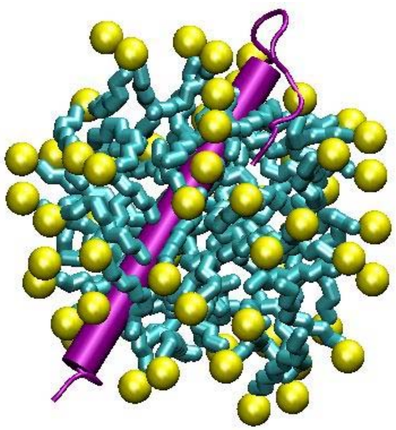
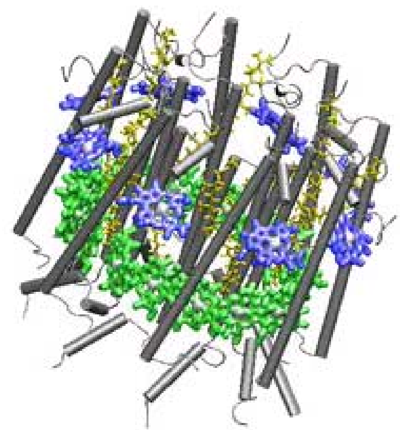
What can be learnt from MD

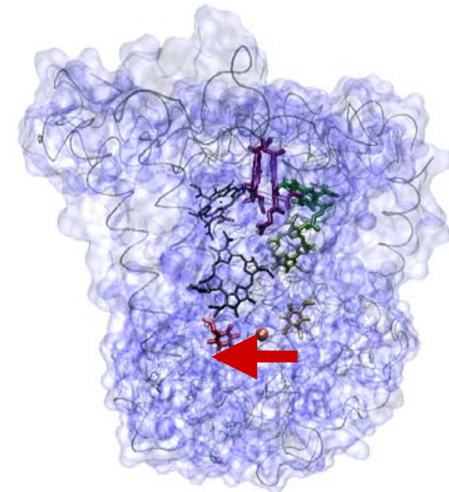
Titin

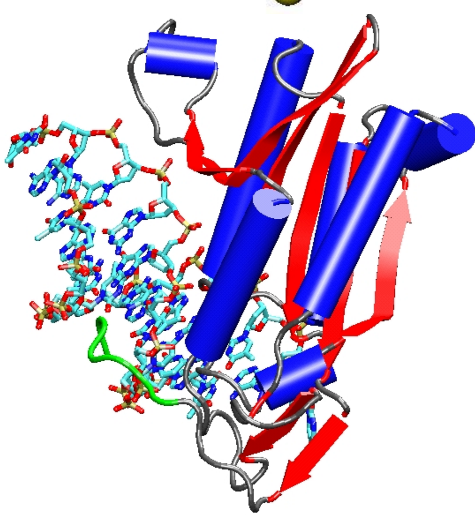
Micelle Light harvesting complex Reaction Center

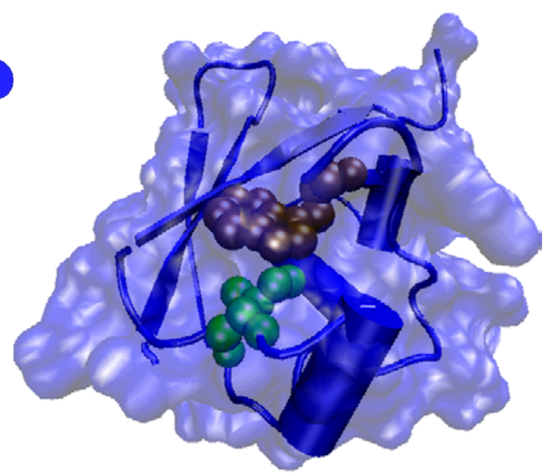
Restriction enzyme Ubiquitin Biotin - Avidin

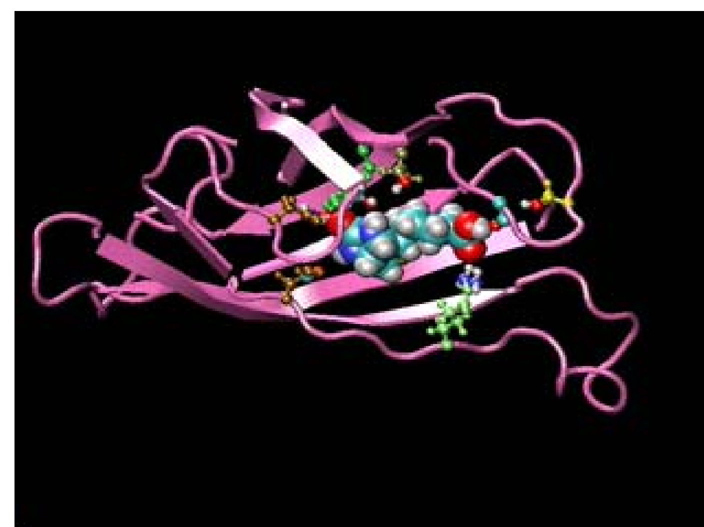




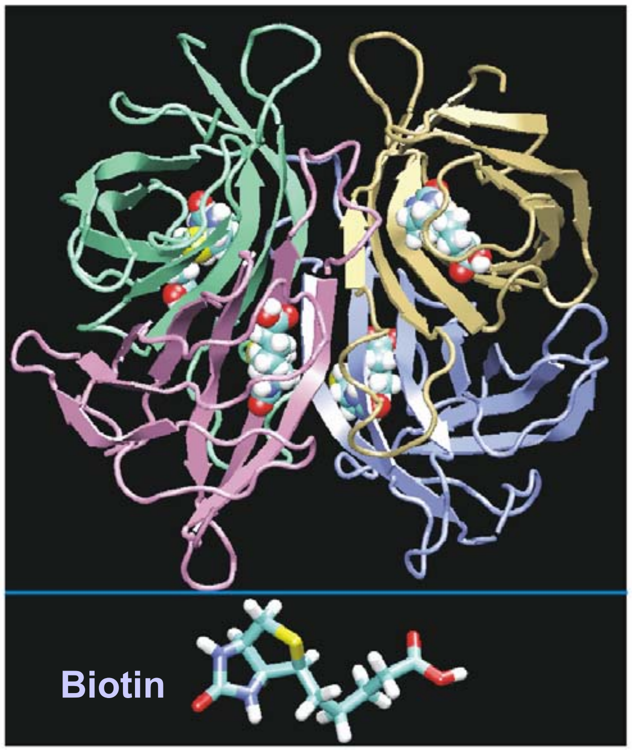


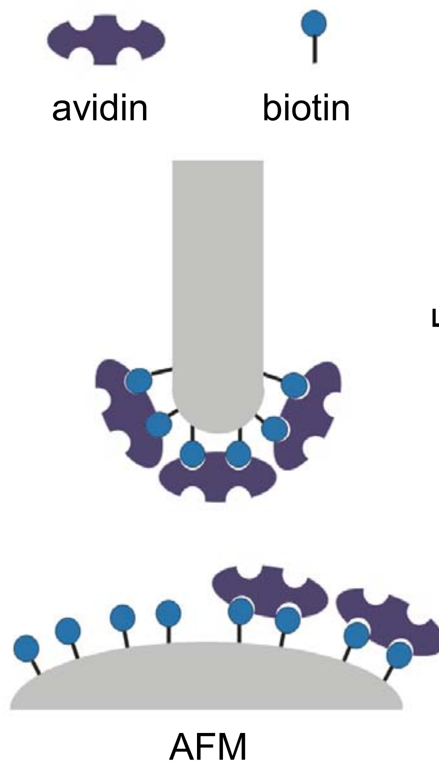




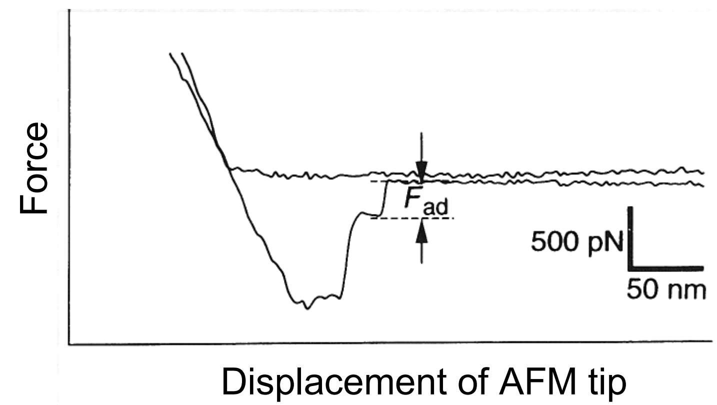


Atomic Force Microscopy Experiments of Ligand Unbinding



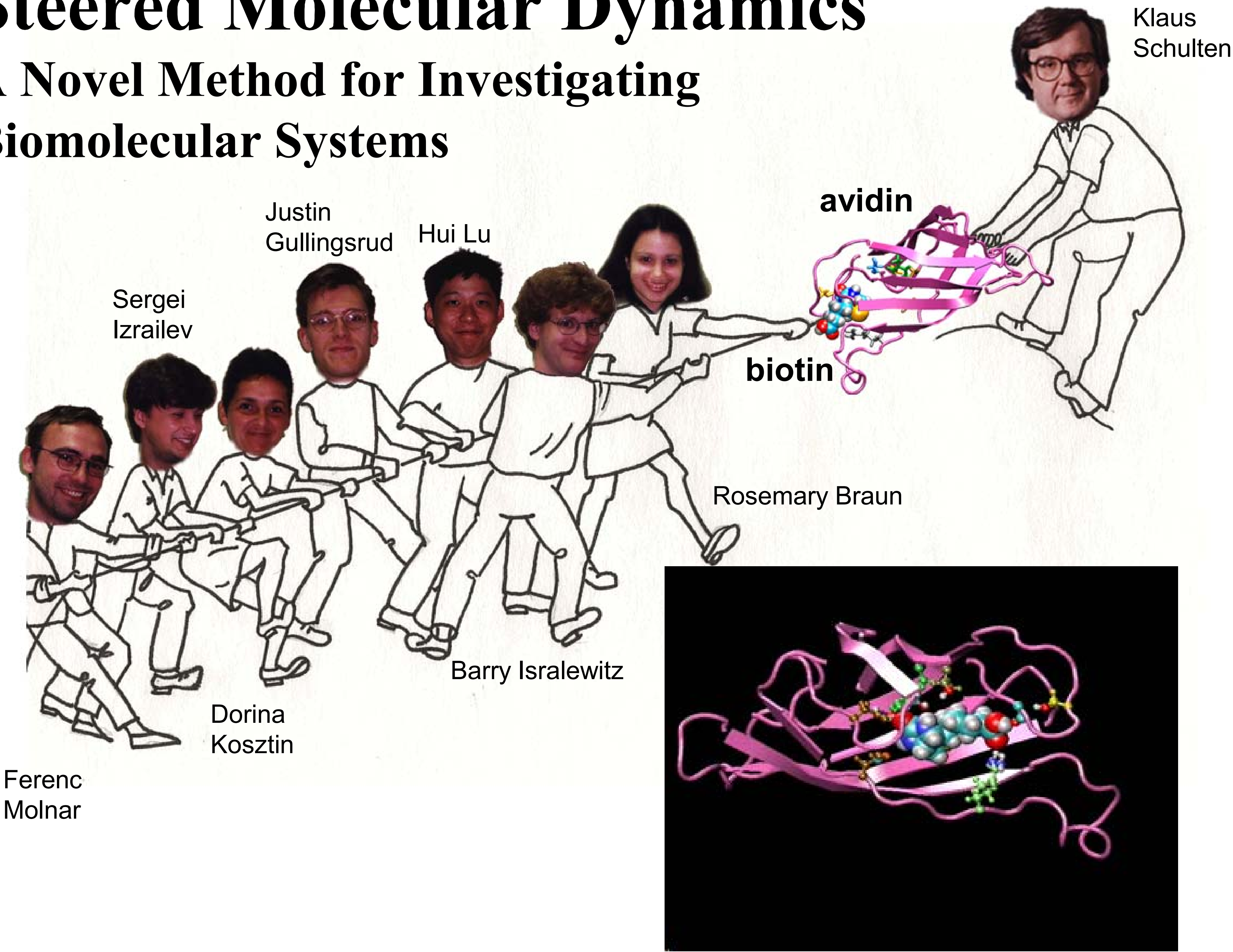


Florin et al., Science 264:415 (1994)



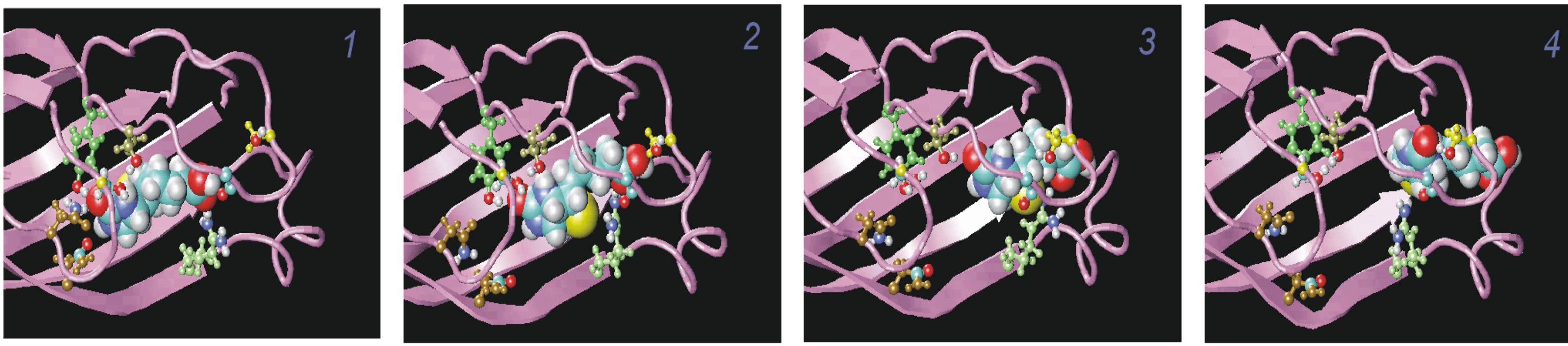
Steered Molecular Dynamics

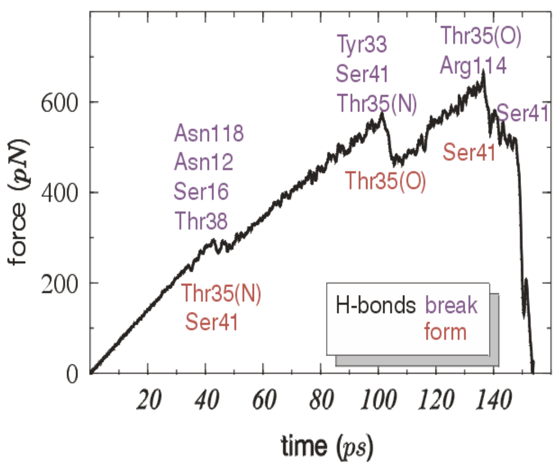
A Novel Method for Investigating Biomolecular Systems

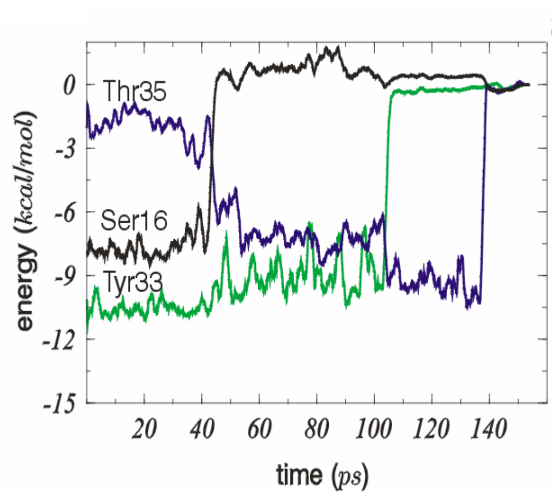


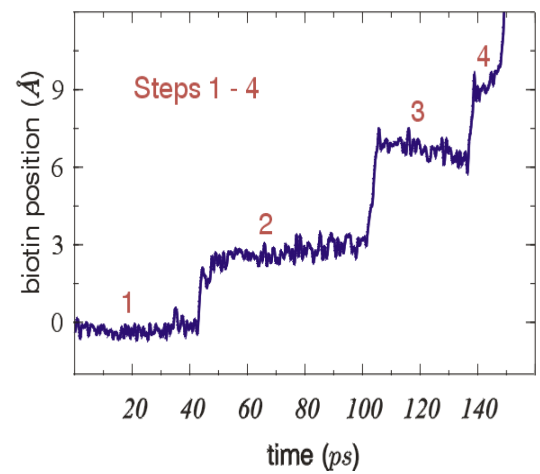
SMD of Biotin Unbinding: What We Learned

