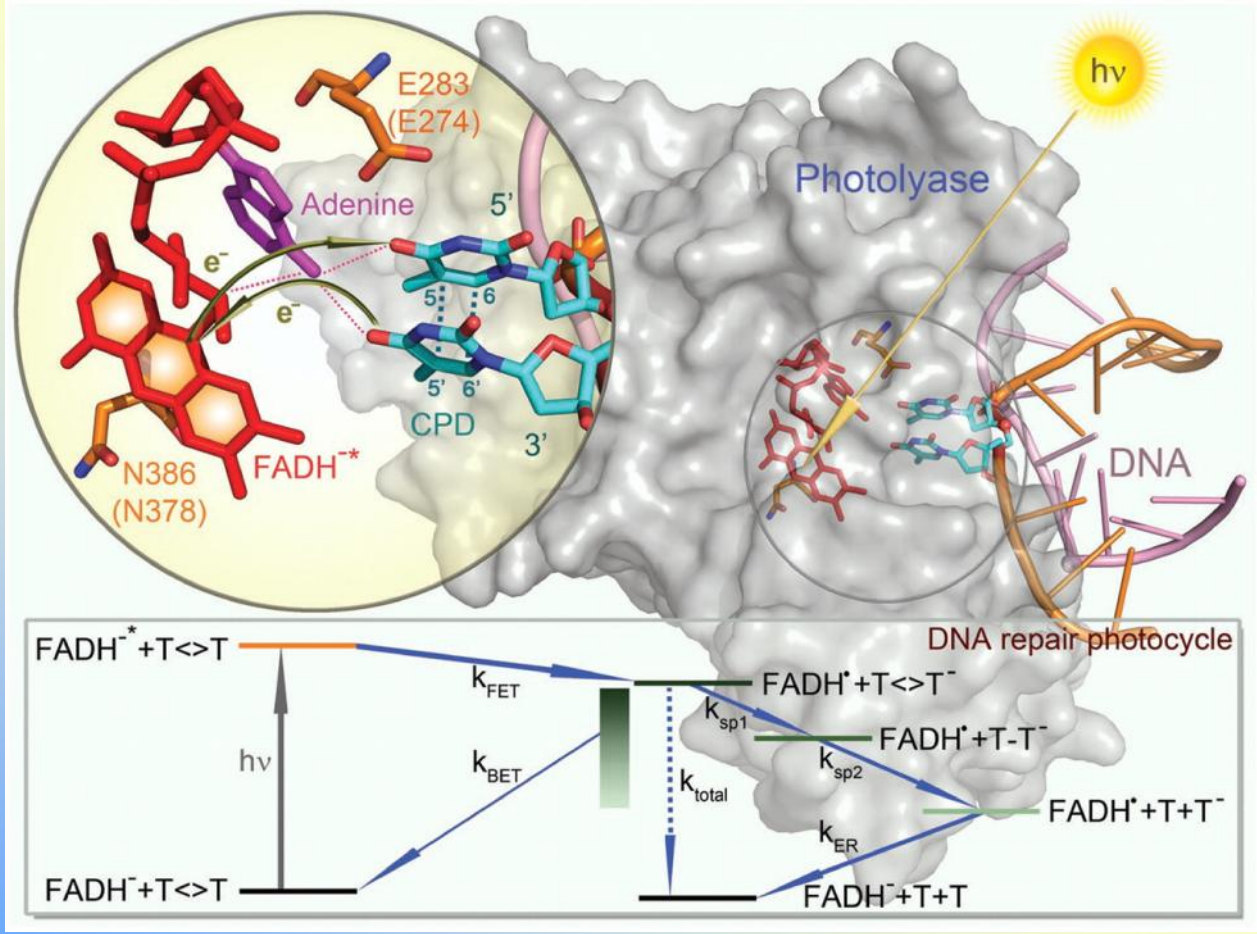
Electron transfer in DNA



Electron transfer in DNA repair



Liu Z et al. PNAS 2011;108:14831-14836

