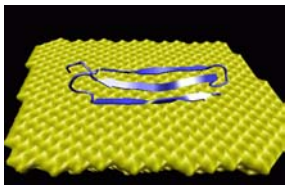
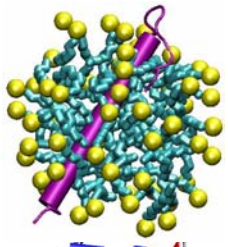


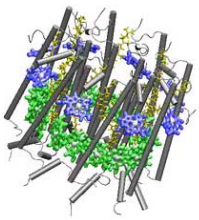
What can be learnt from MD

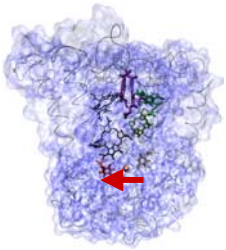
Gold binding protein

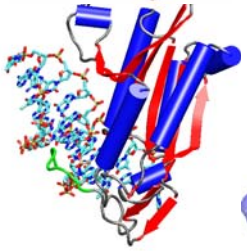
Micelle Light harvesting complex Reaction Center

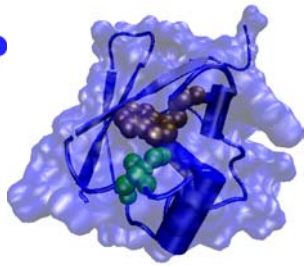
Restriction enzyme Ubiquitin avidin-biotin

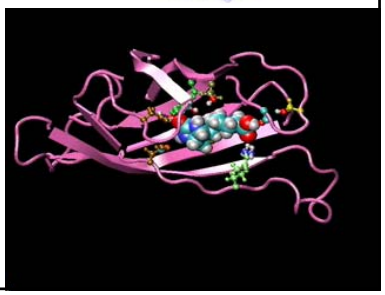


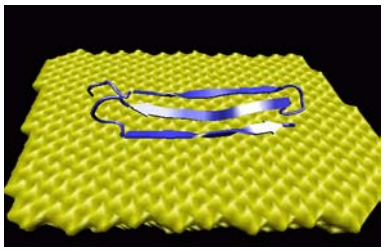












Gold Binding Protein: 1. Structure Prediction

Protein-mineral interaction is of interest from biological and materials science perspectives: Teeth, abalone shells, or nanomaterials

Proteins have been genetically engineered which bind to Au and alter crystal morphology (GBPs). Binding mechanism unknown; structure prediction and molecular dynamics simulations may provide insight.

Best binders: multiple repeats of 14 amino acids; lead to Au crystals with dominant (111) surfaces; rich in polar amino acids serine and threonine.

(111) Gold crystals

GBP-1: Anti-parallel β-sheet (high confidence).	
H-K	M|HGKTQATSGTIQSM|HGKTQATSGTIQSM|HGKTQATSGTIQSM|HGK
Sim	Similar sequences have β-sheet structure.

3 repeats

Holley-Karplus (HK) and alignment (Sim) results. In the sequences, blue signifies beta sheet and black signifies random coil.

Gold Binding Protein - 2. Simulation

Molecular dynamics carried out using the program NAMD2.

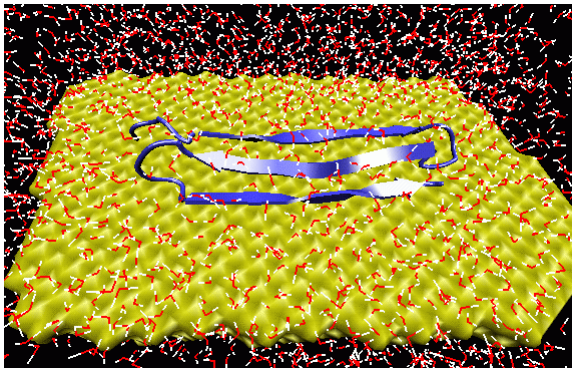
Au surfaces created with known FCC structure and 4.07Å lattice spacing;

GBP sequence mapped to β-sheet and manually positioned on Au surface;

Force field: CHARMM22, TIP3P water, periodic boundary conditions, full electrostatics (PME)

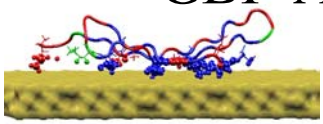
Constant pressure and temperature. Au held fixed.

Total system size: ~13,000 atoms.

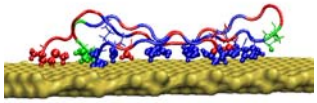


$$U_{surf} = 2\pi \sum_{l=0}^{\infty} n_l \varepsilon \sigma^2 \left[\frac{2}{5} \left(\frac{\sigma}{z + d_l} \right)^{10} - \left(\frac{\sigma}{z + d_l} \right)^{4} \right]$$

GBP-Au Contacts



(111)

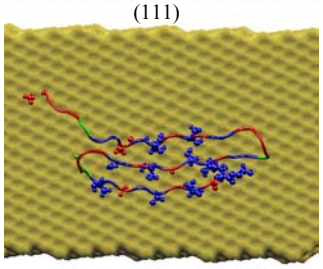


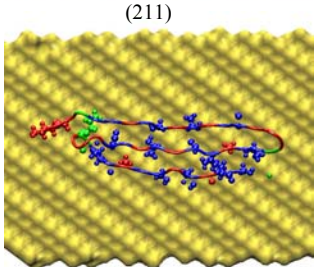
(211)

Useful insights for new design!