biotin slips in steps, guided by side groups, water lubricated





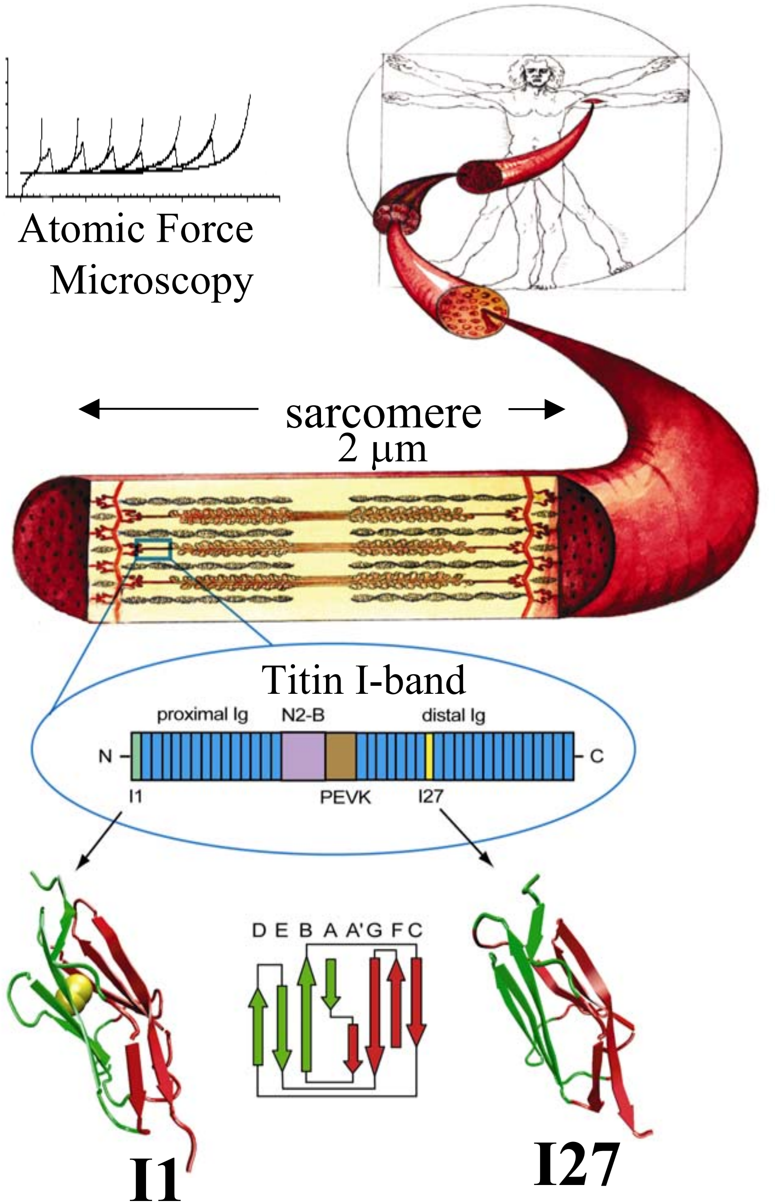


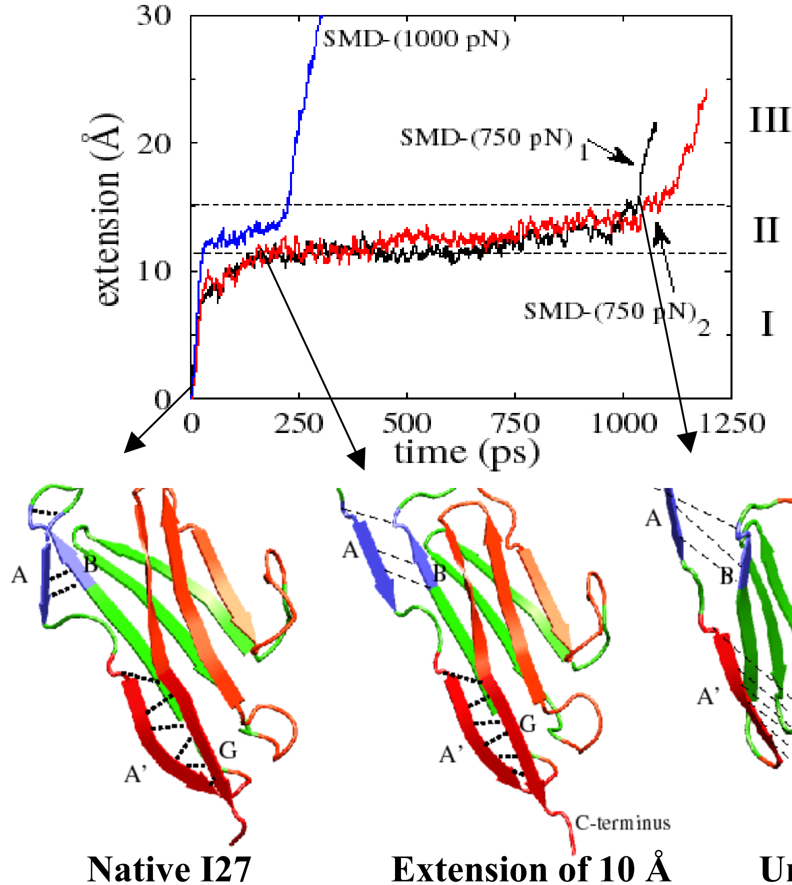


Israilev *et al*., Biophys. J., **72**, 1568-1581 (1997)

http://www.ks.uiuc.edu

Unfolding of Titin Ig Domains





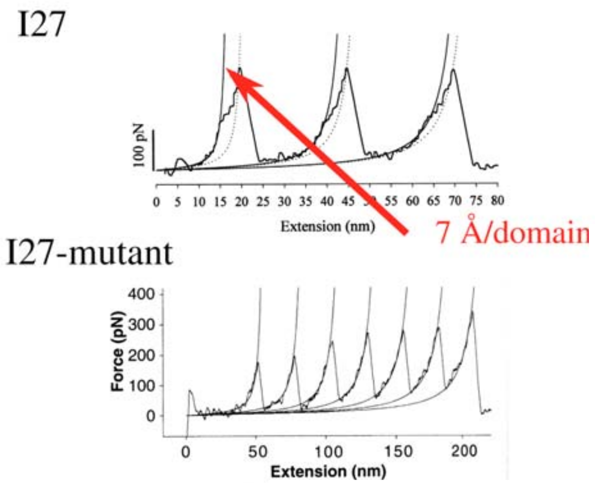
Collaboration with **J. Fernandez** *Mayo Clinic*

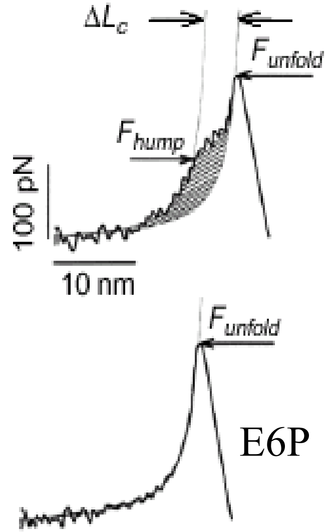
H. Lu, B. Isralewitz, A. Krammer, V. Vogel, and K. Schulten, *Biophys. J.*, **75**, 662-671 (1998)

P. Marszalek, H. Lu, H. Li, M. Carrion-Vazquez, A. Oberhauser, K. Schulten, and J. Fernandez, *Nature*, **402**, 100-103 (1999)

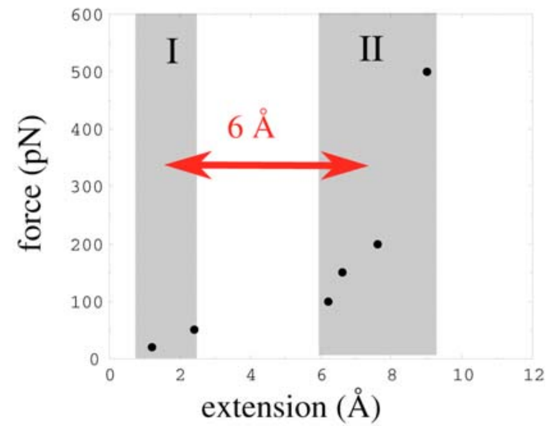
Titin Ig Mechanical Unfolding Intermediate

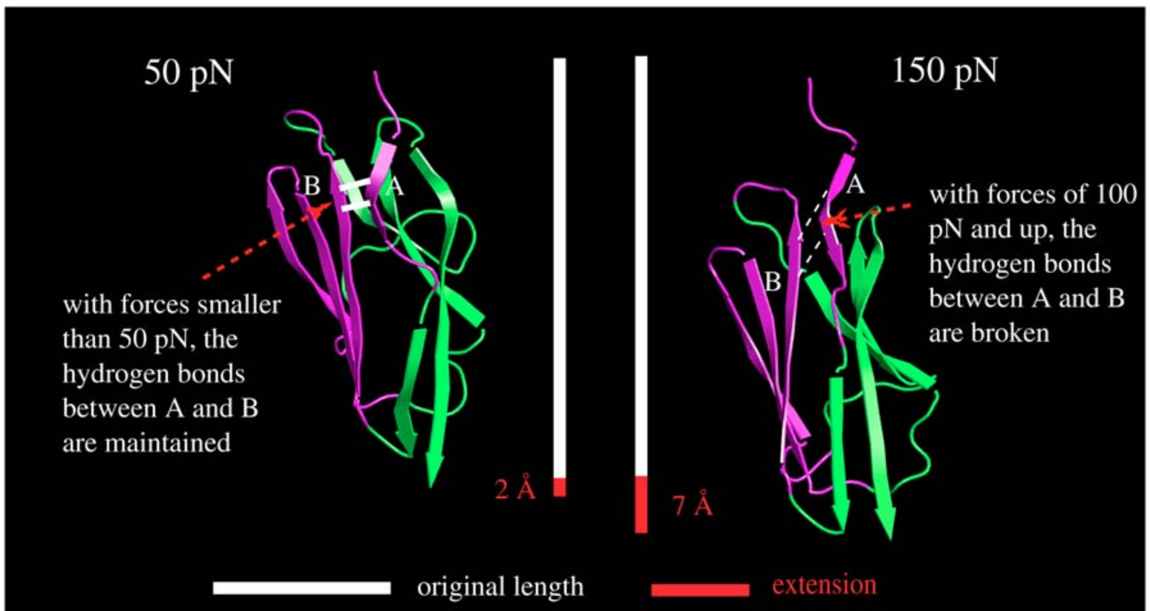
AFM force-extension profile





SMD simulations with constant forces





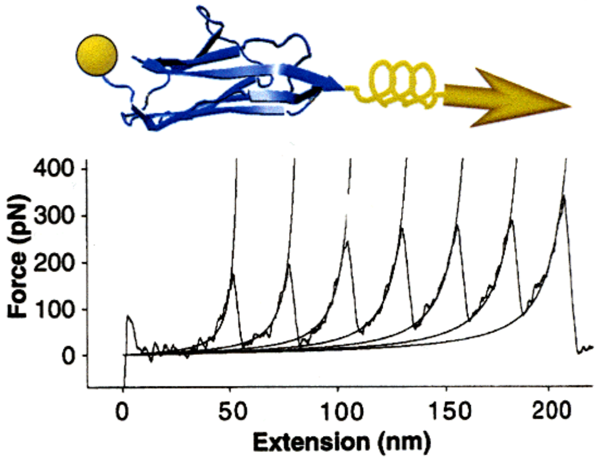
Marszalek, Lu, Li, Carrion, Oberhauser, Schulten, and Fernandez, Nature, **402**, 100 (1999).

Hui Lu

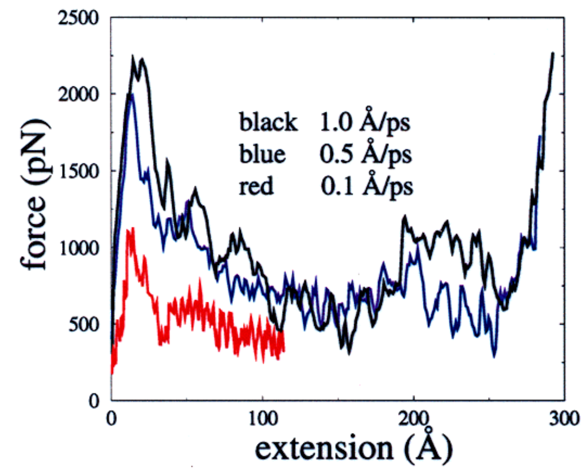
Quantitative Comparison

Bridging the gap between SMD and AFM experiments

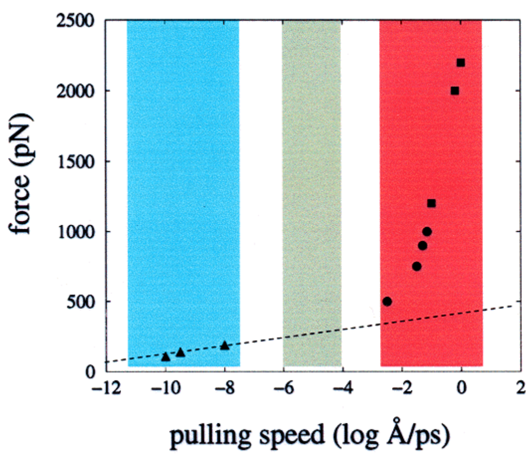
Steered Molecular Dynamics (SMD)



Force-extension curve



Force-pulling velocity relationship



AFM range

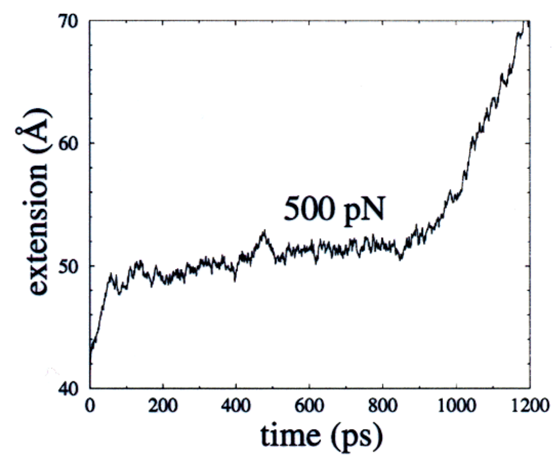
Current SMD range

Target simulation range

▲ AFM data

■ ● SMD data

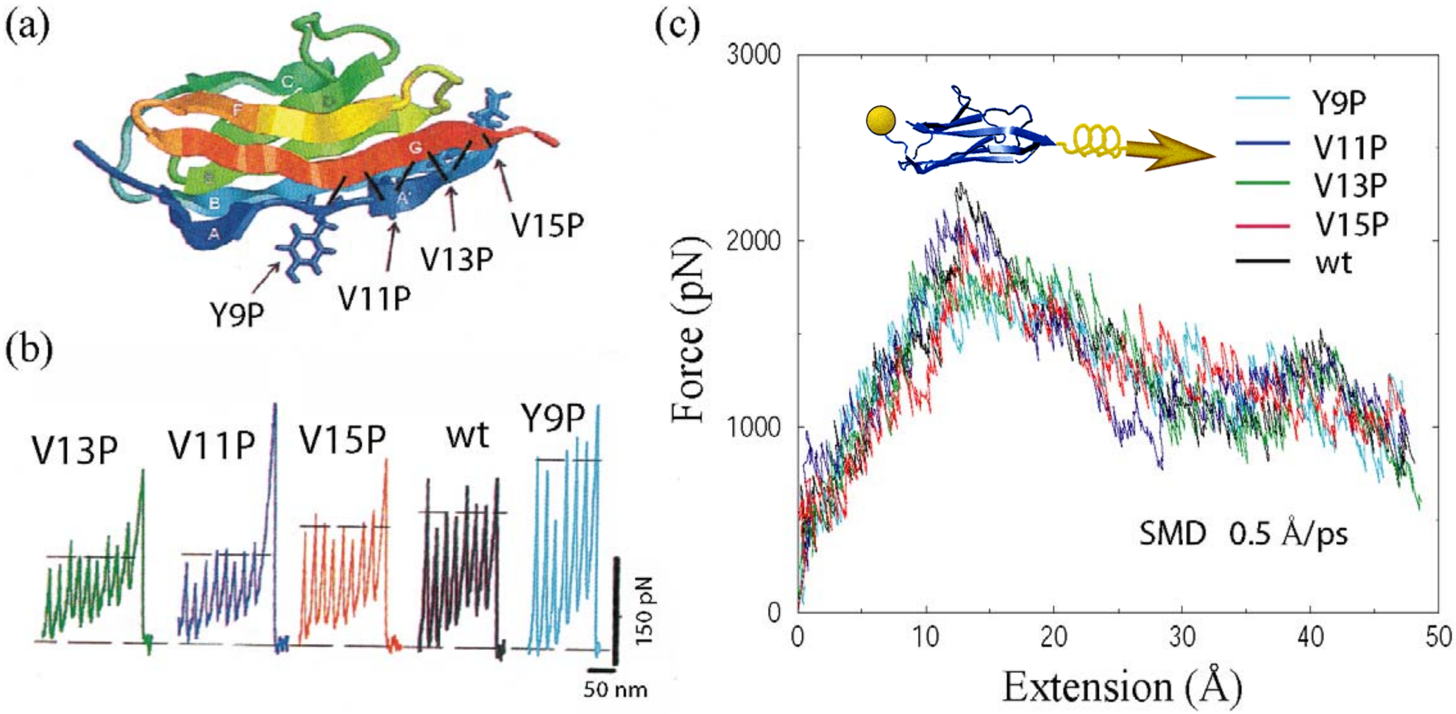
------ Extrapolation of AFM data



Extension curve

Hui Lu, Barry Isralewitz

Mechanical Stability of I27 Mutants

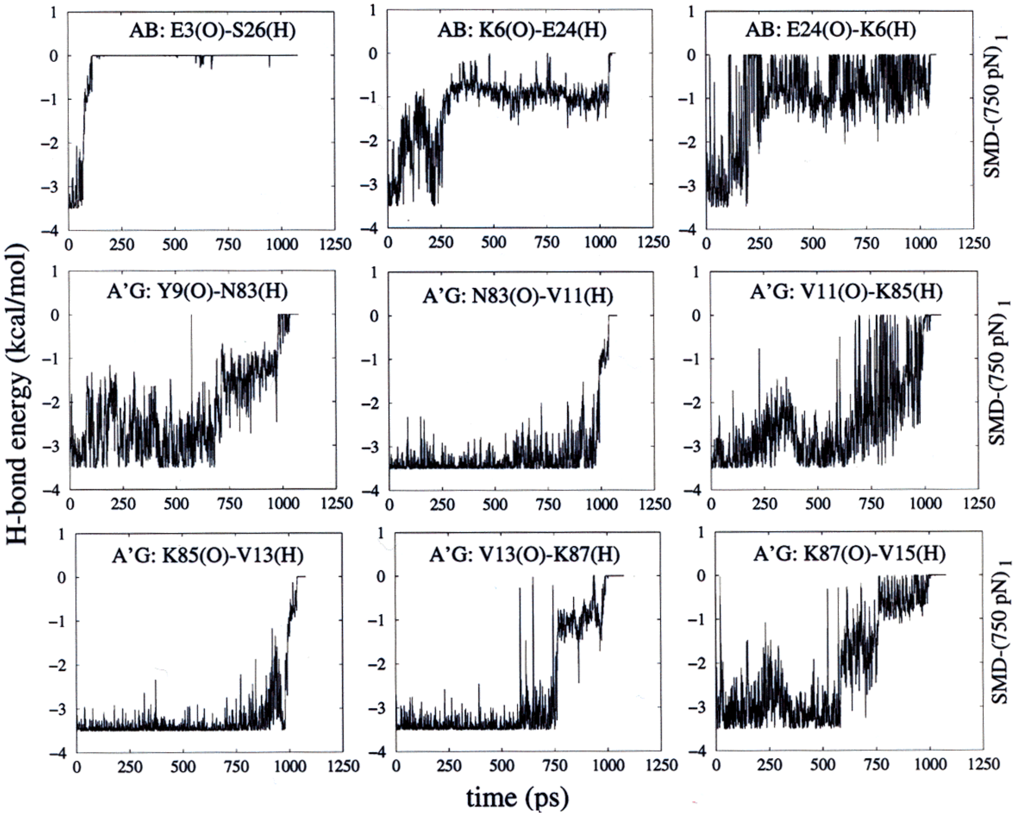


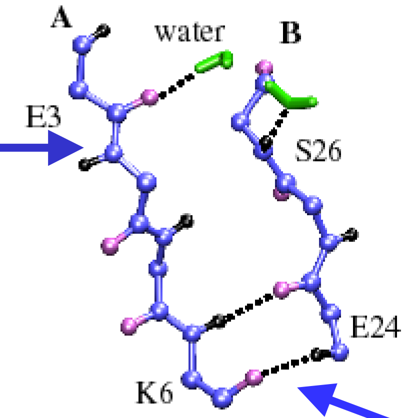
Point mutations of titin modules have the potential for disrupting the finely tuned elasticity of titin