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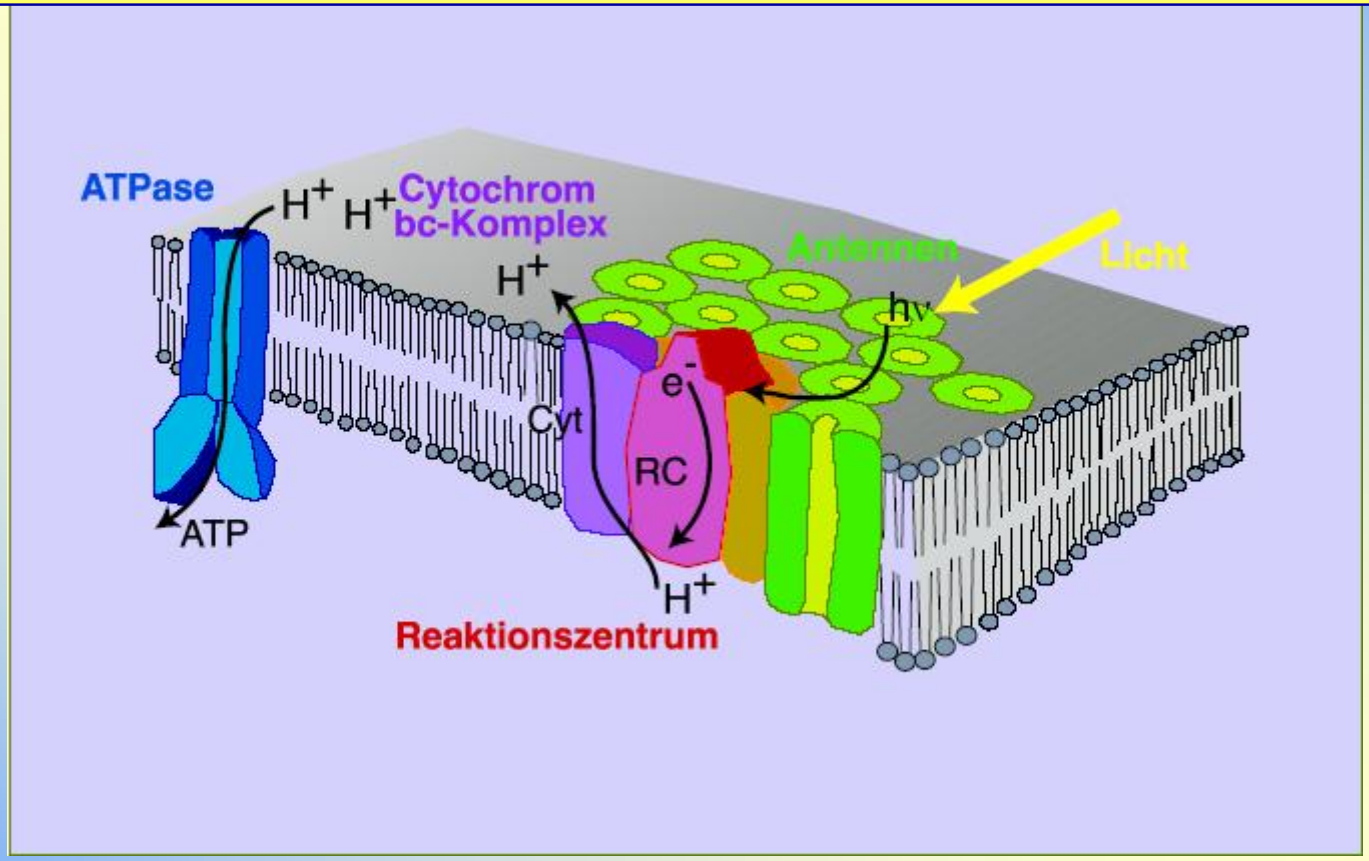
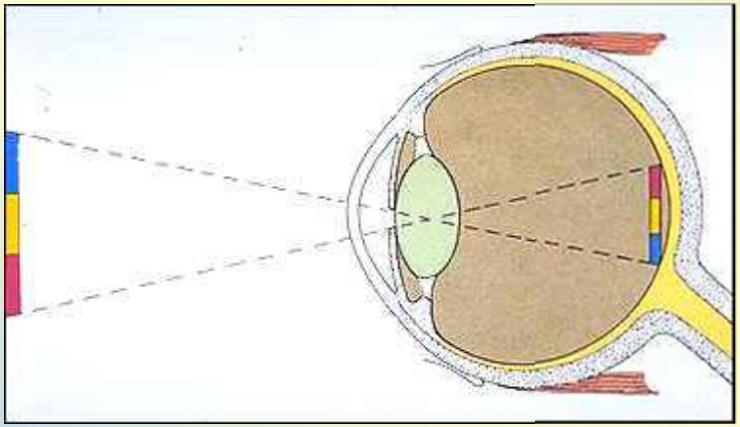