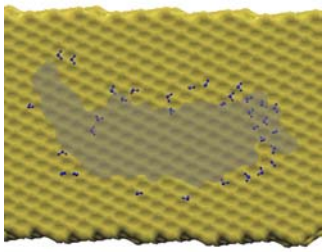
surface contacts: polar amino acids Thr, Ser

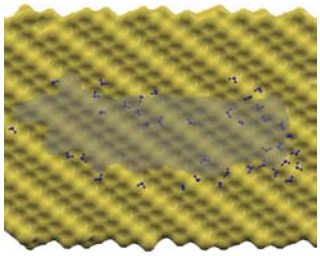
repeats exhibit additive interaction





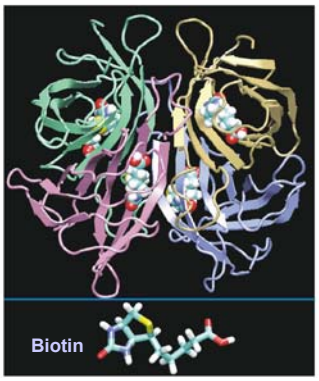
less inter-stitial water

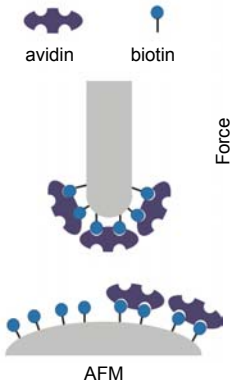




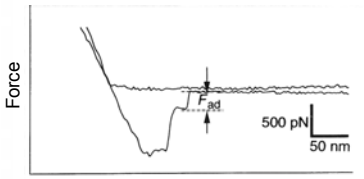
more inter-stitial water

Atomic Force Microscopy Experiments of Ligand Unbinding





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

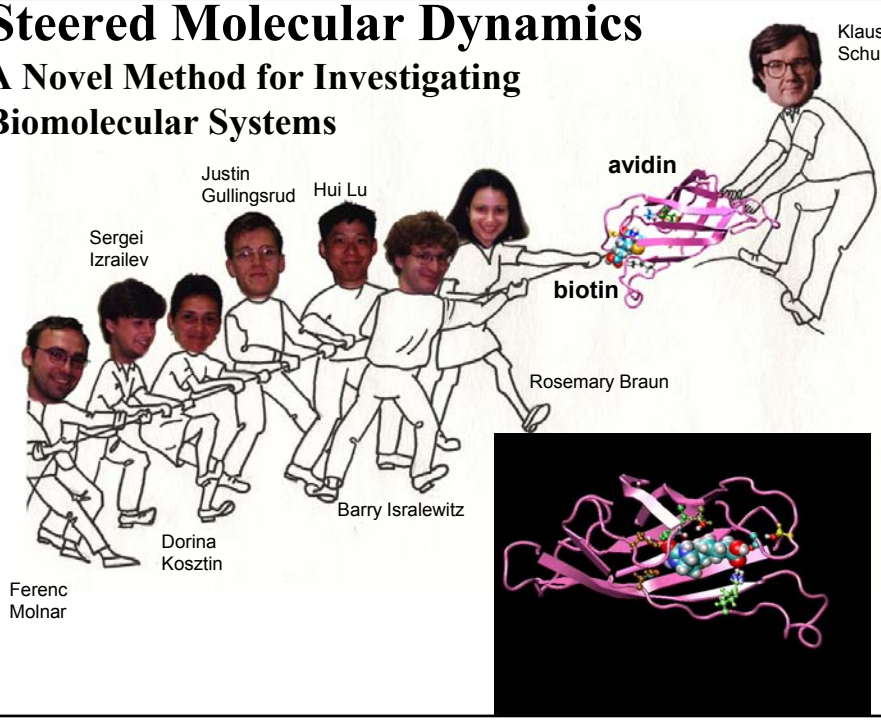


Displacement of AFM tip

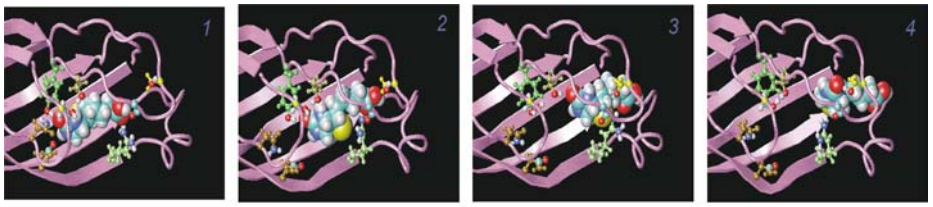
NIH Resource for Macromolecular Modeling and Bioinformatics
Theoretical Biophysics Group, Beckman Institute, UIUC

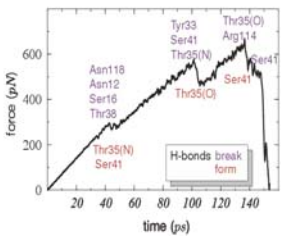
Steered Molecular Dynamics

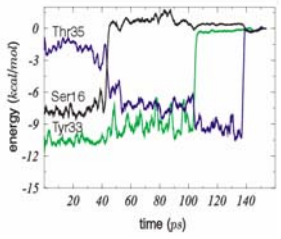
A Novel Method for Investigating Biomolecular Systems

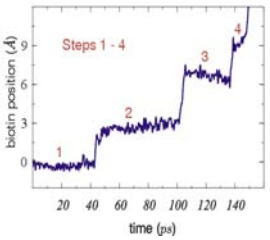


Atomic Force Microscopy and Steered Molecular Dynamics Complement Each Other !