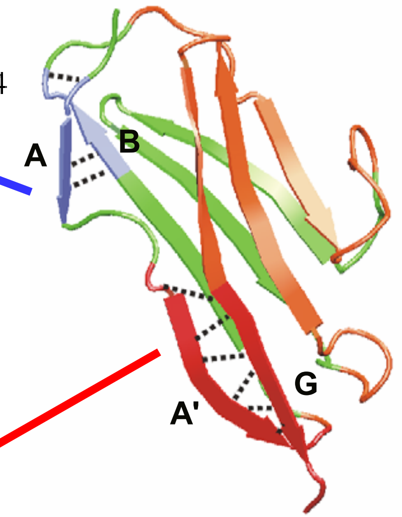
Li *et al*. *Nature Struct. Biol.* **7**:1117-1120 (2001)

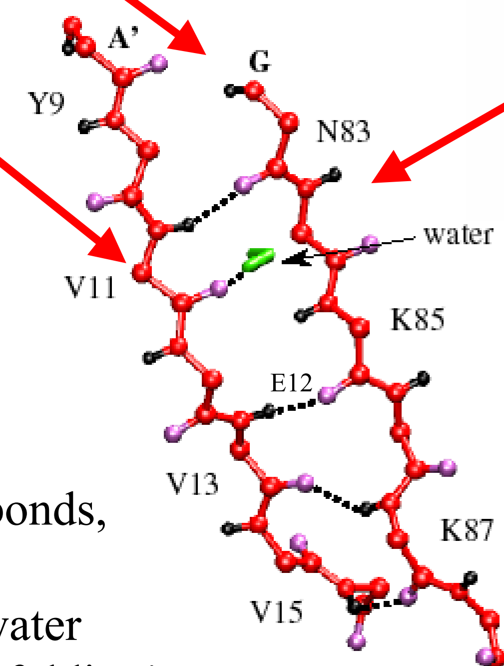
Hui Lu, Mu Gao

Water-Backbone Interactions Control Unfolding

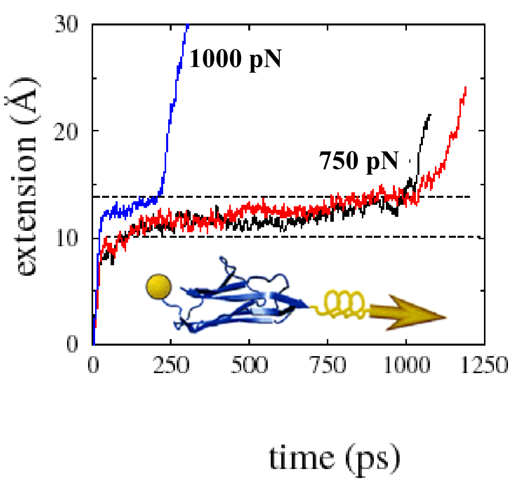








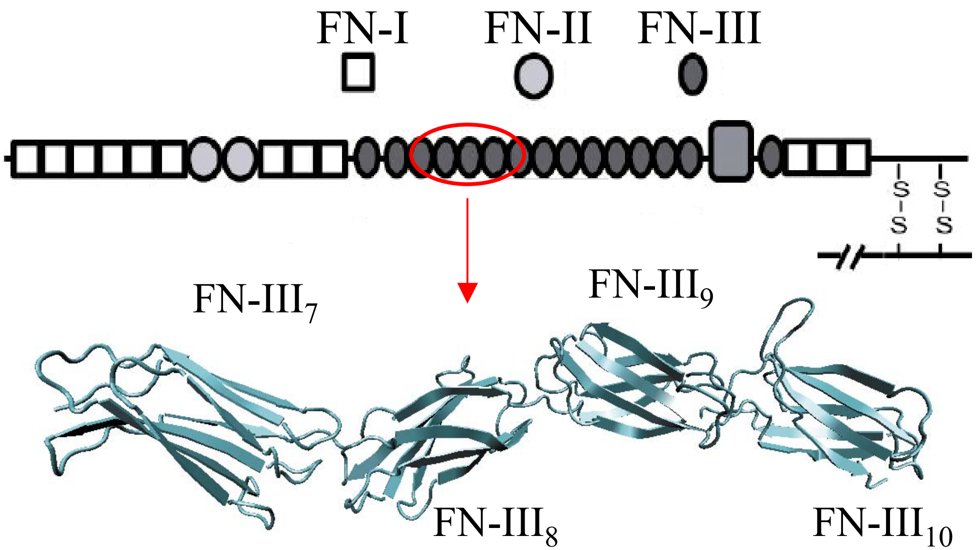
water greases protein folding !

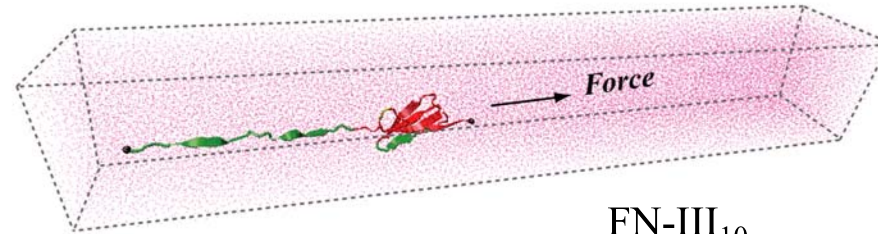


During stretching, water molecules attack repeatedly interstrand hydrogen bonds, about 100 times / ns; for forces of 750 pN water fluctuation controls unfolding!

Hui Lu and Klaus Schulten, Biophys J.79: 51-65 (2000)

Stretching Fibronectin Modules

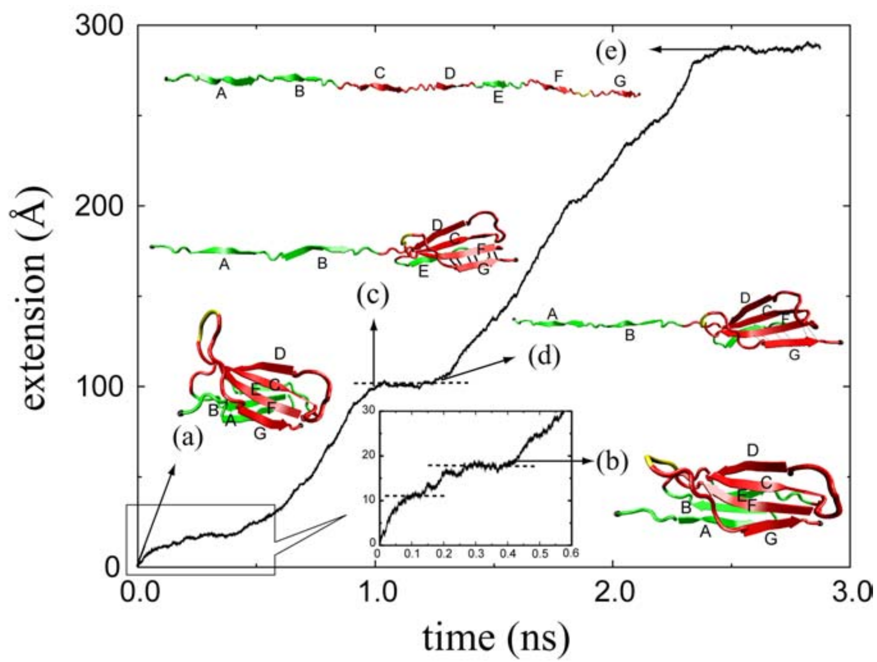




FN-III$_{10}$

(55×60×367 Å^3, **126,082 atoms**)

Atomic Force Microscopy
Flourescence Resonance Energy Transfer



A. Krammer, H. Lu, B. Isralewitz, K. Schulten, and V. Vogel, *Proc. Natl. Acad. Sci. USA*, **96**, 1351-1356 (1999) *11,000 atoms*

D. Craig, A. Krammer, K. Schulten, and V. Vogel, *Proc. Natl. Acad. Sci. USA*, **98**, 5590-5595 (2001) *11,000 atoms*

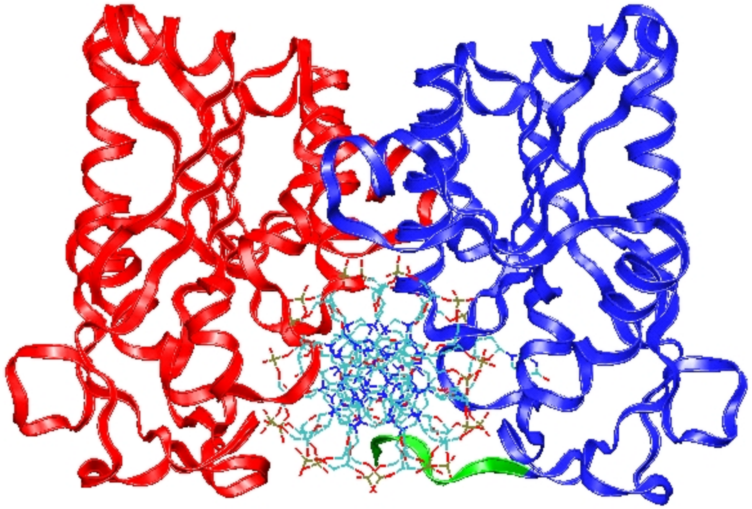
A. Krammer, D. Craig, W. Thomas, K. Schulten, and V. Vogel. *Matrix Biology*, **21**, 139-147 (2002) *100,000 atoms*

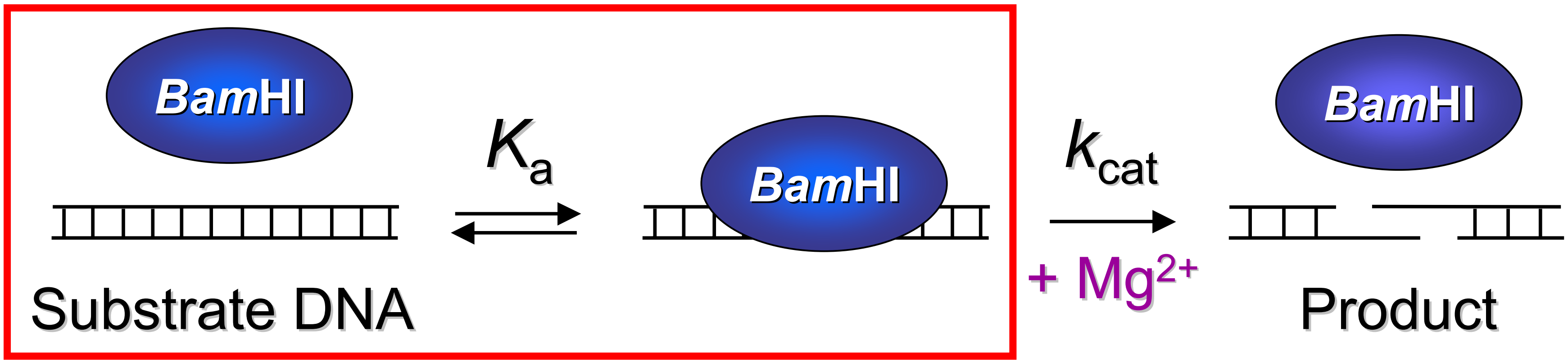
Collaboration with
V. Vogel, U. Wash
University of Washington

Type II Restriction Endonuclease - *Bam*HI

213 a.a./monomer
Binds the recognition sequence:
5'-G'GATCC-3'

Newman, M. *et al*. (1995)
Science **269**, 656-663

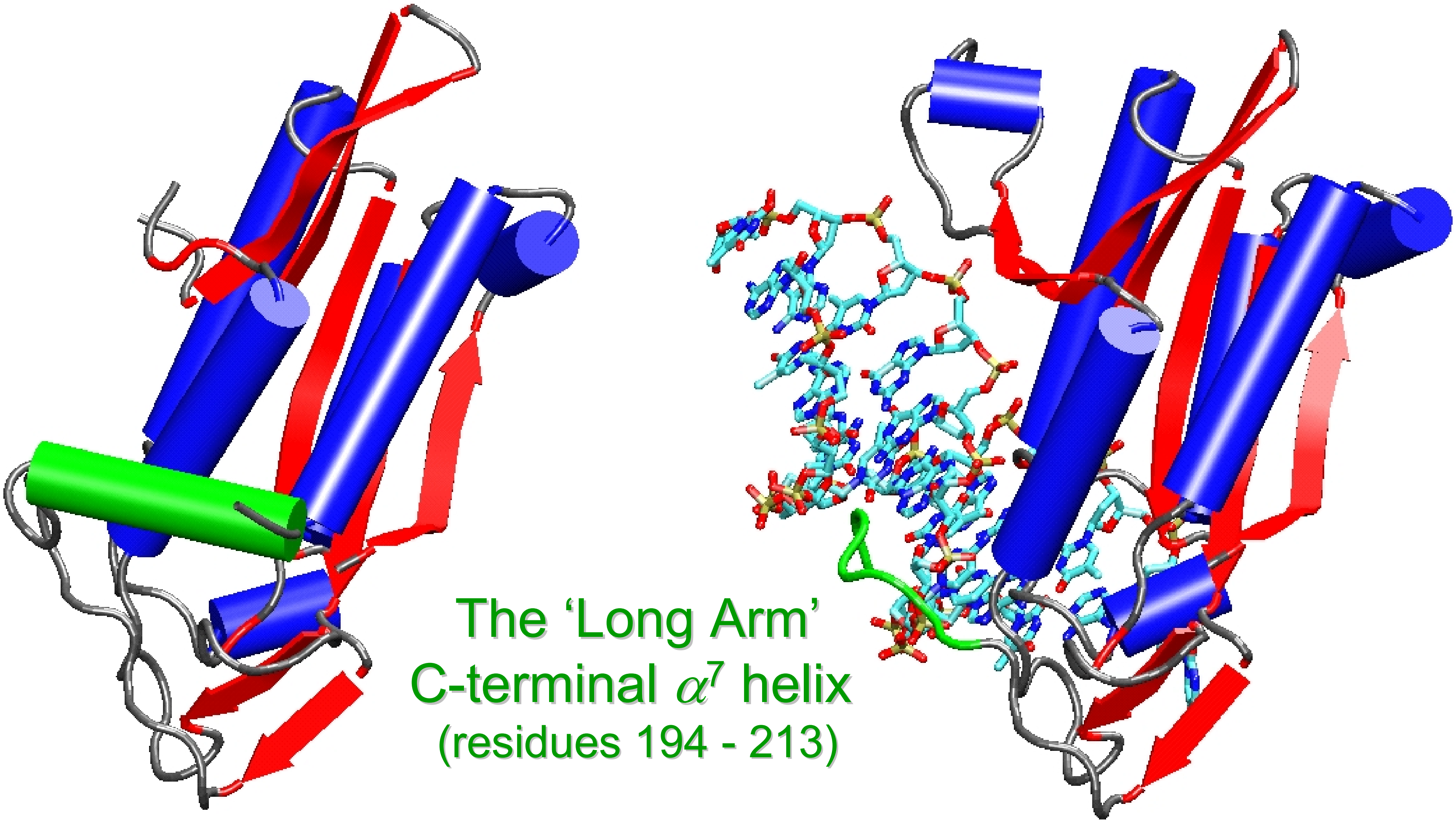




Cognate DNA : K_d ~ 600 pM

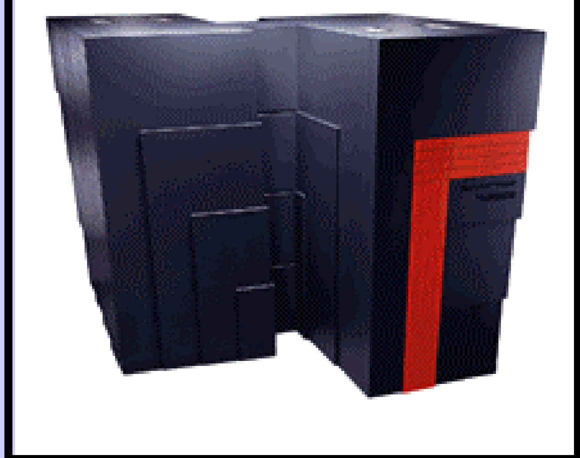
Substrate Free

Specific Complex



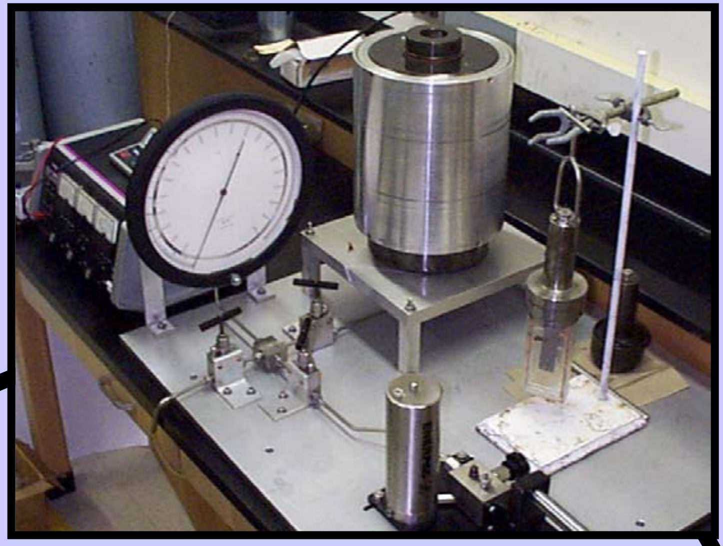
Newman, M. *et al*. (1994) *Structure* **2**, 439-452
Newman, M. *et al*. (1995) *Science* **269**, 656-663