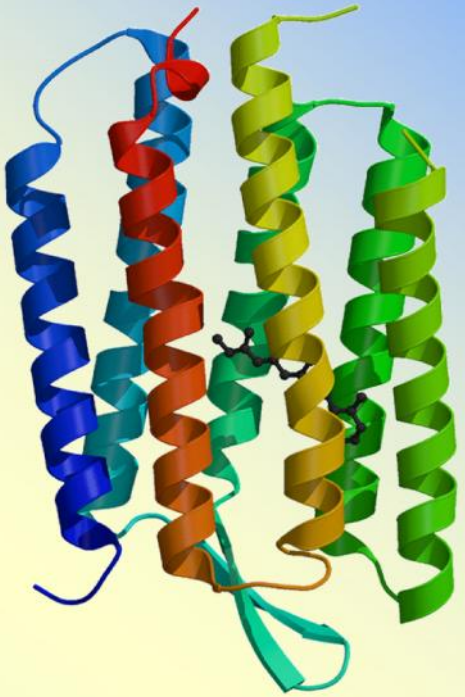
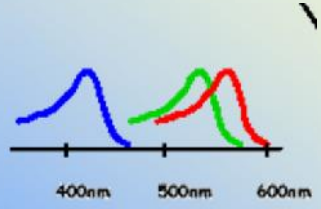
Bacterial Reaction Center