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

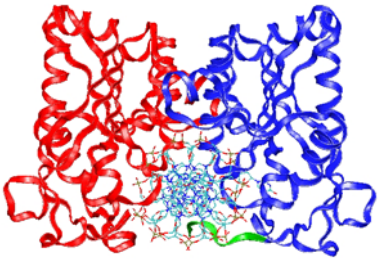
http://www.ks.uiuc.edu

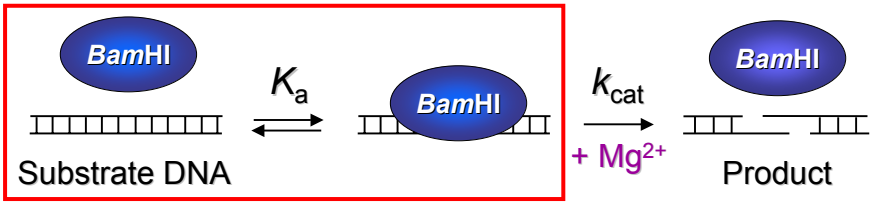
NIH Resource for Macromolecular Modeling and Bioinformatics
Theoretical Biophysics Group, Beckman Institute, UIUC

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

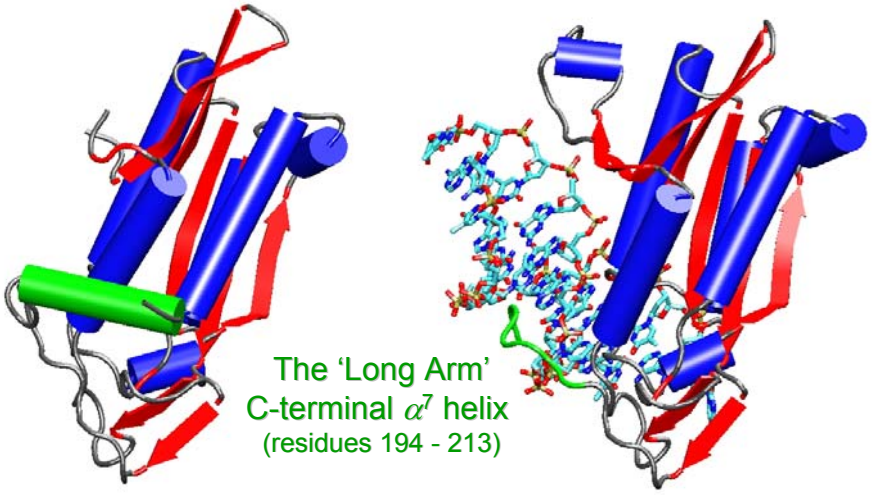




Cognate DNA : K_d ~ 600 pM

Substrate Free

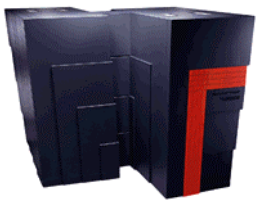
Specific Complex



The 'Long Arm'
C-terminal α^7 helix
(residues 194 - 213)

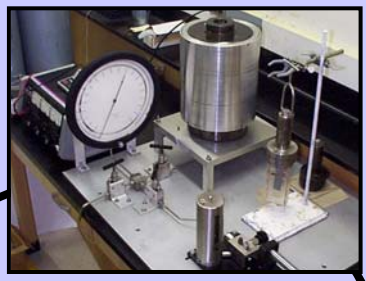
Newman, M. *et al*. (1994) *Structure* **2**, 439-452
Newman, M. *et al*. (1995) *Science* **269**, 656-663

Cray T3E



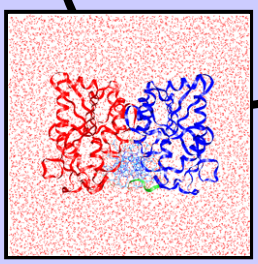
Th. Lynch,
S. Sligar,
D. Kosztin

High pressure gel electrophoresis

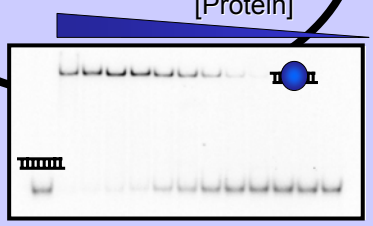


Theory

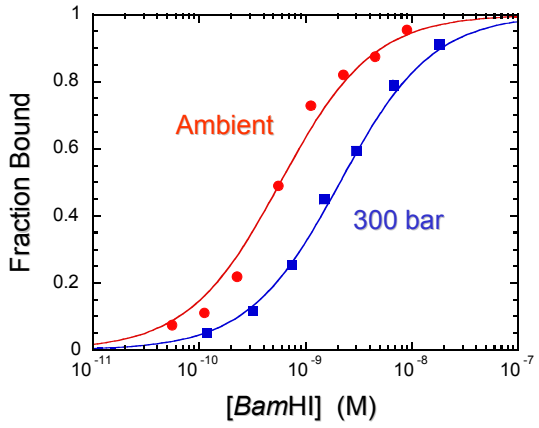
Experiment



[Protein]



Hydrostatic Pressure Effect on K_d



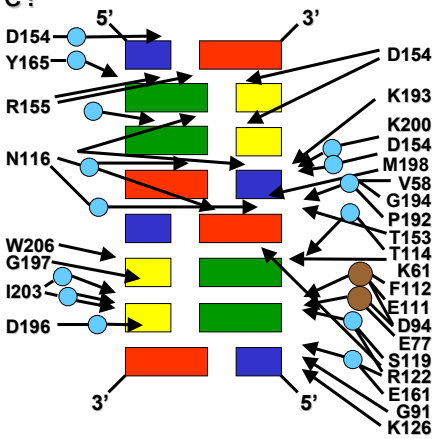
Kd (nM)	P (bar)
0.7 ± 0.1	1
1.5 ± 0.1	150
2.5 ± 0.3	300
4.6 ± 0.4	500

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

- A - T
- G - C
- Water
- Ca^{2+}



Interaction energies between *Bam*HI and DNA

Molecular Dynamic Simulations

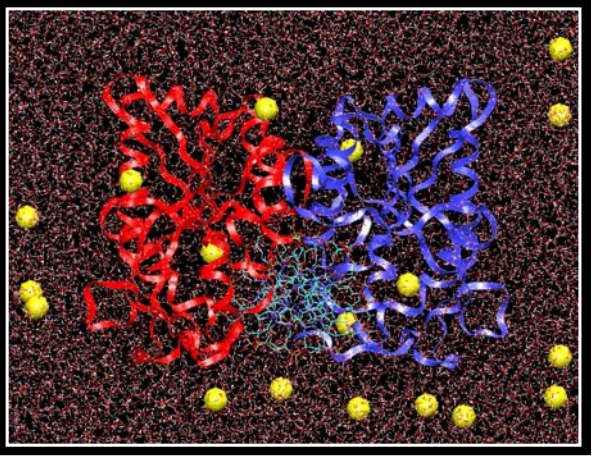
Particle Mesh Ewald Periodic Boundary Conditions