Cray T3E



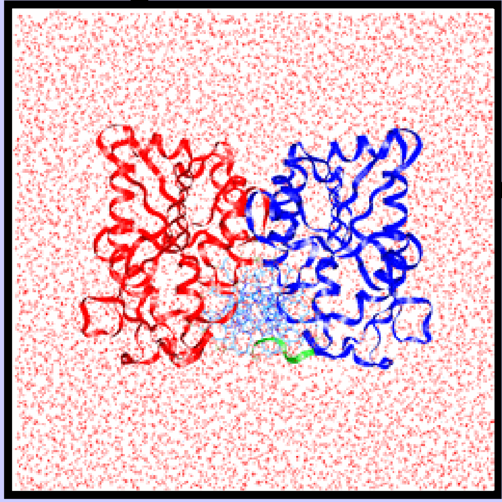
Th. Lynch,
S. Sligar,
D. Kosztin

High pressure gel electrophoresis

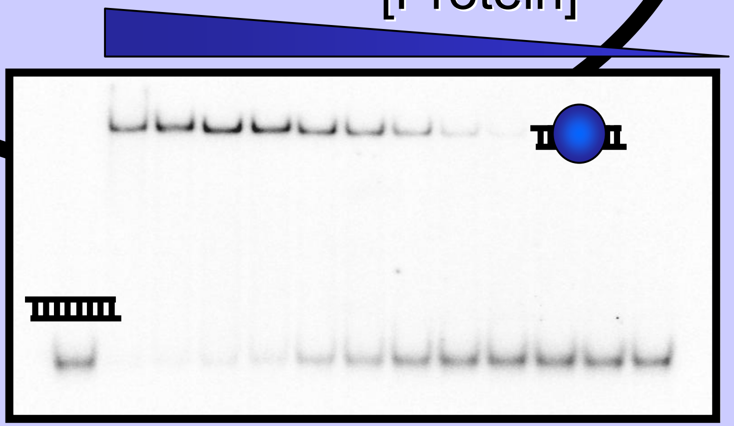


Theory

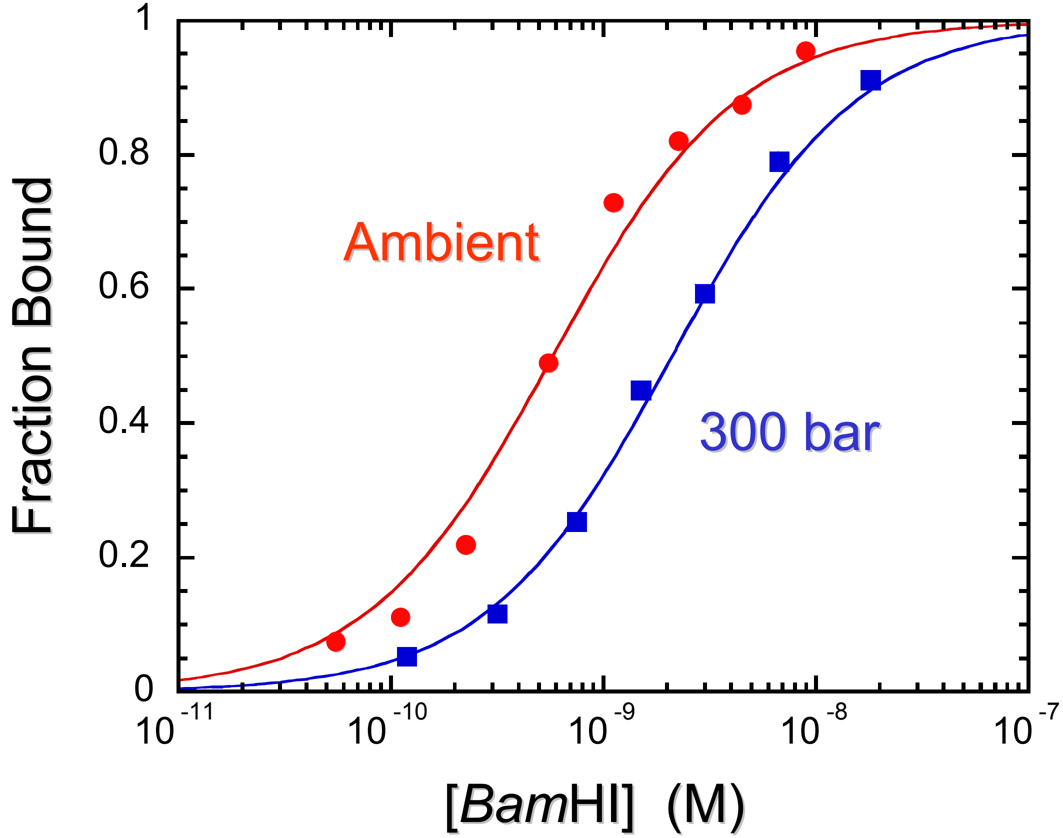
Experiment



[Protein]



Hydrostatic Pressure Effect on K_d



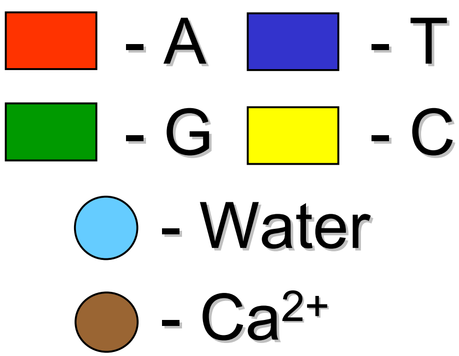
K_d (nM)	P (bar)
0.7 ± 0.1	1
1.5 ± 0.1	150
2.5 ± 0.3	300
4.6 ± 0.4	500

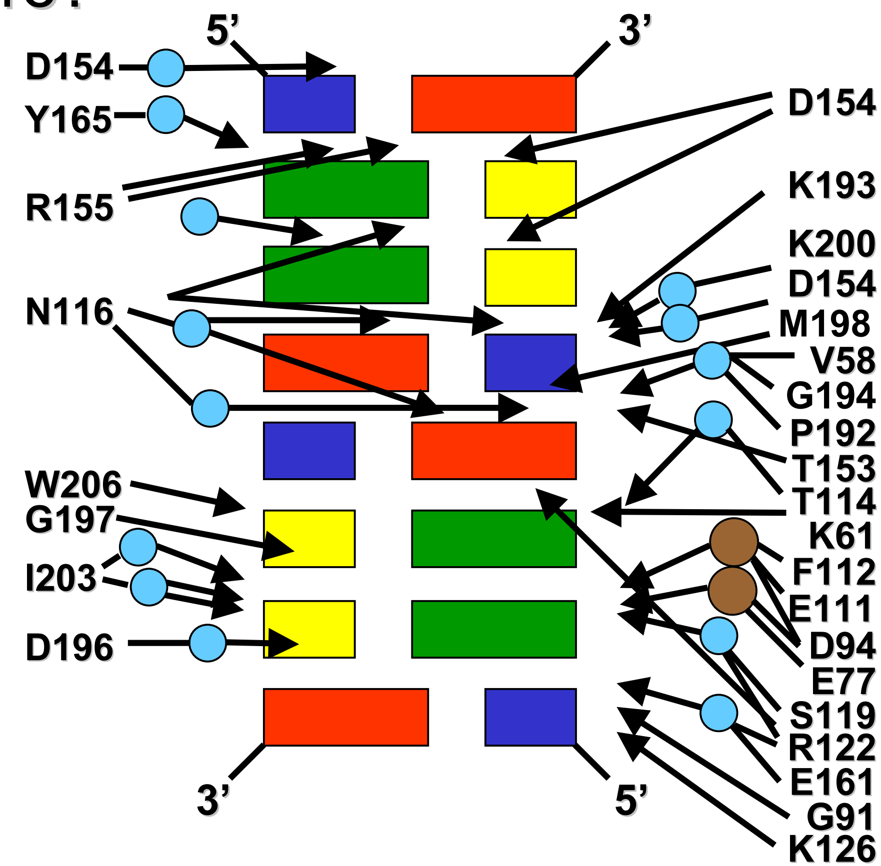
Thomas W. Lynch, Dorina Kosztin, Mark A. McLean, Klaus Schulten, and Stephen G. Sligar. Biophysical Journal, 82:93-98, 2002.

Pressure Effects on Specific Interactions

How do we identify the individual structural elements that are affected by pressure?