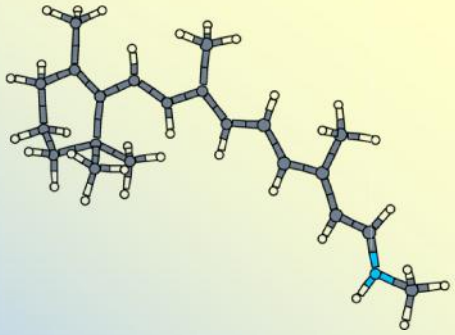


Vision









Focus: understanding on the atomic scale

the **structure** and **dynamics** determine

the **function** and **properties** of biological molecules

prediction of experimentally relevant data

molecular design of materials with desired properties

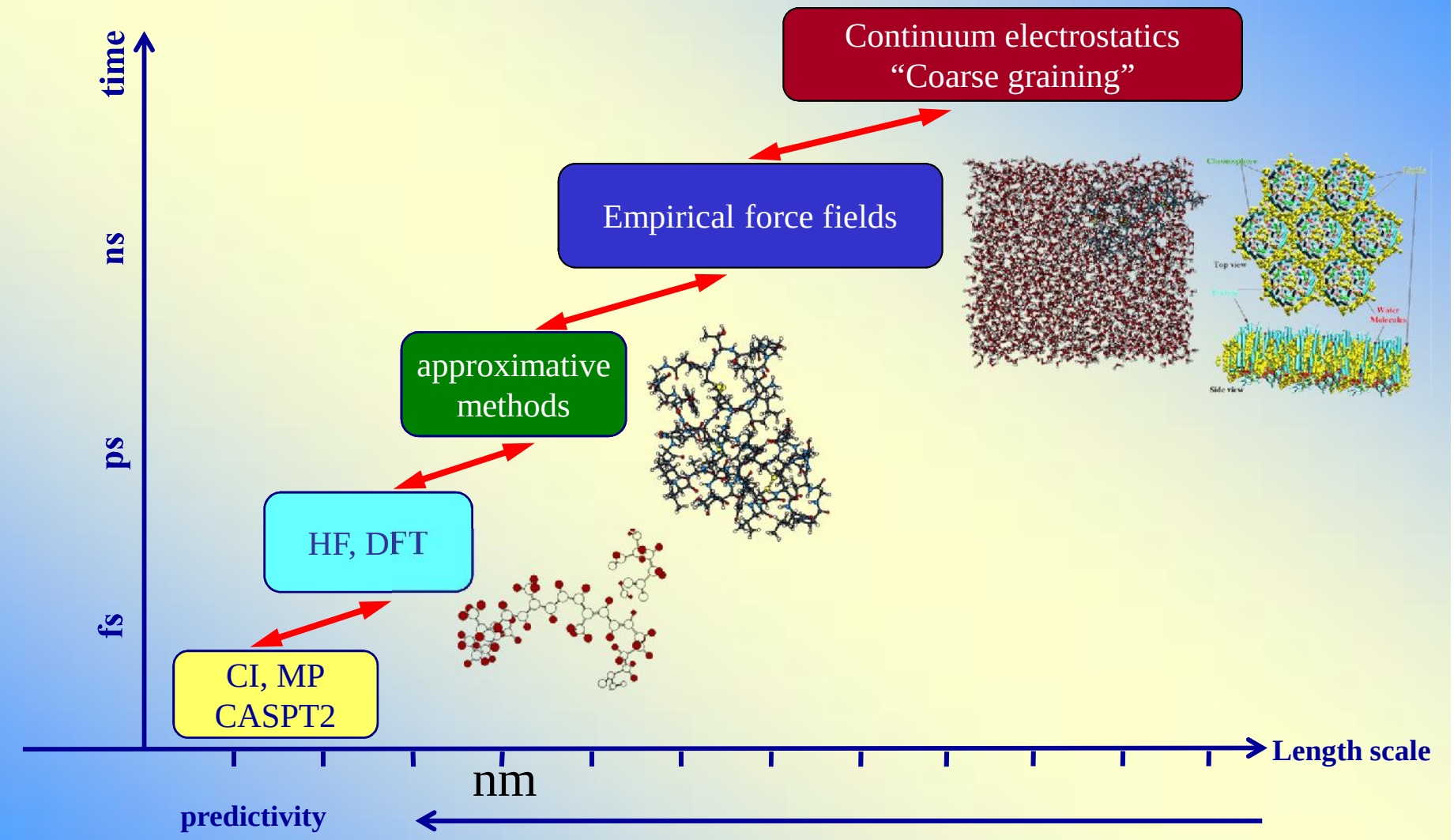
$\Downarrow$

solution of quantum mechanical many-body problem: ε_i, ψ_i

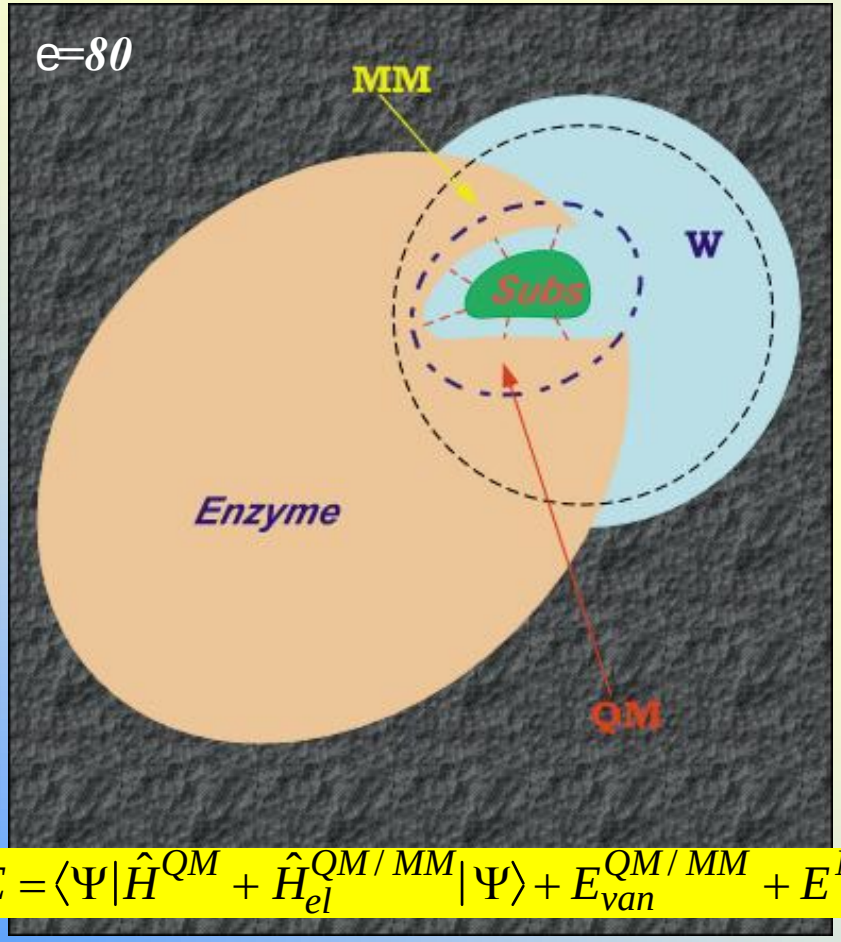
$$\hat{H}\ \Psi\left(\{\vec{x}_i\};\{\vec{R}_I\}\right) = E\ \Psi\left(\{\vec{x}_i\};\{\vec{R}_I\}\right)$$

$$\hat{H} = \hat{T}_e + \hat{T}_i + V_{ee} + V_{ie} + V_{ii}$$

Available Methods



Hybrid QM/MM



$$E = \langle \Psi | \hat{H}^{QM} + \hat{H}_{el}^{QM/MM} | \Psi \rangle + E_{van}^{QM/MM} + E^{MM}$$

Quantum mechanics (QM)

- Bonds created/broken
- Computationally costly
- DFT, AI: ~ 50 atoms
- Semi-empirical: ~100–1000

Molecular mechanics (MM)

- Efficient for up to 100,000 atoms
- Generally – structural properties

Hybrid QM/MM

- Chemical reactions
- DFT (AI) / MM: reaction paths
- Semi-empirical / MM: “Potential of mean force”, rates of reactions

Contact with Experimental Reality

$\{ \vec{R}_I(t), \vec{P}_I(t) \}$, $E_{tot}[n(\vec{r})]$, $\{ \vec{R}_I \}_{\mathrm{BZ}}$, ε_i, $\nu_i(\vec{r})$, $n(\vec{r})$, $\vec{p}$, $\vec{\vec{\sigma}}$, $\vec{j}(\vec{r})$

electronical / optical spectra

STM/AFM imaging

vibrational / IR spectra

electronic and nuclear magnetic resonance

X-ray and neutron diffraction

thermodynamic measurements

Nobel prizes for computational chemistry

1998 – for quantum chemistry
to John Pople & Walter Kohn

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"*.