NpT ensemble Pressure control: Nose-Hoover

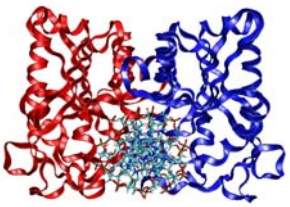
> 65,000 atoms

32 counterions - Na^+

1 ns trajectories



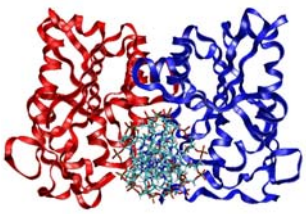
Simulation snapshots



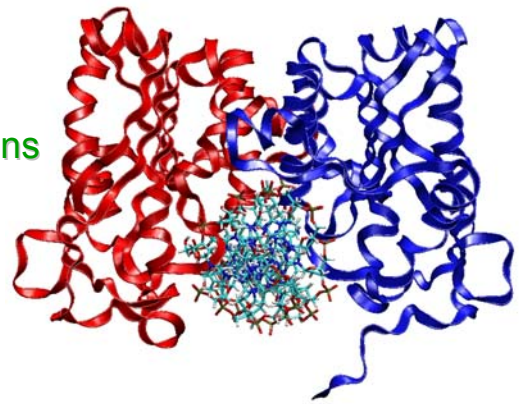
t = 0

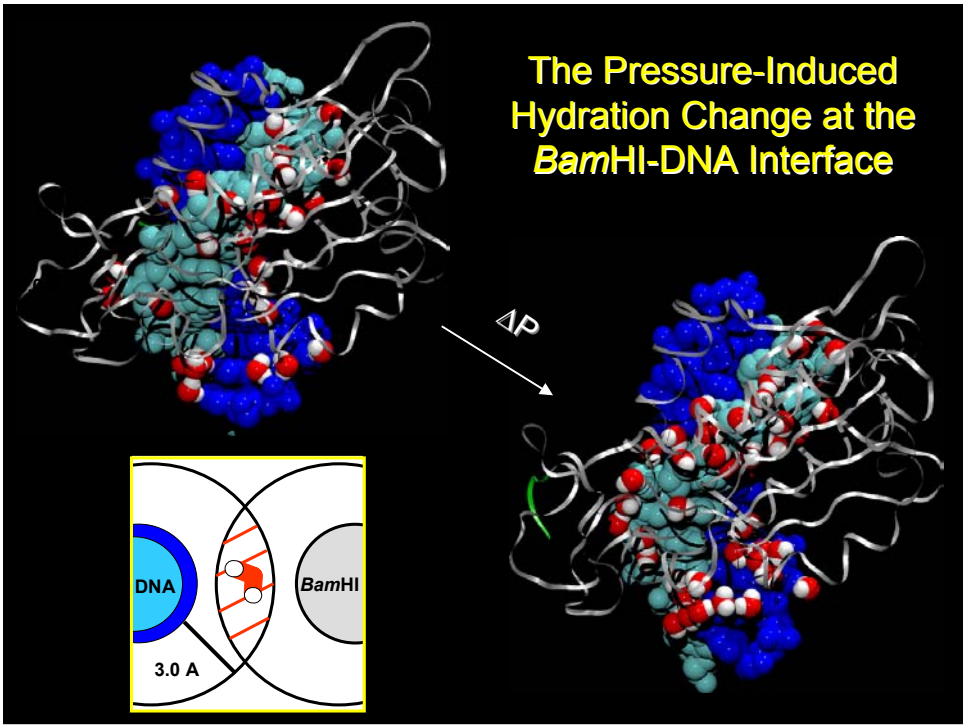
P ~ 400 bar

Ambient pressure

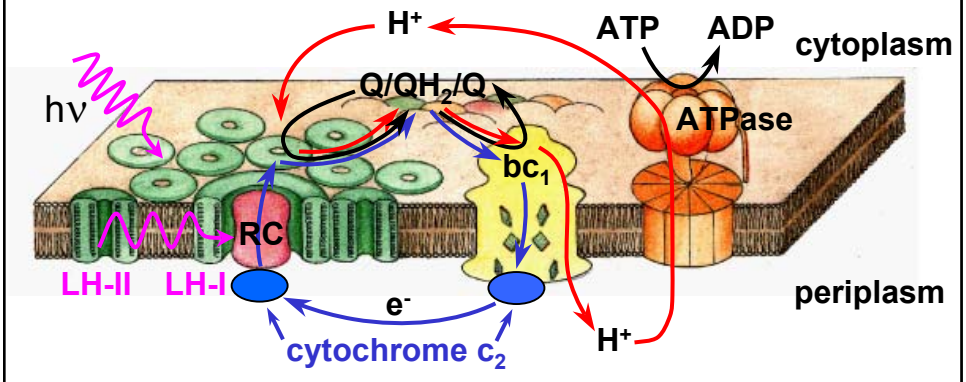


t = 1 ns





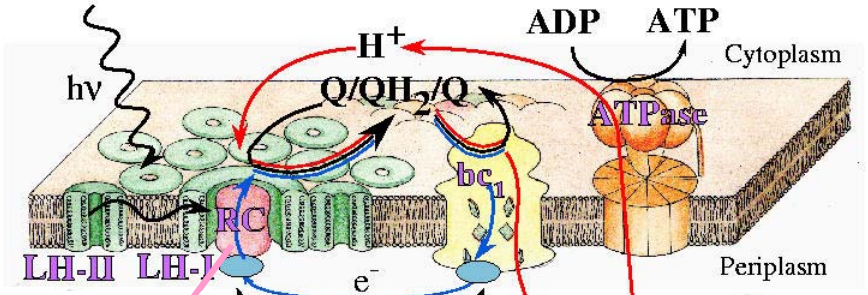
Photosynthetic Apparatus of Purple Bacteria