X-ray analysis
Direct and Water Mediated Contacts





Interaction energies between *Bam*HI and DNA

Molecular Dynamic Simulations

Particle Mesh Ewald

Periodic Boundary Conditions

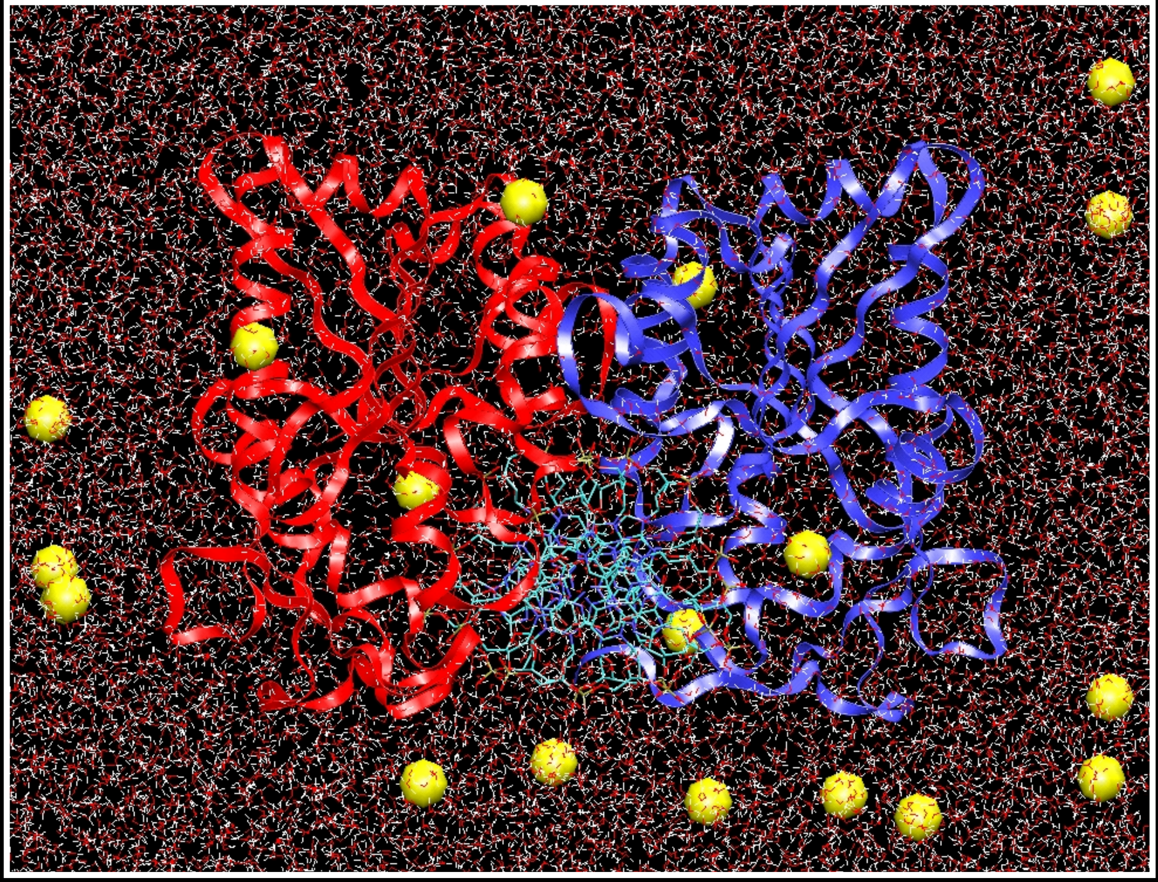
NpT ensemble

Pressure control: Nose-Hoover

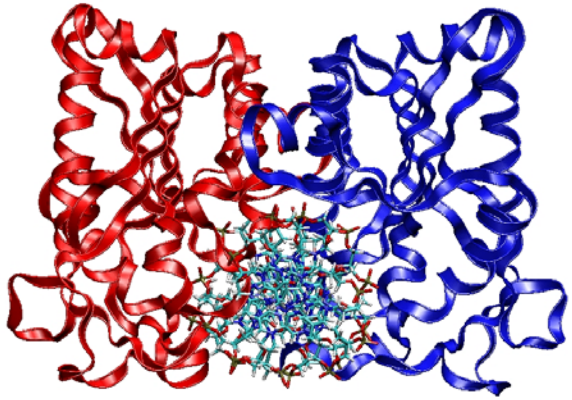
> 65,000 atoms

32 counterions - Na^+

1 ns trajectories

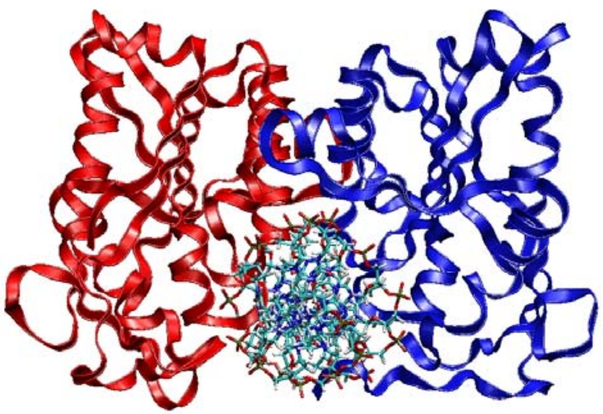


Simulation snapshots



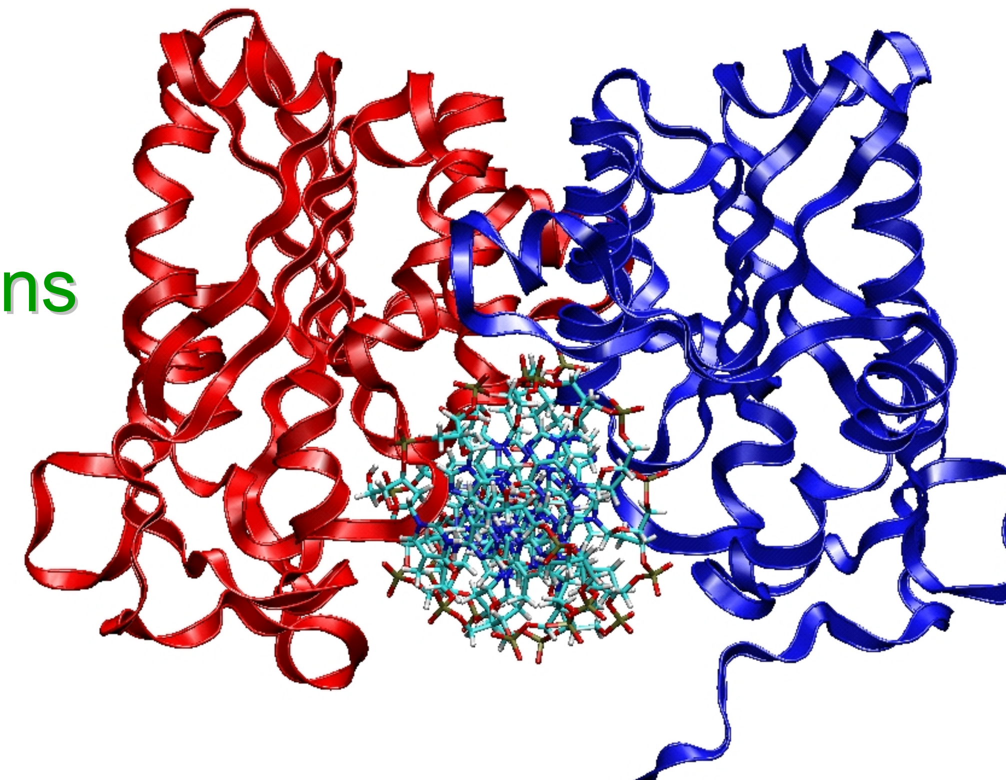
t = 0

Ambient pressure

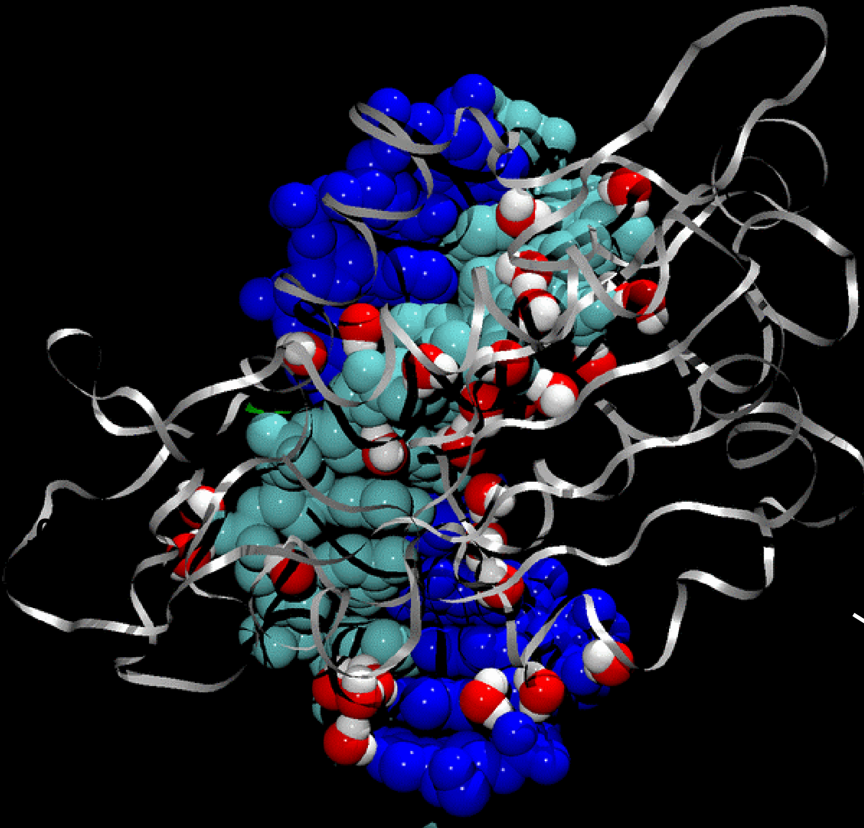


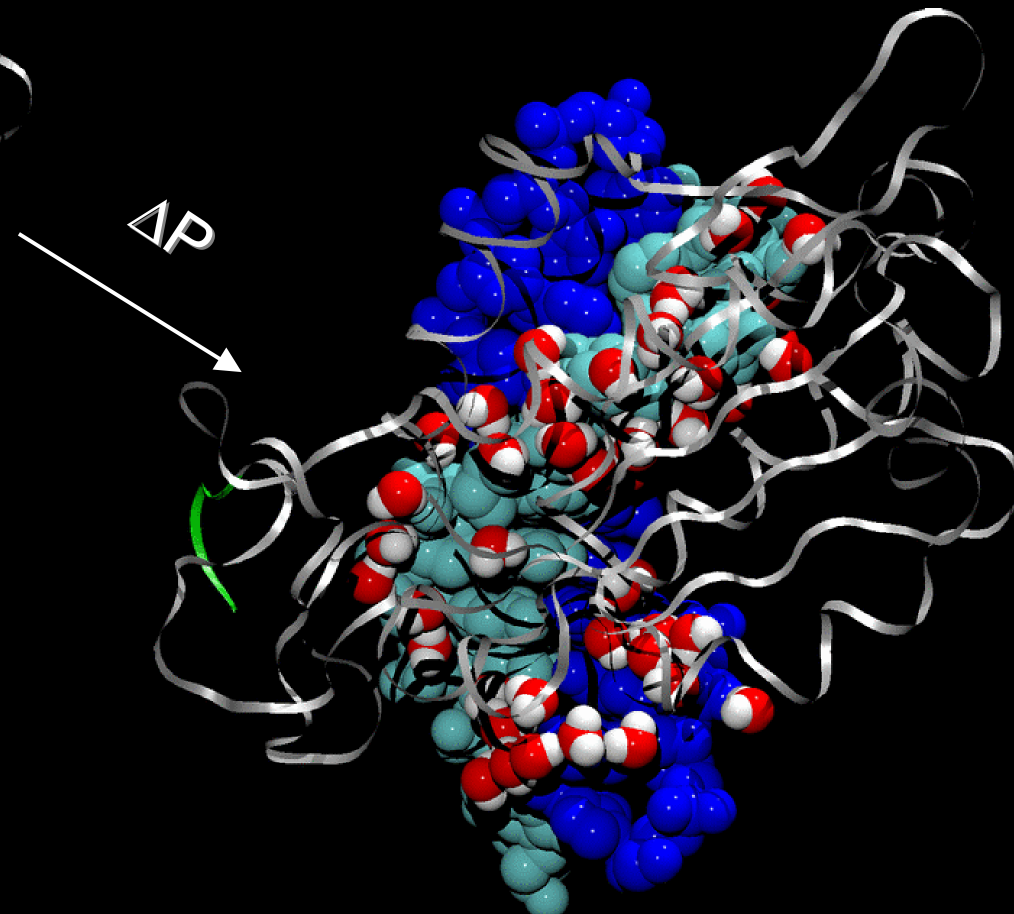
t = 1 ns

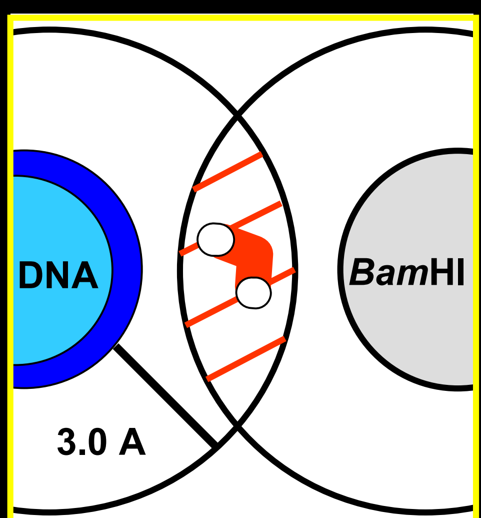
P ~ 400 bar



The Pressure-Induced Hydration Change at the *Bam*HI-DNA Interface

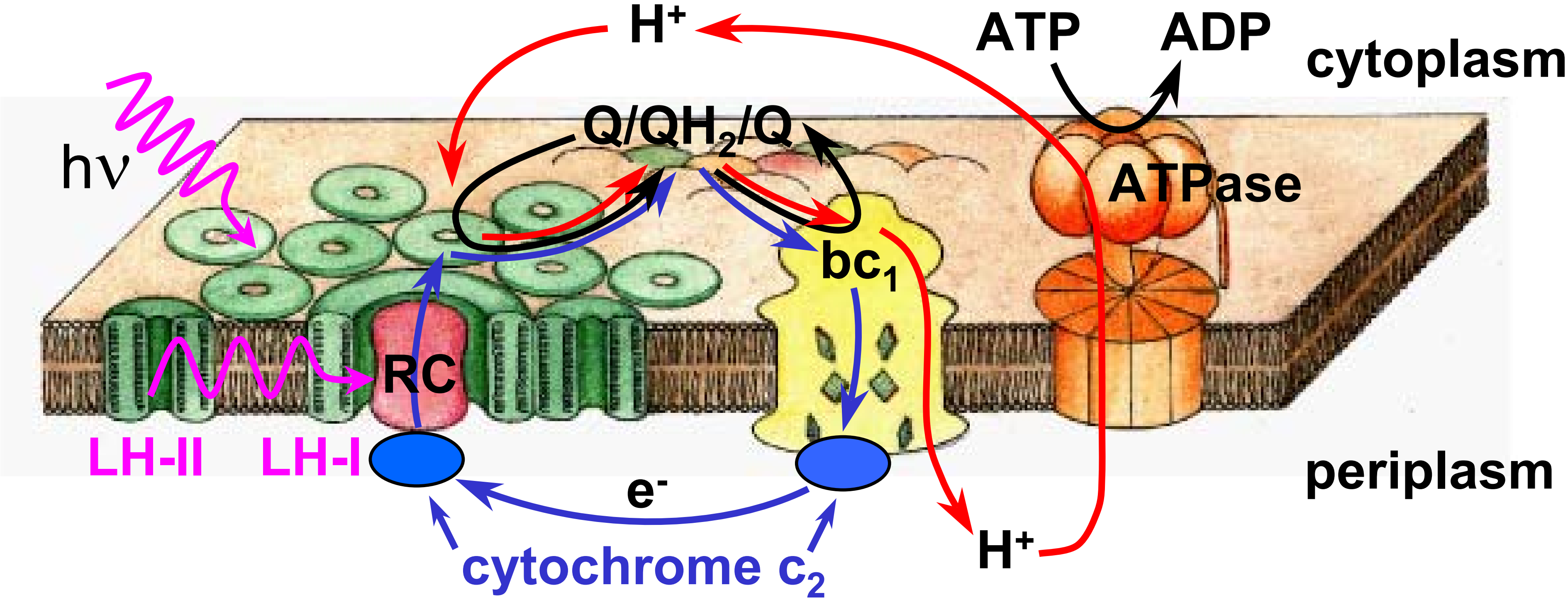






Thomas W. Lynch, Dorina Kosztin, Mark A. McLean, Klaus Schulten, and Stephen G. Sligar. Biophysical Journal, 82:93-98, 2002.

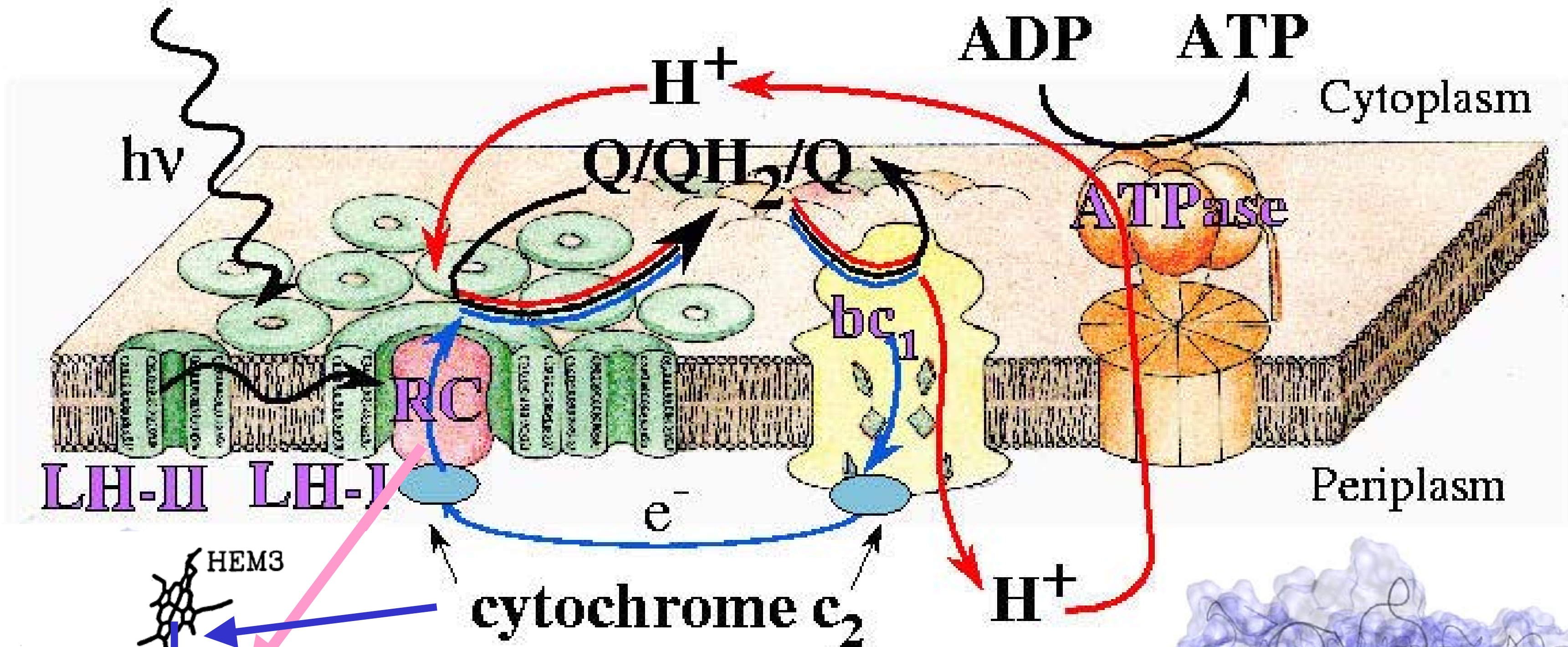
Photosynthetic Apparatus of Purple Bacteria

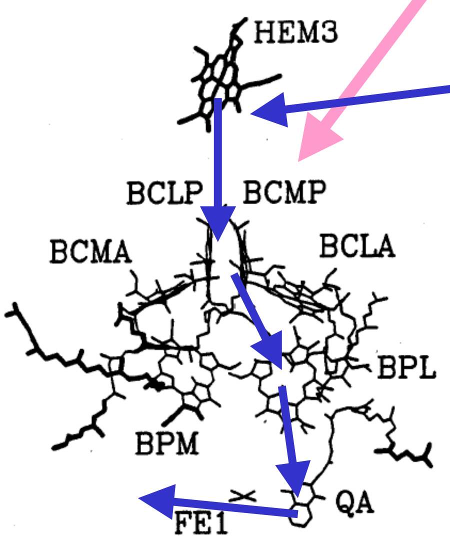


RC - Photosynthetic Reaction Center

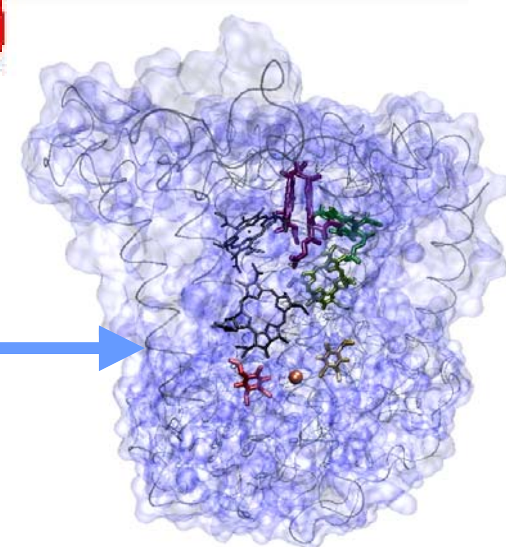
LH – Light Harvesting Complex

Role of Thermal Disorder on Electron Transfer in the Photosynthetic Reaction Center



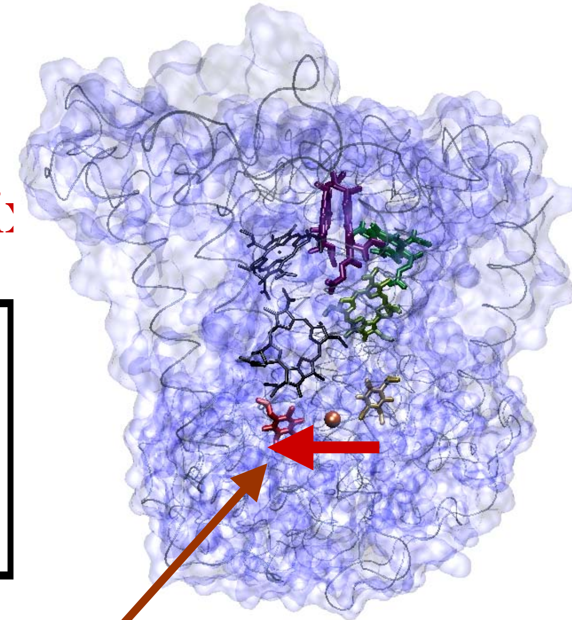


We wanted to describe how electron transfer is coupled to the thermal motion of the surrounding protein.



Electron Transfer Process Coupled to the Protein Matrix

We assumed that the electron transfer
$Q_A^- Q_B \rightarrow Q_A Q_B^-$ is coupled to an **ensemble of oscillators representing the protein matrix**



Hamiltonian $\hat{H}_{\mathrm{qo}}^{(s)} = \begin{pmatrix} \hat{H}_r^{(s)} & v \\ v & \hat{H}_p^{(s)} + E \end{pmatrix}$

Protein matrix is a bath of oscillators linearly coupled to the electron transfer according to

$$\hat{H}_r = \sum_j \left(\frac{\hat{p}_j^2}{2M_j} + \frac{1}{2} M_j \omega_j^2 q_j^2 \right)$$

$$\hat{H}_p = \sum_j \left(\frac{\hat{p}_j^2}{2M_j} + \frac{1}{2} M_j \omega_j^2 \left(q_j - \frac{c_j}{M_j \omega_j^2} \right)^2 \right)$$

Dong Xu and Klaus Schulten. Chemical Physics, 182: 91--117, 1994.

Klaus Schulten. In D. Bicout and M. J. Field, editors, Proc. Ecole de Physique des Les Houches, pp 85--118, Les Editions de Physique, Springer, Paris, 1995.

Klaus Schulten. Science, 290:61--62, 2000.

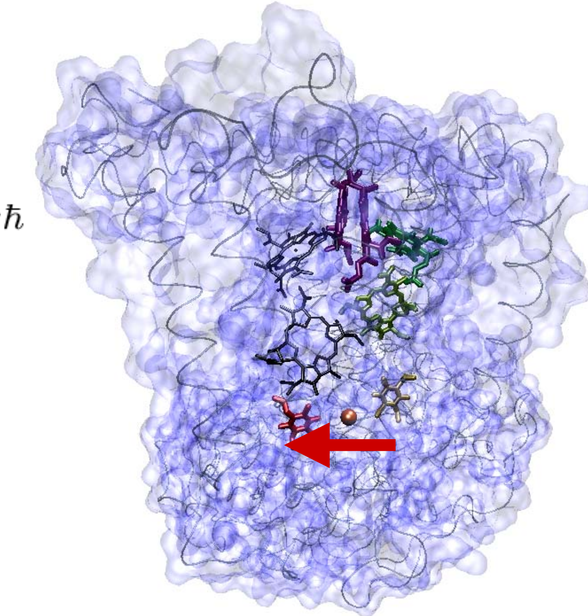
Electron Transfer Process Coupled to the Protein Matrix

Relaxation rate

$$k_{\rm rel} = \frac{2v^2}{\hbar^2} \int_0^{+\infty} dt \cos(\quad tE/\hbar) \cos(Q_1(t)/\pi\hbar)\, e^{-Q_2(t)/\pi\hbar}$$

$$Q_1(t) = \int_0^{\infty} d\omega\, \omega^{-2} J(\omega) \sin\omega t$$

$$Q_2(t) = \frac{\pi}{2} \int_0^{\infty} d\omega\, \omega^{-2} J(\omega) \coth\frac{\hbar\omega}{2kT} (1 - \cos\omega t)$$



1994

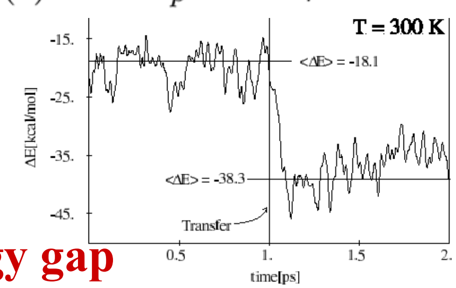
$$\frac{J(\omega)}{\omega} = \frac{\sigma^2}{k_B T} \int_0^{\infty} dt\, C(t) \cos\omega t$$

$$C_{\epsilon\epsilon}(t) = \frac{\langle (\epsilon(t) - \langle\epsilon\rangle) (\langle\epsilon(0) - \langle\epsilon\rangle) \rangle}{\langle\epsilon(0) - \langle\epsilon\rangle \rangle^2}$$

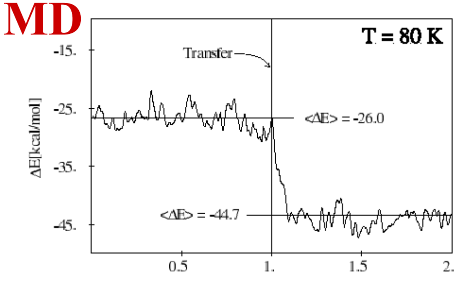
energy gap correlation function

σ **rms deviation of energy gap**

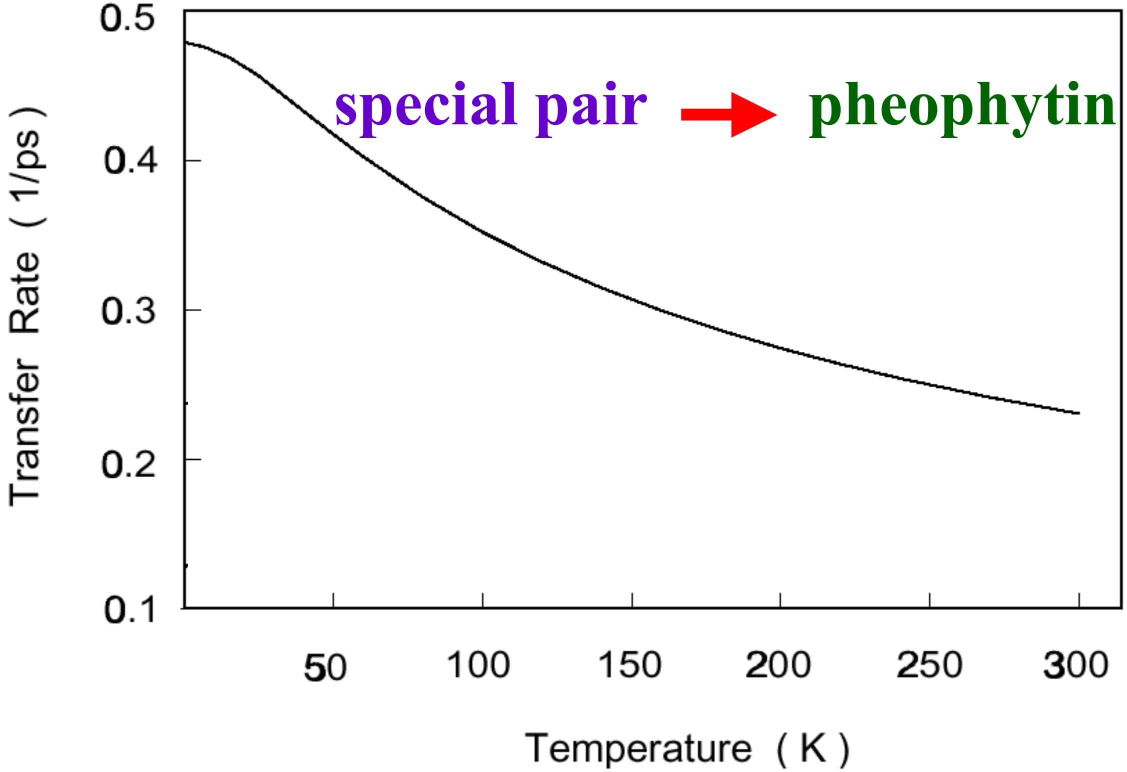
$$\epsilon(t) = \hat{H}_p - \hat{H}_r + E$$