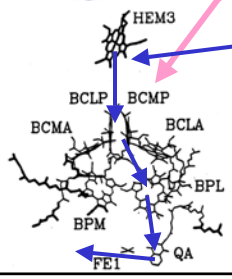


RC - Photosynthetic Reaction Center

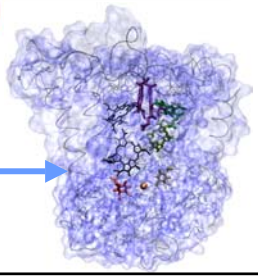
LH – Light Harvesting Complex

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



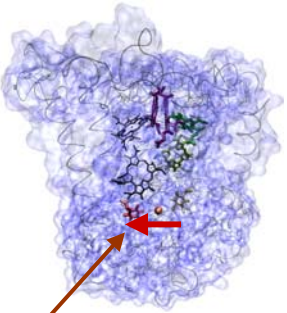


We wanted to describe how electron transfer is coupled to the thermal motion of the surrounding protein.



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 matri**



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

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.

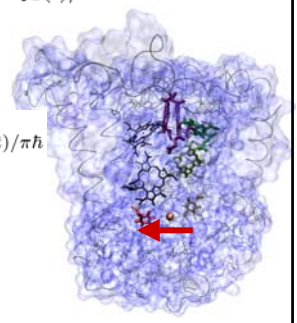
Klaus Schulten. In D. Bicout and M. J. Field, editors, Proc. Ecole de Physique des Les Houches, pp 85--118, Les Editions de Physique, Springer, Paris, 1995.

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

Electron Transfer Process Coupled to the Protein Matrix

Rate for an ensemble of oscillators (spin boson model, Legett et al)

$$k_{qb}(R \rightarrow P) = \frac{v^2}{\hbar^2} \int_{-\infty}^{+\infty} dt\, e^{itE/\hbar}\, e^{iQ_1(t)/\pi\hbar}\, e^{-Q_2(t)/\pi\hbar}$$



Relaxation rate

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

$$Q_1(t) = \frac{\pi}{2} \sum_j \frac{c_j^2}{\hbar\omega_j^3} \sin\omega_j t$$

$$Q_2(t) = \frac{\pi}{2} \sum_j \frac{c_j^2}{\hbar\omega_j^3} \coth\frac{\hbar\omega_j}{2kT} [1 - \cos(\omega_j t)]$$

But we didn't know all the coupling constants c_j? All we needed to know was J

$$J(\omega) = \frac{\pi}{2} \sum_j \frac{c_j^2}{\omega_j}\, \delta(\omega - \omega_j)$$

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

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

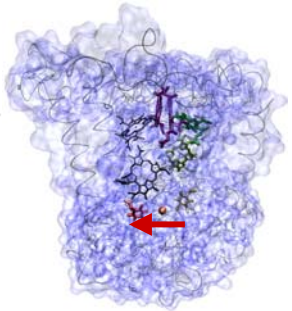
Electron Transfer Process Coupled to the Protein Matrix

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

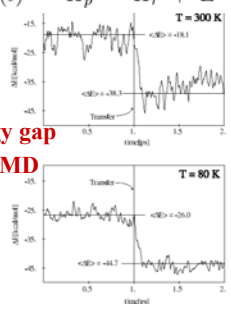
$$\frac{J(\omega)}{\omega} = \frac{\sigma^2}{k_B T} \int_0^{\infty} dt\, C(t) \cos\omega t$$

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

energy gap correlation function

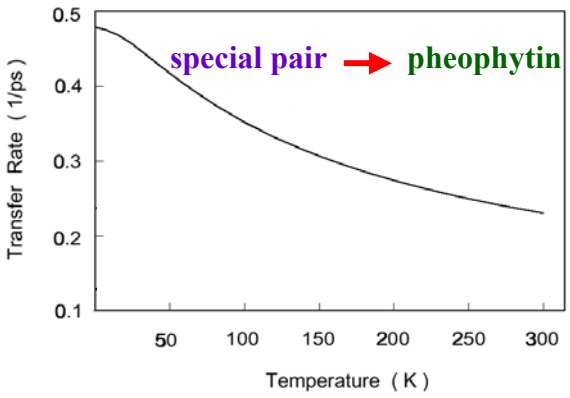
σ **rms deviation of energy gap**

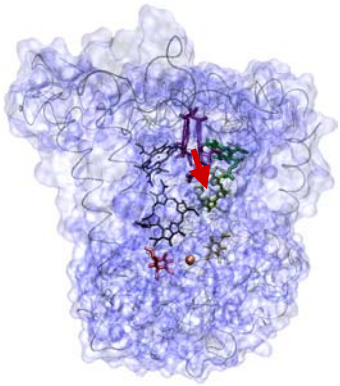
$$\epsilon(t) = \hat{H}_p - \hat{H}_r + E$$



energy gap from MD 1989

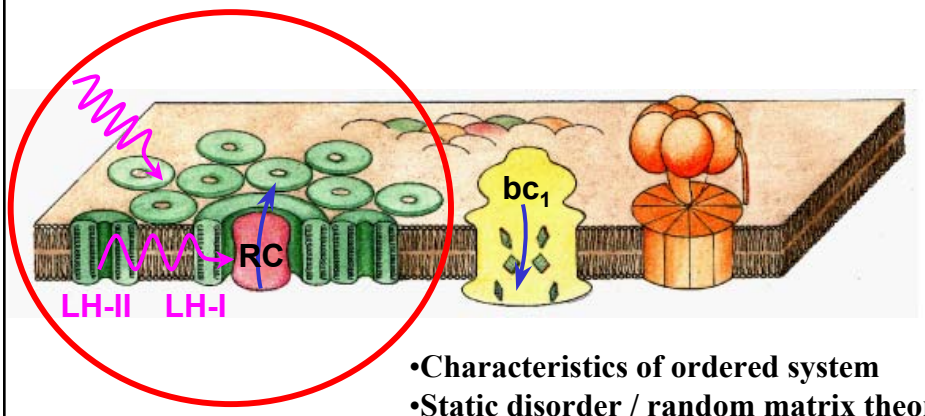
Temperature Dependence of Electron Transfer Rate





Dong Xu

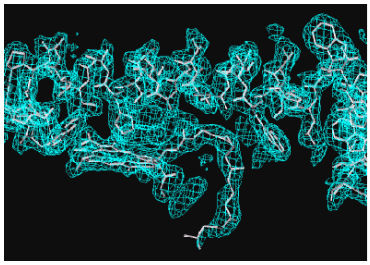
How does the Light Harvesting System Function with Thermal Disorder?

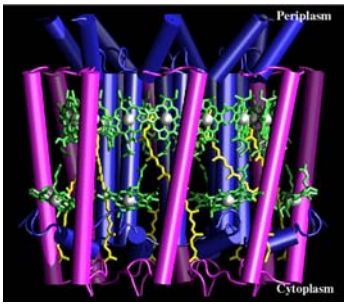


- Characteristics of ordered system
- Static disorder / random matrix theory
- Dynamics disorder / linear response th.
- Dynamic disorder / polaron model
- Role of carotenoids

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

molecular replacement





Summary of Crystallographic Data

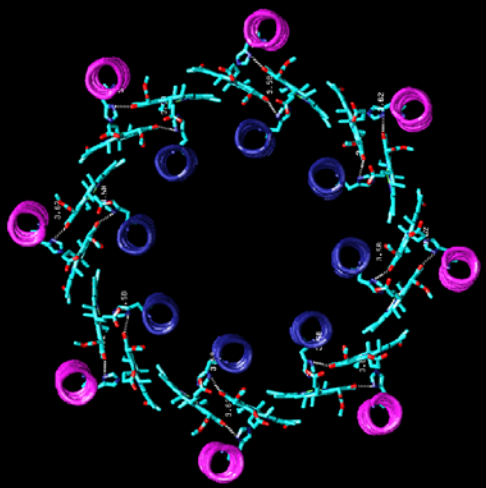
• space group	P4212
• resolution range	8-2.4 A
• unique reflection	30309
• completeness	87.2
• R-factor (%)	21.1
• free R-factor (%)	23.2

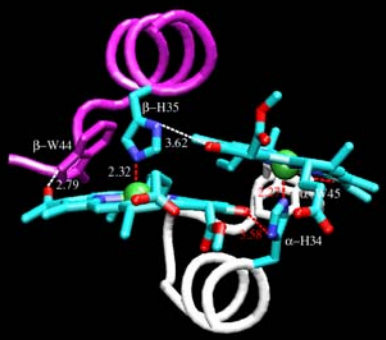
Koepke et al., Structure, **4**, 581 (1996)

Xiche Hu

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

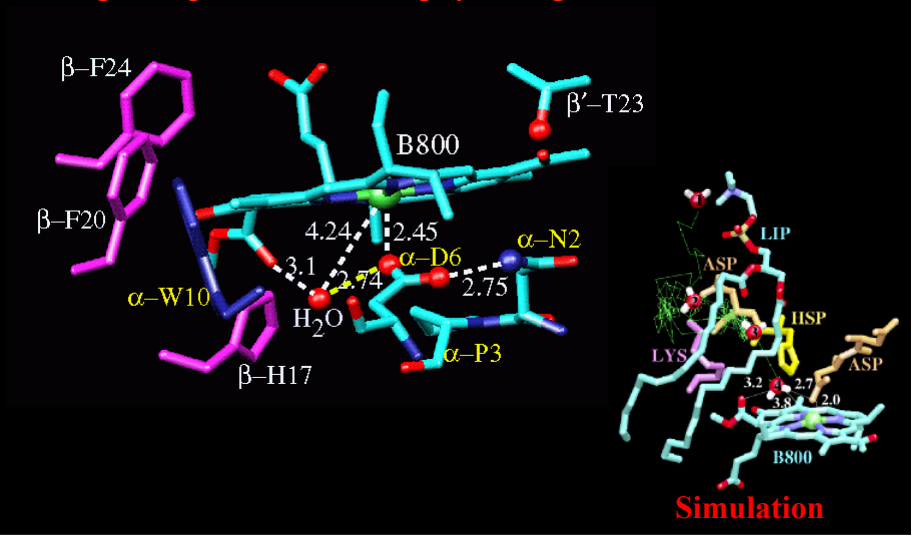




Spectrum tuned through local and excitonic interactions as well as disorder

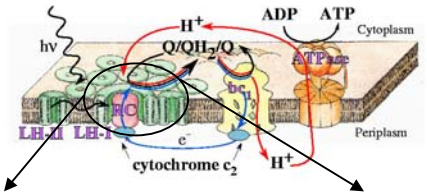
B800 BChl-a Binding Site

New ligation pattern of chlorophyll's Mg atom!

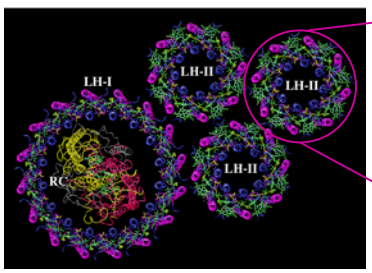


The light harvesting system displays a hierarchy of integral, functional units

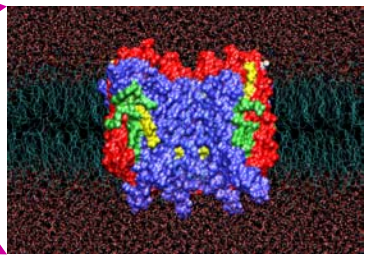
Photosynthetic membrane generates ATP using light energy



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

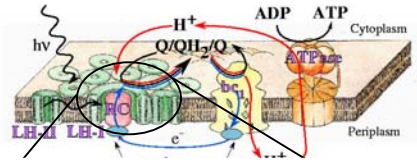


Light harvesting complex II absorbs light and converts it into electronic excitations of BChls