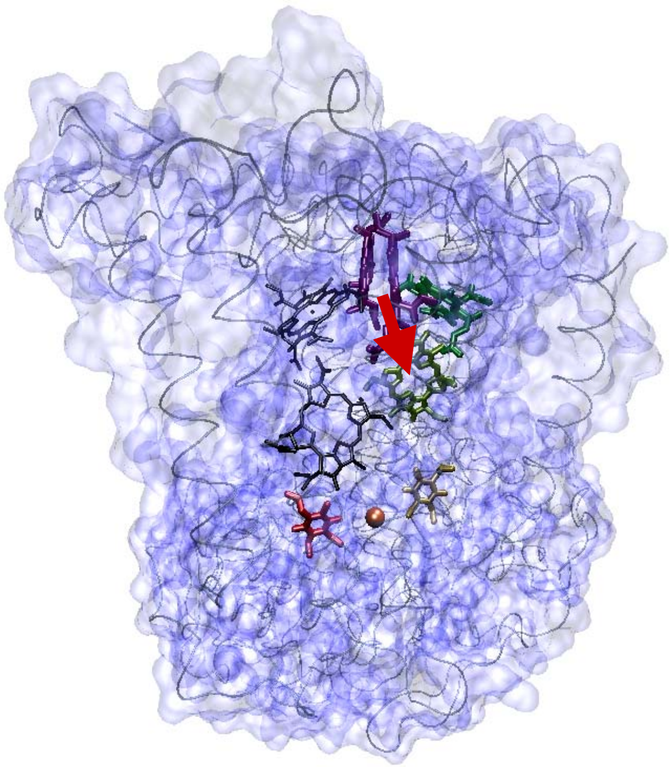


energy gap from MD 1989



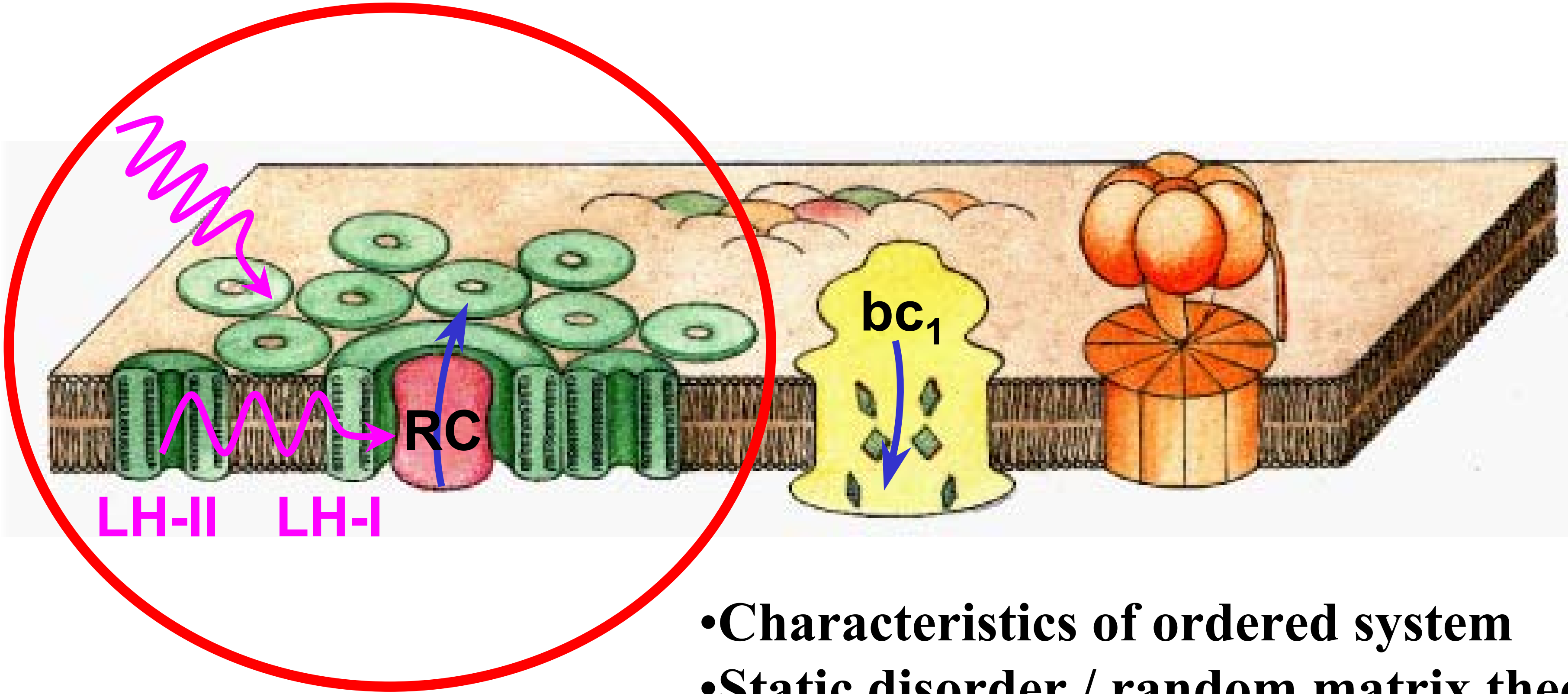
Temperature Dependence of Electron Transfer Rate





Dong Xu and Klaus Schulten. Chemical Physics, 182: 91--117, 1994.

How does the Light Harvesting System Function with Thermal Disorder?

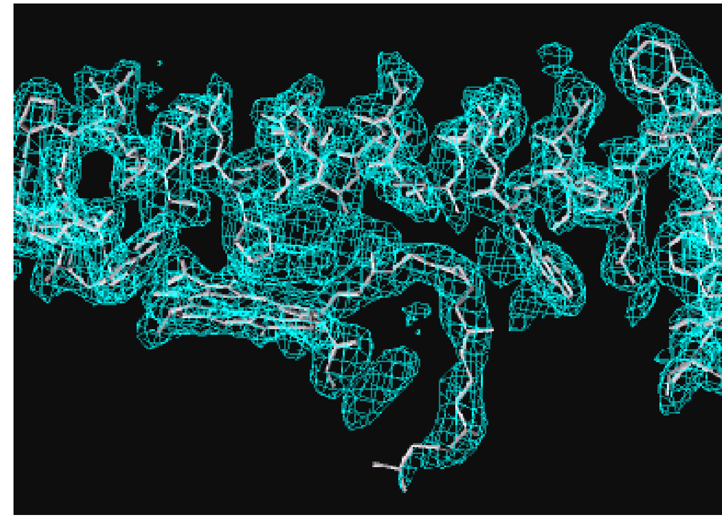


- Characteristics of ordered system
- Static disorder / random matrix theory
- Dynamics disorder / linear response th.
- Dynamic disorder / polaron model
- Role of carotenoids

Structure of LH-II of *Rs. molischianum* Obtained Through a Computationally Derived Search Model

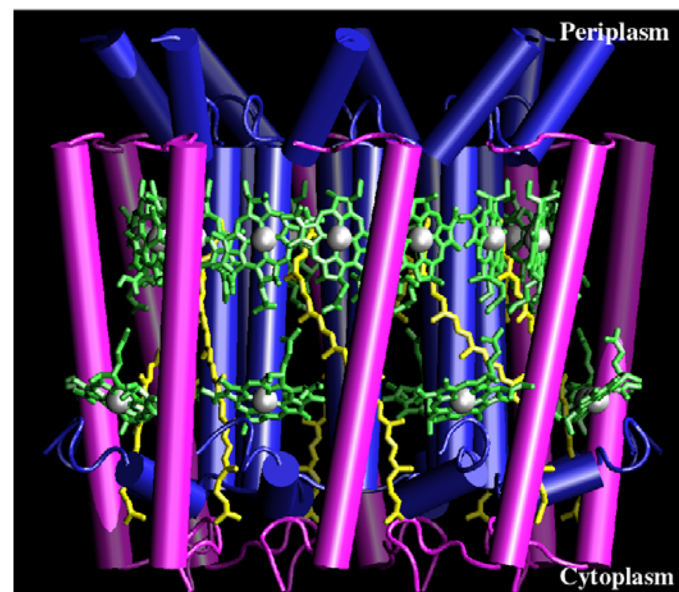
$\rho = \Sigma_j |f_j| \exp[\phi_j]$

molecular replacement



Summary of Crystallographic Data

- space group P4212
- resolution range 8-2.4 A
- unique reflection 30309
- completeness 87.2
- R-factor (%) 21.1
- free R-factor (%) 23.2

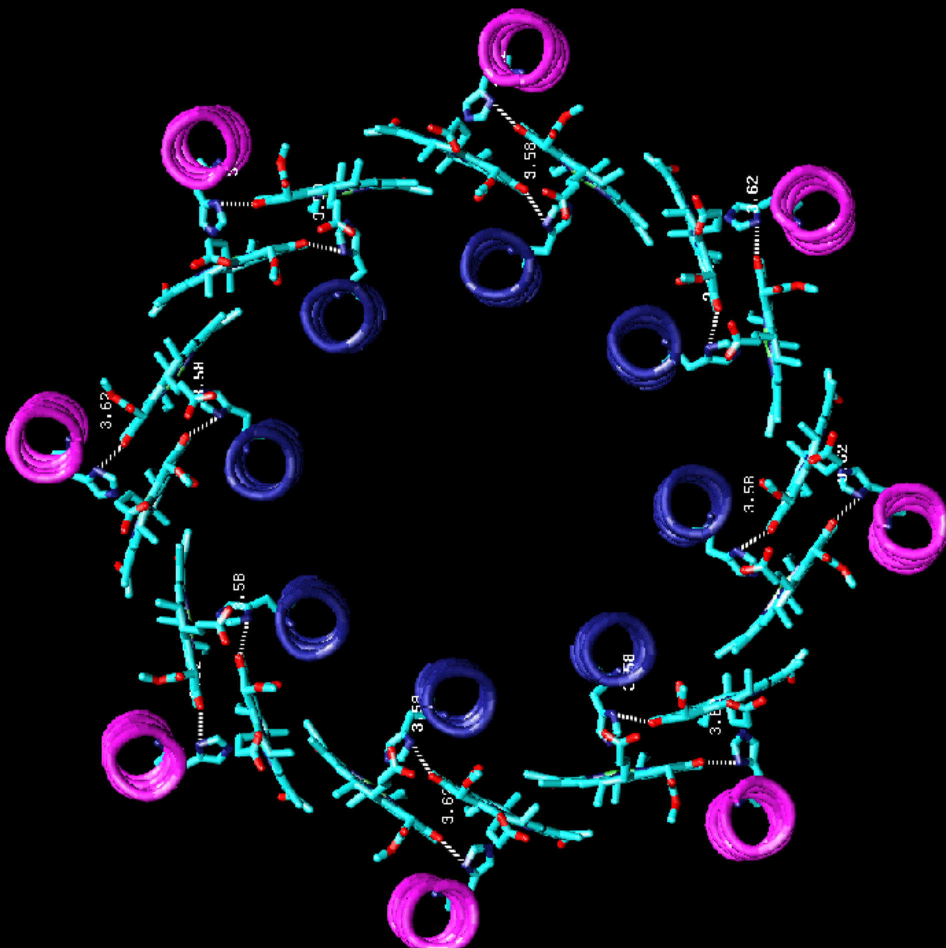


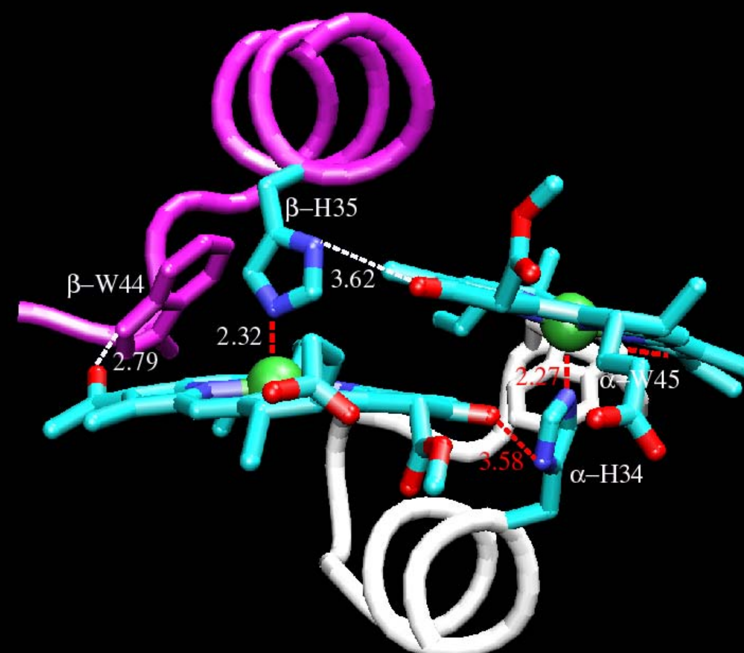
Xiche Hu

Koepke et al., Structure, **4**, 581 (1996)

B850 BChls of LH-II of *Rs. molischianum*

New aggregation pattern of chlorophylls, first discovered by R. Cogdell et all in LH-II of Rps. acidophila

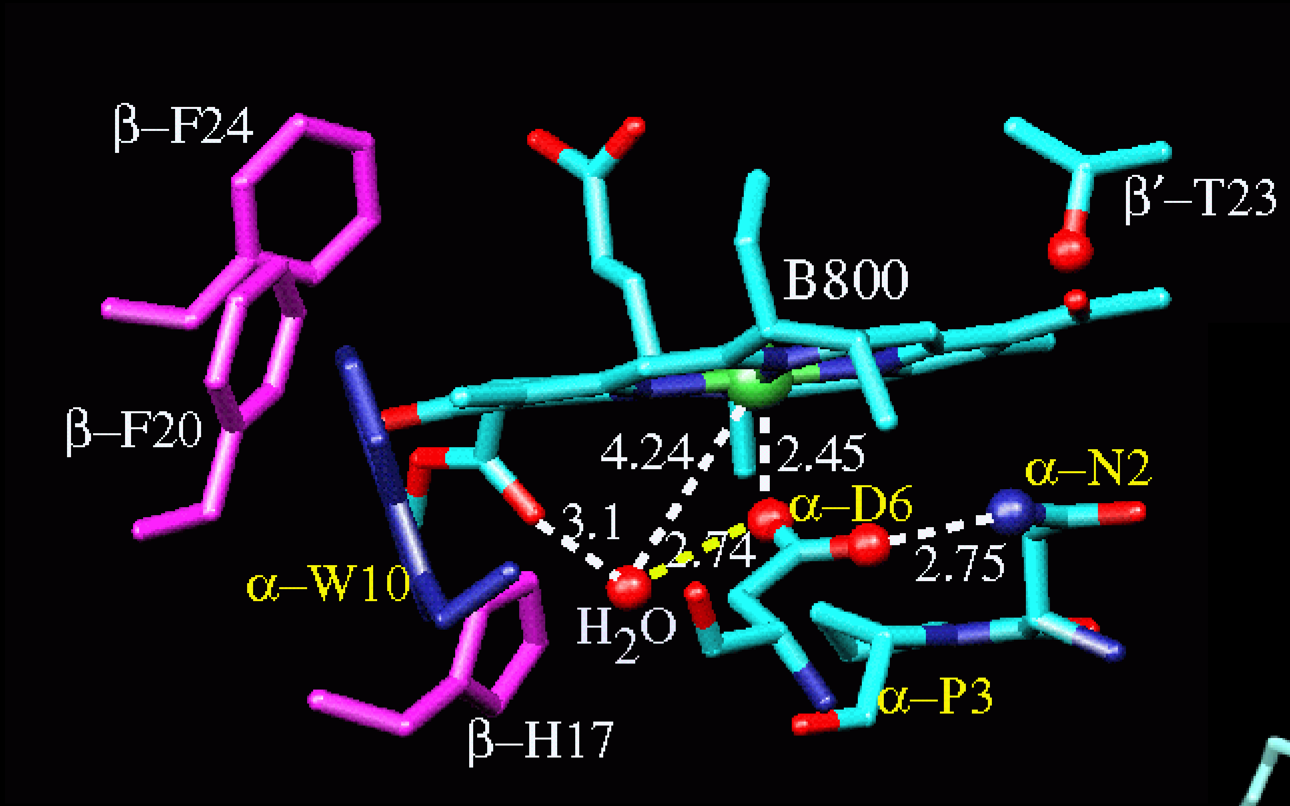


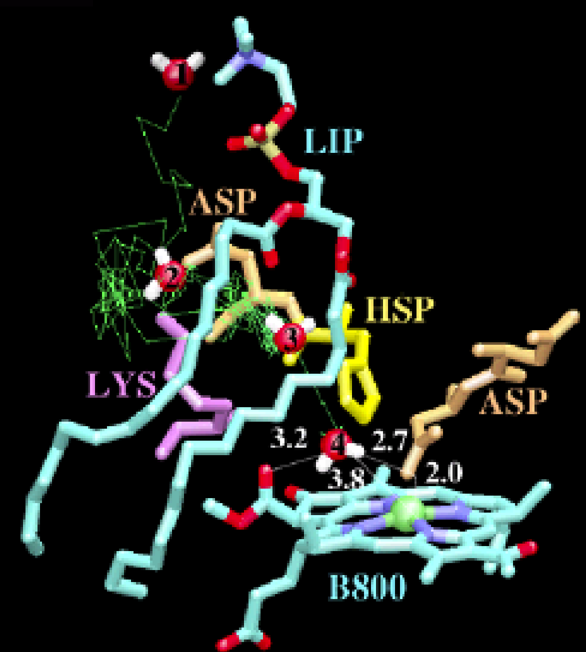


Spectrum tuned through local and excitonic interactions as well as disorder

B800 BChl-a Binding Site

New ligation pattern of chlorophyll's Mg atom!