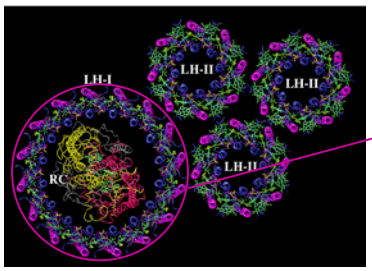
Molecular modeling of integral, functional units with more than 10^6 atoms necessary

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)
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)

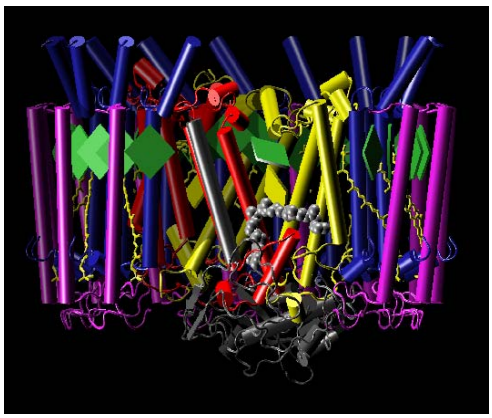


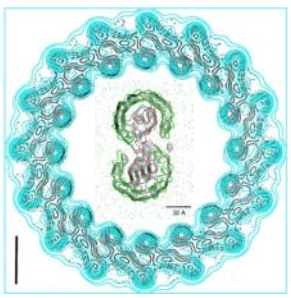
We need to know also the structure of the LH-I ring! We use again modeling, replacing subunit of LH-II by that of LH-I

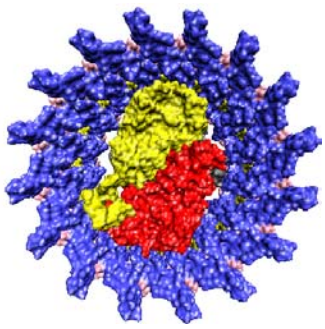
Molecular modeling of integral, functional units with more than 10^6 atoms necessary

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

Model agrees well with EM map



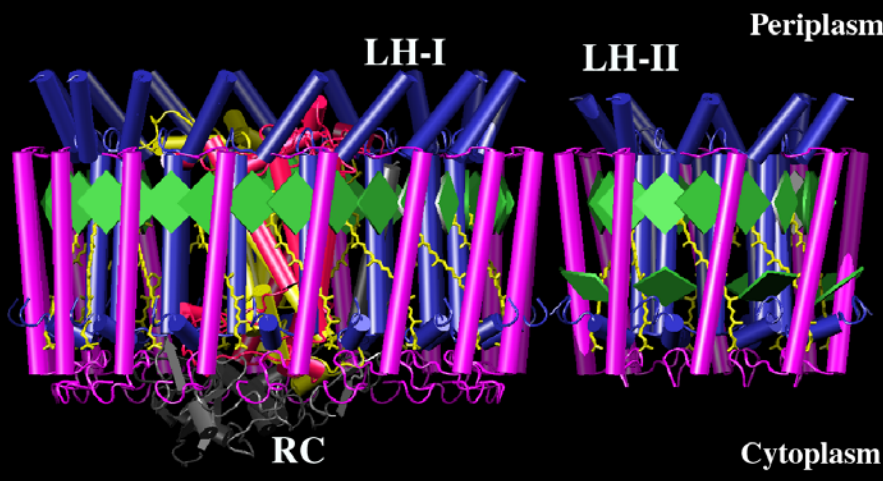




Xiche Hu

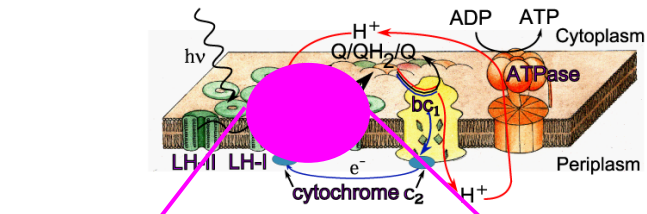
View from top

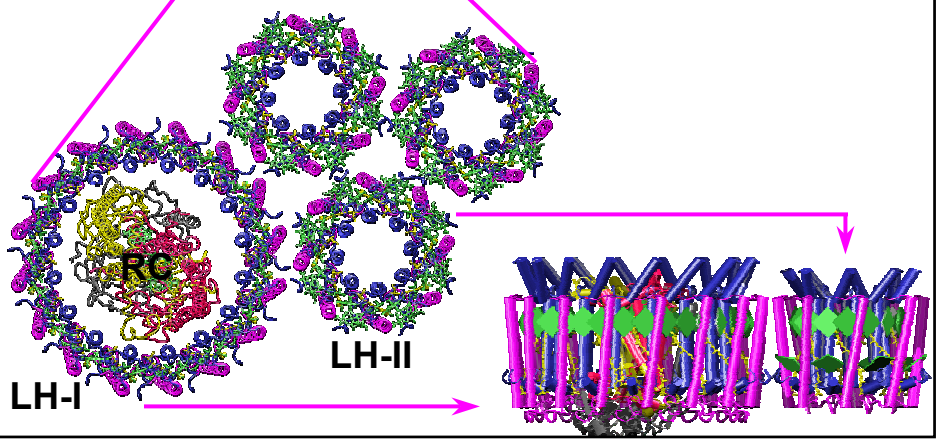
Pigment Organization in the Bacterial Photosynthetic Membrane



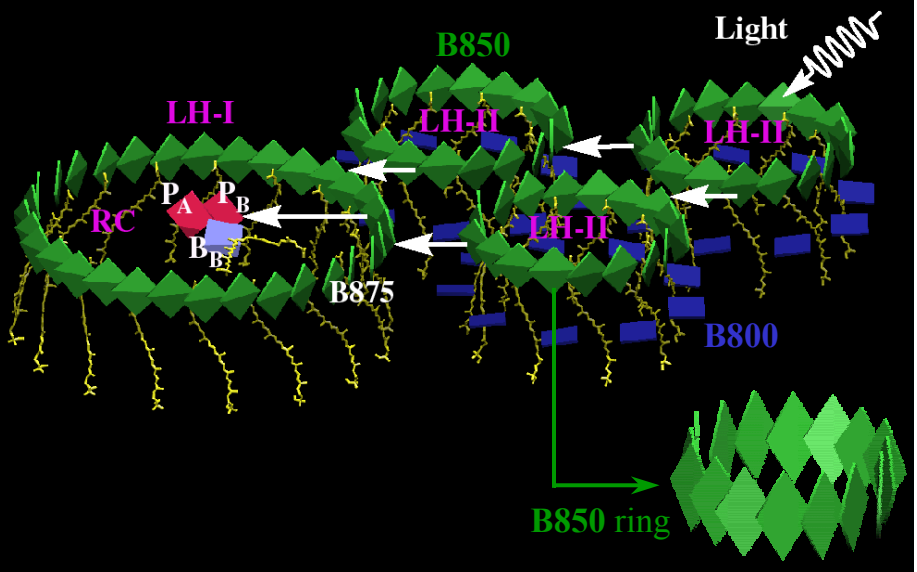
Note the conspicuous arrangement of chlorophyll rings!

Structure of Light Harvesting System





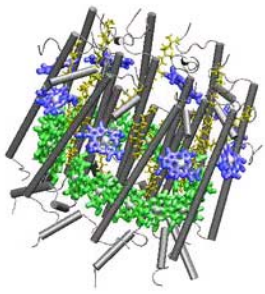
Hierarchical aggregate of *chromophores*



The Effect of Dynamic Disorder

Molecular Dynamics (MD) Simulation

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



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

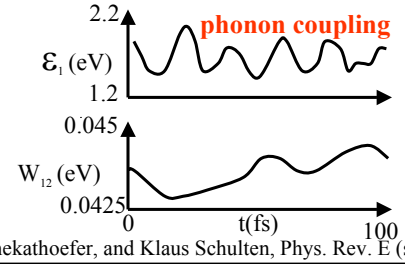
Followed by 0.8ps simulation, trajectory output every 2fs with quantum chemistry calc. of exc. energy, interpolated to "sample" every 0.5 fs

from QC

from MD

$$\hat{H}(t)^{exc} = \begin{pmatrix} \epsilon_1(t) & & & \\ & \epsilon_2(t) & W_{ij}(t) & \\ & & \ddots & \\ & & & \epsilon_{16}(t) \end{pmatrix}$$

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



Ana Damjanovic, Ioan Kosztin, Ulrich Kleinekathoefer, and Klaus Schulten, Phys. Rev. E (submitted)

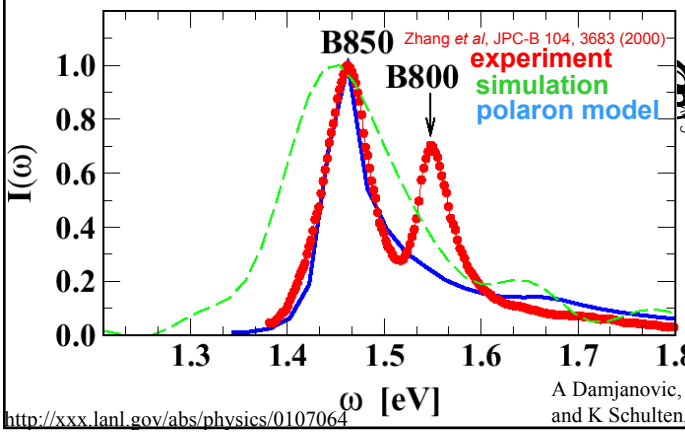
Absorption Spectrum – B850 Excitons

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

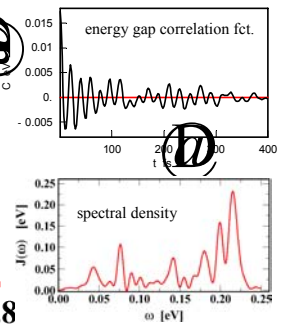
$$\Phi_k(t) = \int_0^t d\tau (t-\tau) \mathcal{D}(\tau) F_k(\tau)$$

phonon contribution

exciton contribution



From MD/QC simulation

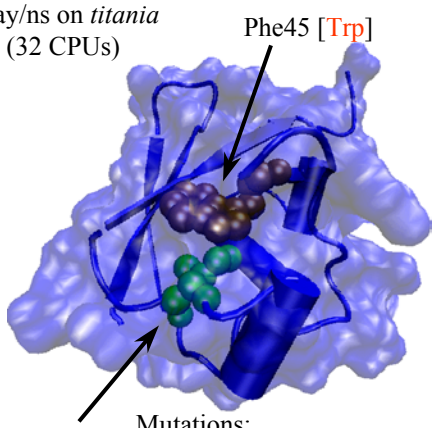


A Damjanovic, I Kosztin, U Kleinekathoefer, and K Schulten, Phys. Rev. E (subm.)

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

Folding of Ubiquitin

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



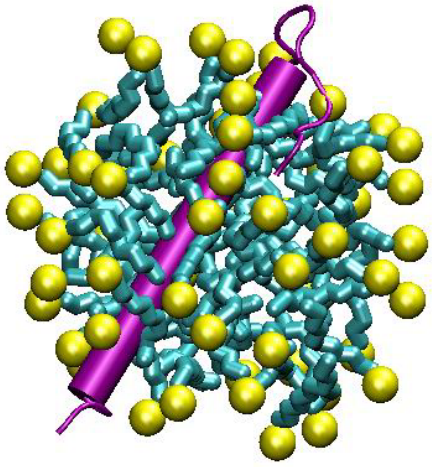
Mutations:
Val61 – MD simulations
Ala61 – experiment and MD simulations

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