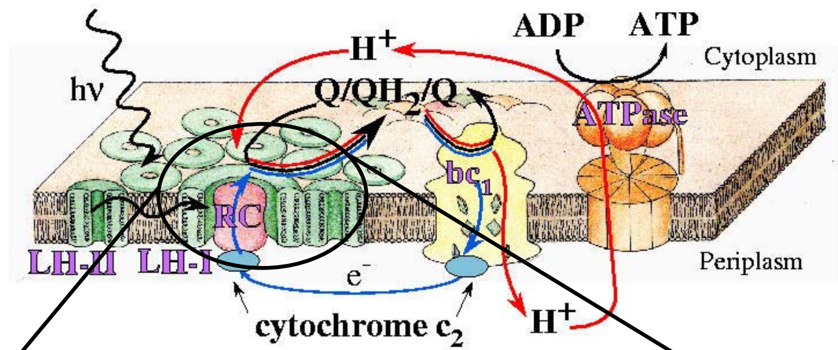




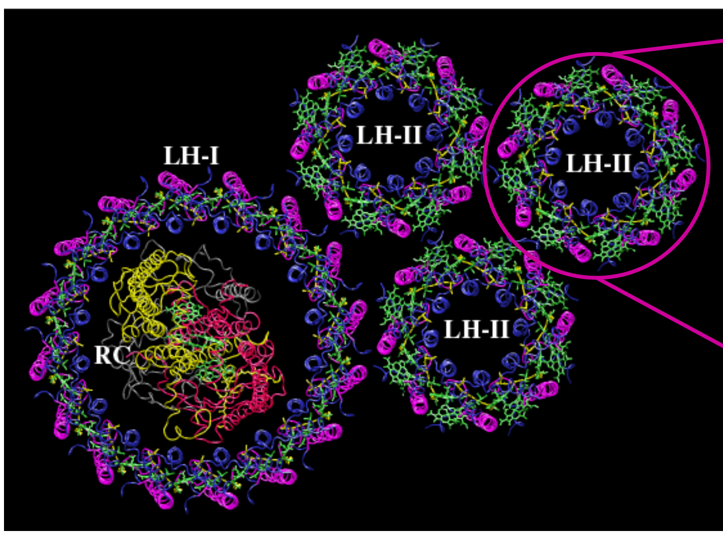
Simulation

The light harvesting system displays a hierarchy of integral, functional units

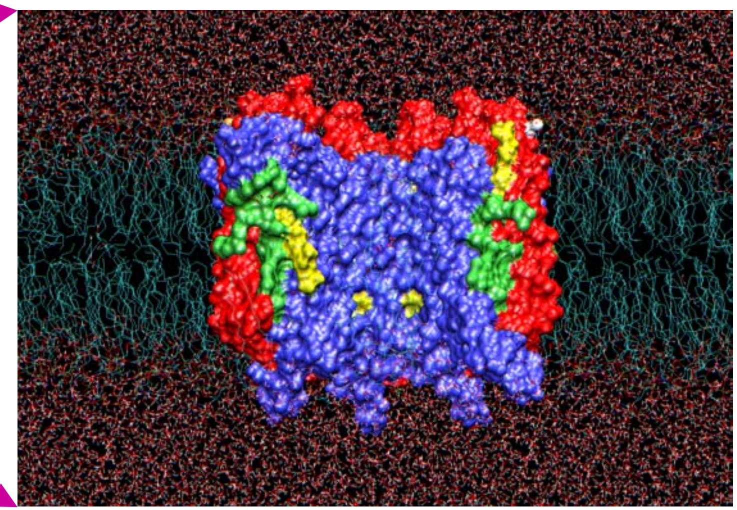
Photosynthetic membrane generates ATP using light energy



Hu and Schulten, Biophys J., **75**, 683-694 (1998)
Ritz *et al*., J. Lumin., **76-77**, 310-321 (1998)
Hu *et al*., PNAS, **95**, 5935-5941 (1998)
Koepke *et al*., Structure, **4**, 581-597 (1996)
Hu *et al*., J. Phys. Chem., **B 101**, 3854-3871 (1997)
Cory *et al*., J. Phys. Chem., **B 102**, 7640-7650 (1998)
Damjanovic *et al*., Phys. Rev. E, **59**, 3293-3311 (1999)



Light harvesting unit funnels excitation energy to photosynthetic reaction center

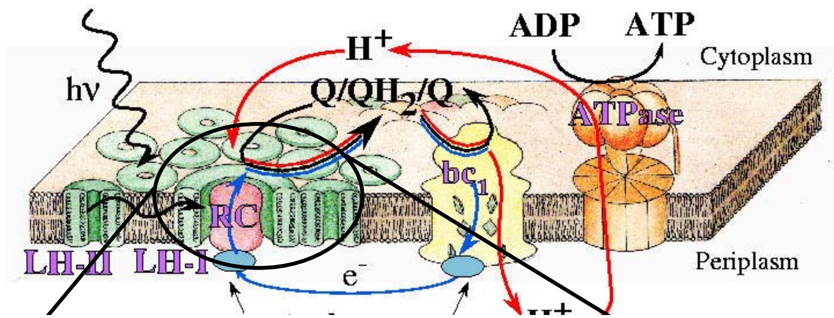


Light harvesting complex II absorbs light and converts it into electronic excitations of BChls

Molecular modeling of integral, functional units with more than 10^6 atoms necessary

The light harvesting system displays a hierarchy of integral, functional units

Photosynthetic membrane generates ATP using light energy



Hu and Schulten, Biophys J., **75**, 683-694 (1998)
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Hu *et al*., PNAS, **95**, 5935-5941 (1998)
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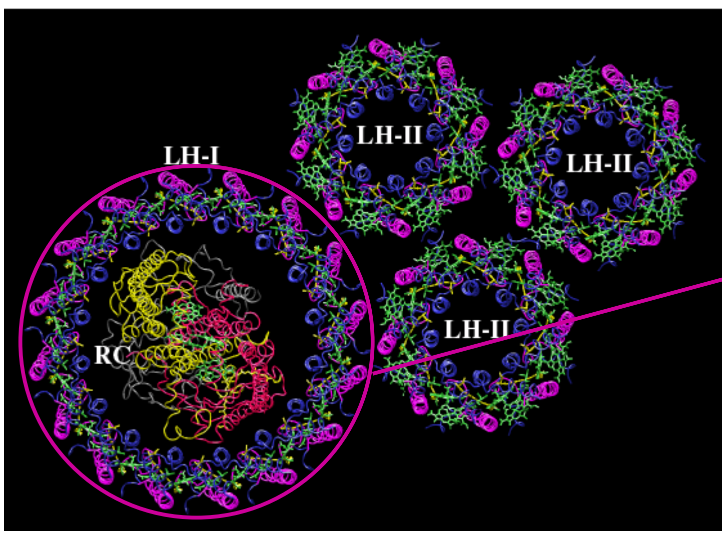
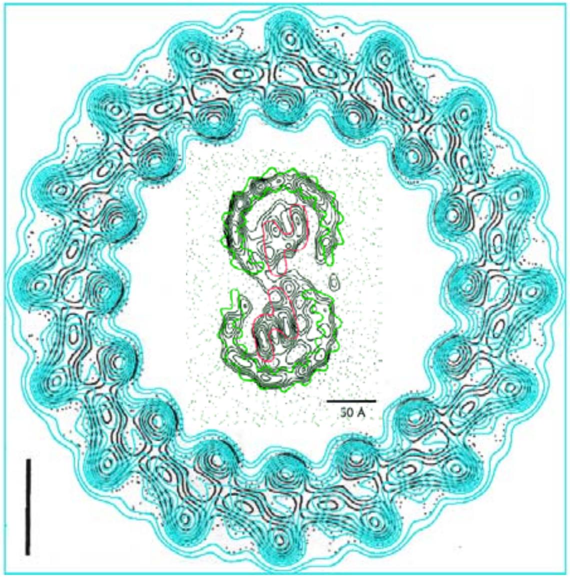


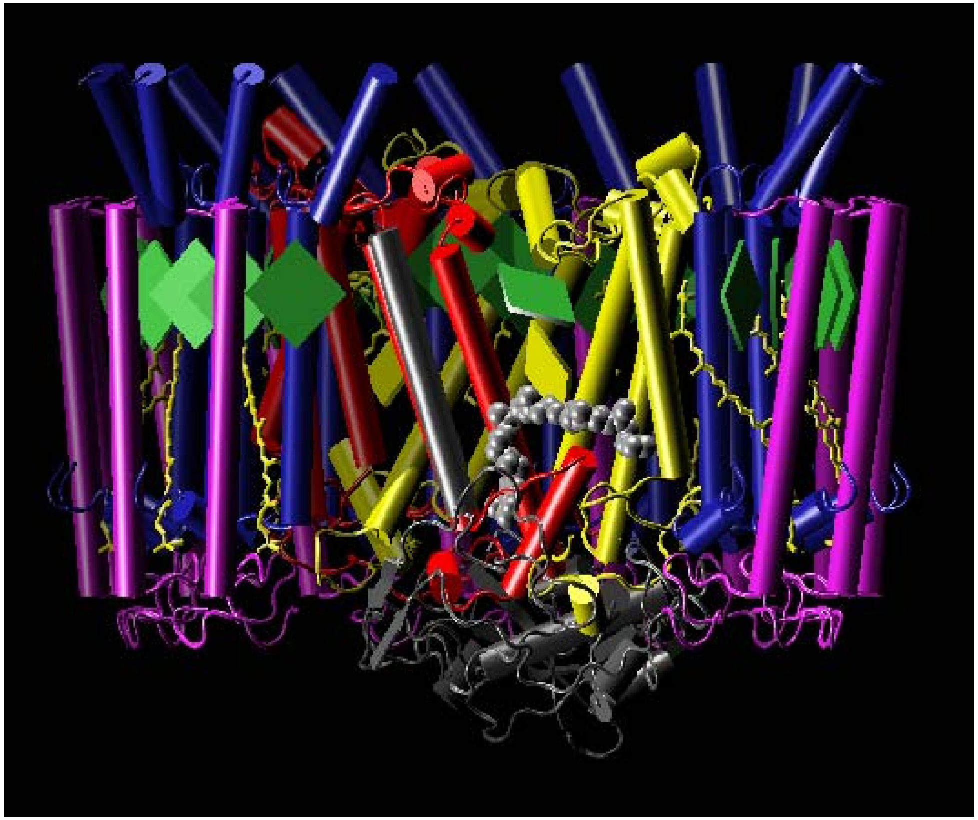
We need to know also the structure of the LH-I ring! We use again modeling, replacing subunit of LH-II by that of LH-I

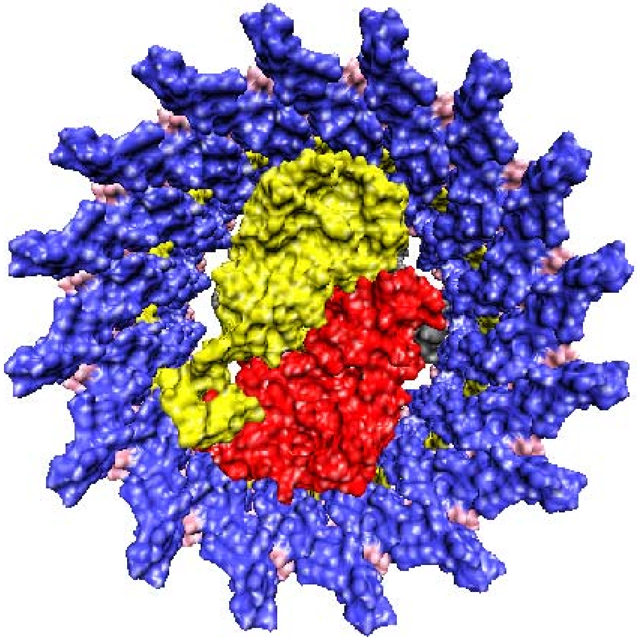
Molecular modeling of integral, functional units with more than 10^6 atoms necessary

LH-I – RC Complex of *Rb. Sphaeroides*

Model agrees well with EM map







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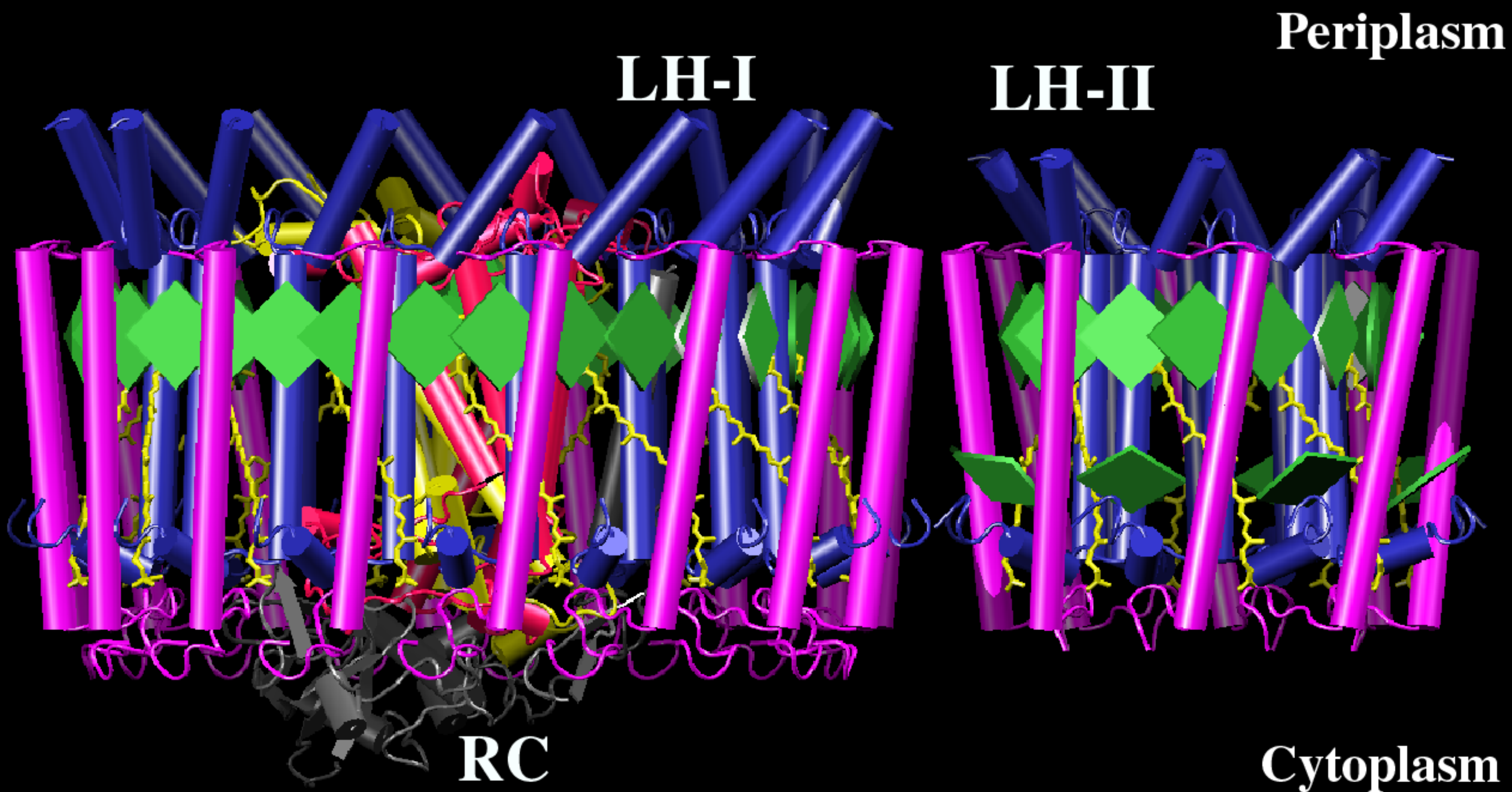
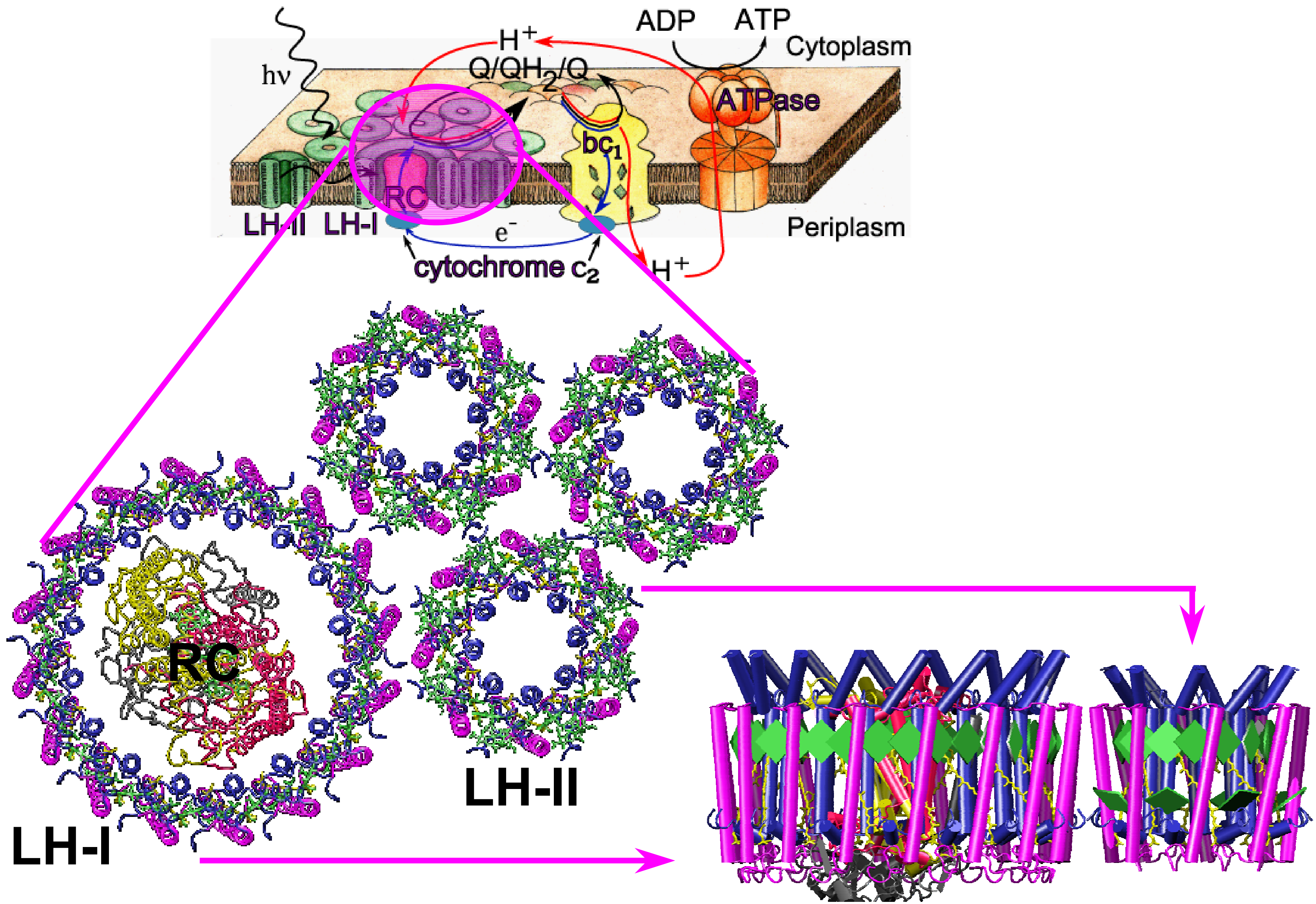
View from top

Pigment Organization in the Bacterial Photosynthetic Membrane

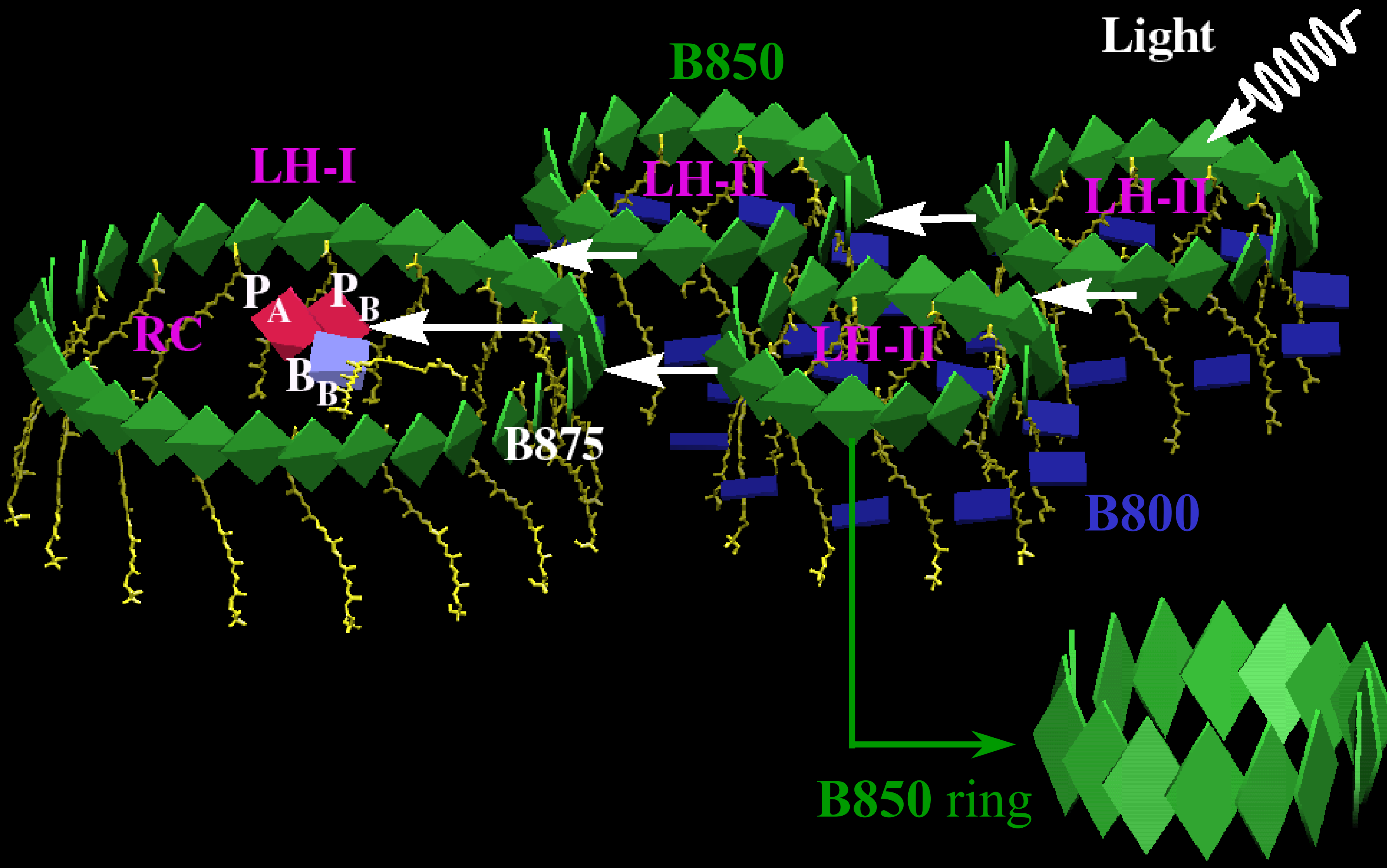


Note the conspicuous arrangement of chlorophyll rings!

Structure of Light Harvesting System



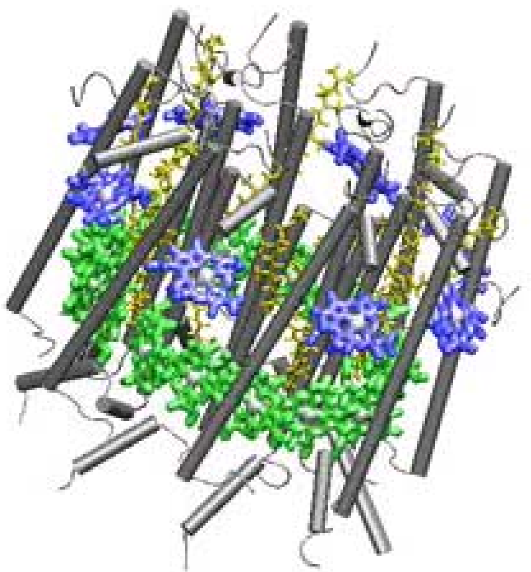
Hierarchical aggregate of *chromophores*

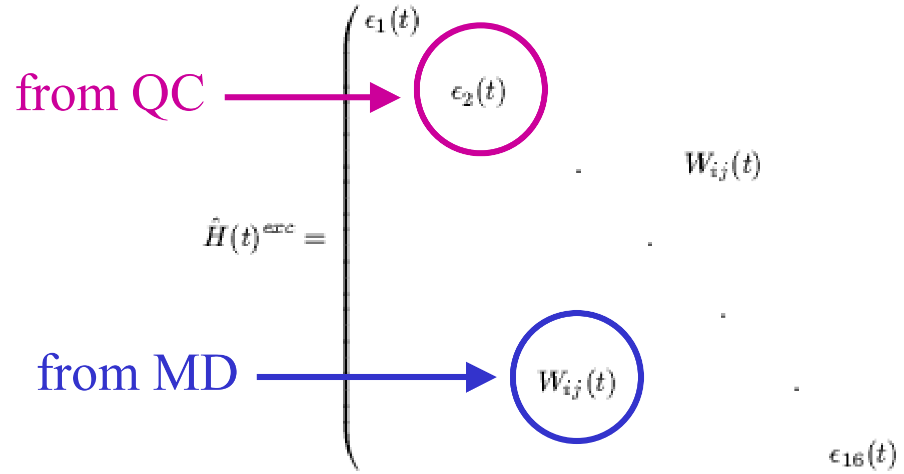


The Effect of Dynamic Disorder

Molecular Dynamics (MD) Simulation

Gaussian 98, HF/CIS, STO-3G basis

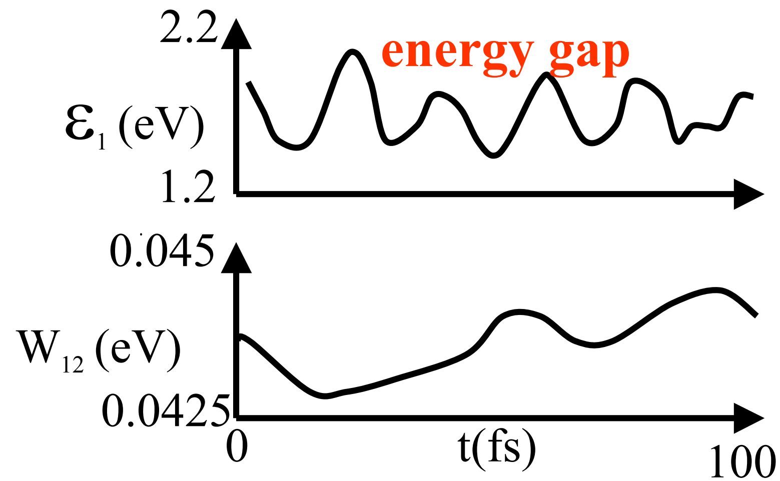




$$W_{jk} = C\left(\frac{\vec{d}_j \cdot \vec{d}_k}{r_{jk}^{\ 3}} - \frac{3(\vec{r}_{jk}\cdot\vec{d}_j)\,(\vec{r}_{jk}\cdot\vec{d}_k)}{r_{jk}^{\ 5}}\right)$$

LH2 in membrane: 85,000 atoms; equilibrated for 2ns with NAMD2; NpT ensemble; periodic boundary condition; full electrostatics (PME)

Followed by 0.8ps simulation, trajectory output every 2fs with quantum chemistry calc. of exc. energy, interpolated to "sample" every 0.5 fs



Ana Damjanovic, Ioan Kosztin, Ulrich Kleinekathoefer, and Klaus Schulten, Phys. Rev. E 65:031919, 2002

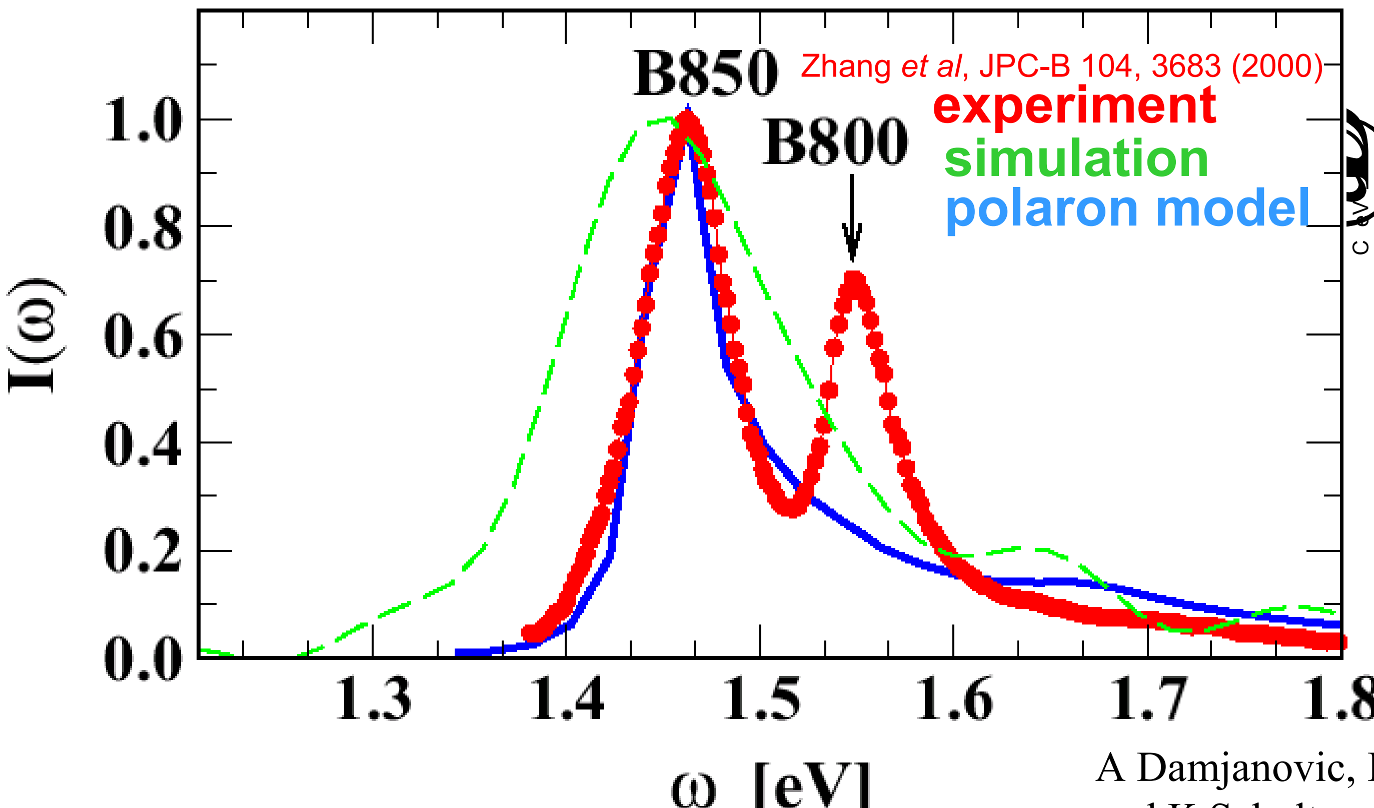
Absorption Spectrum – B850 Excitons

$$I(\omega) \propto \sum_k |d_k|^2 \int_0^\infty dt \exp[-\Phi'_k(t)] \cos[(\omega - \epsilon_k)t + \Phi''_k(t)]$$

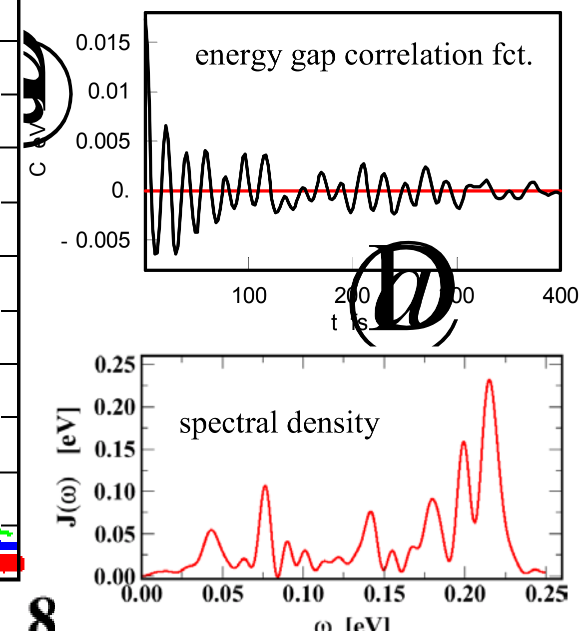
$$\Phi_k(t) = \int_0^t d\tau (t-\tau) \mathcal{D}(\tau) F_k(\tau)$$

$\mathcal{D}(\tau)$ → phonon contribution

$F_k(\tau)$ → exciton contribution



From MD/QC simulation

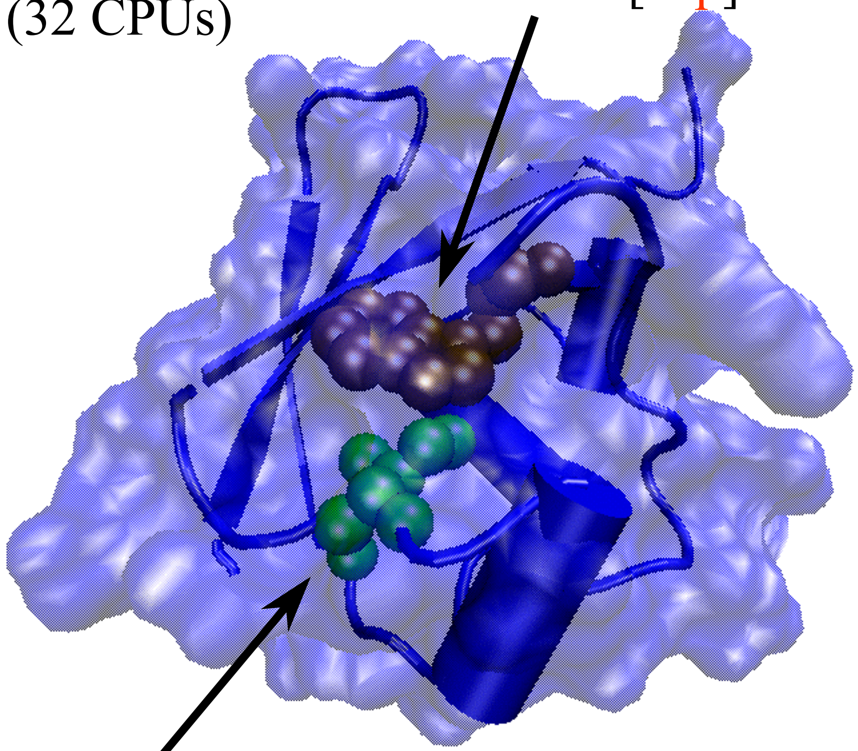


http://xxx.lanl.gov/abs/physics/0107064

A Damjanovic, I Kosztin, U Kleinekathoefer, and K Schulten, Phys. Rev. E **65:031919, 2002**

Folding of Ubiquitin

10,000 atoms
1day/ns on *titania*
(32 CPUs)



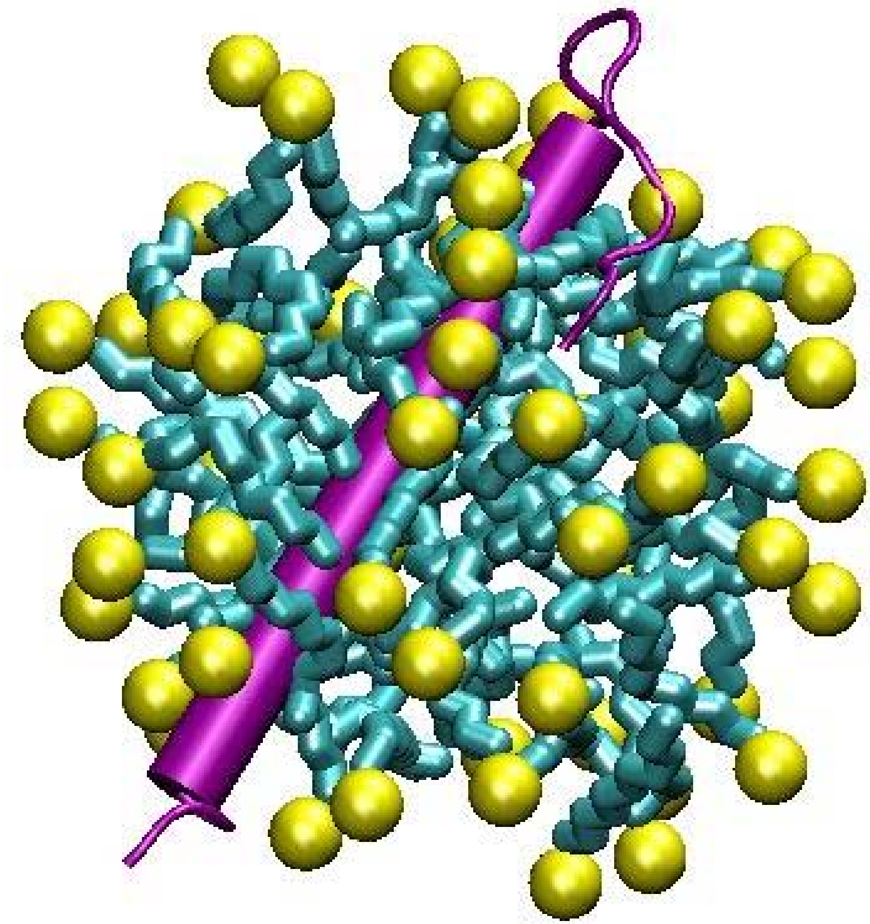
Mutations:
Val61 – MD simulations
Ala61 – experiment and MD simulations

Edgar Larios

- Collaborator:
  M. Gruebele, UIUC
- Goals:
  - Experimental and MD studies of the folding of *ubiquitin*
  - Ultrafast fluorescence study of Trp45 in ubiquitin
- Result:
  - Explained the anisotropy of the fluorescence spectra of Trp in different mutants of ubiquitin

Edgar Larios

Helix Interaction in Micelle



Micellar sphere of 60 SDS molecules
30,000 atoms

Rosemary Braun

- Collaborator:
  D. Engelman, Yale Univ.
- Goals:
  - Examine stability of single and two helices in micelle with respect to mutations
- Results:
  - Equilibrated micell
  - Built the helices

Rosemary Braun, Justin Gullingsrud