Oak Ridge National Laboratory

Managed by UT-Battelle for the Department of Energy

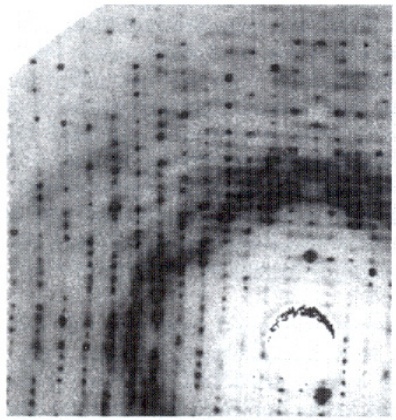
University of Tennessee

ORNL

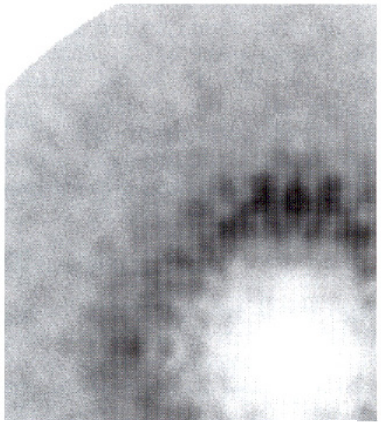
Center for Molecular Biophysics

Jeremy C. Smith

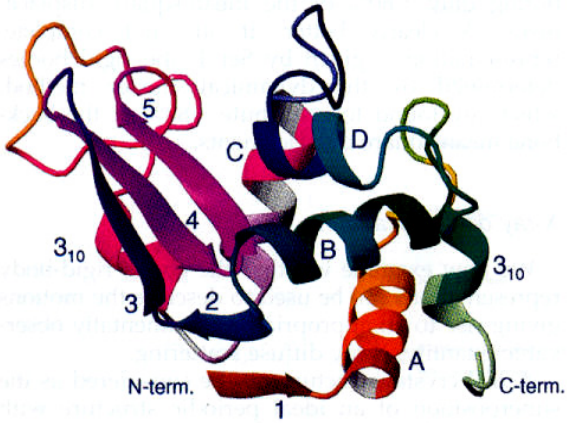
Molecular Dynamics of Lysozyme Unit Cell

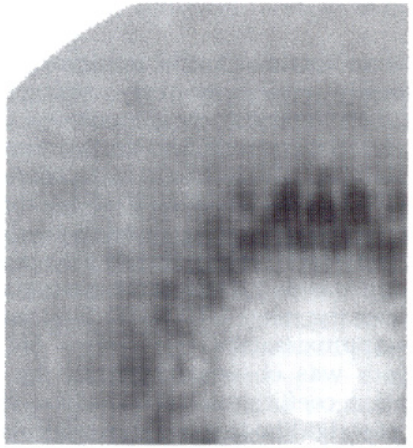


Experimental



Full Trajectory





Nat. Struct. Mol.Biol
1 124 (1994)
Comp. Phys. Comm.
91 331 (1995)
J Mol Biol
279 303 (1998)

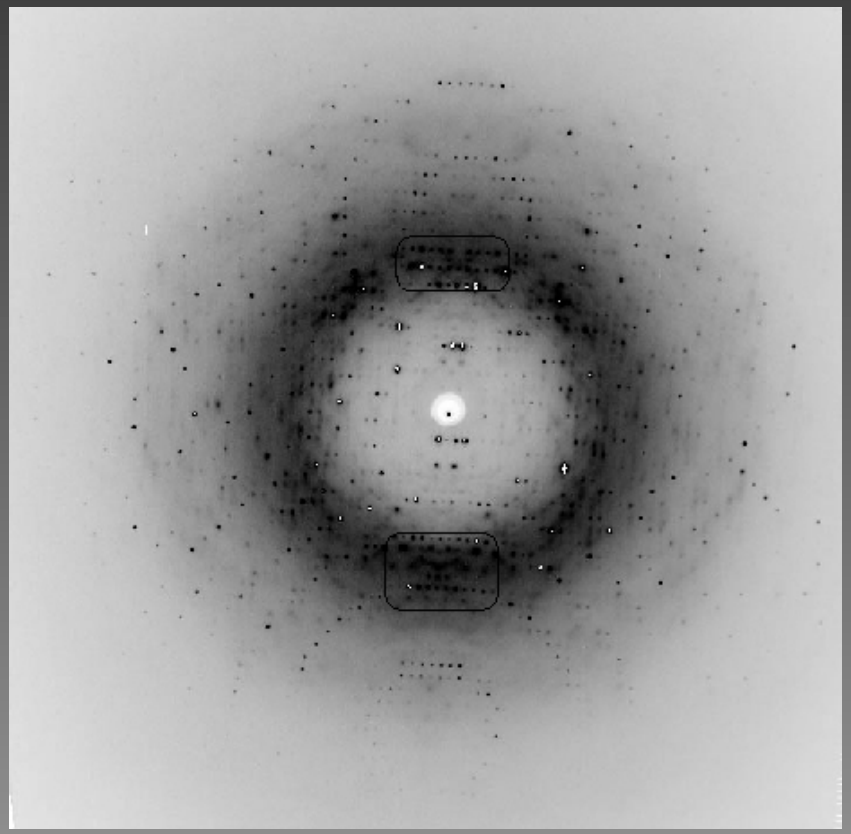
Rigid-Body Decomposition

Rigid-Body Fit
(R-factor re: Full Trajectory = 5.3%)

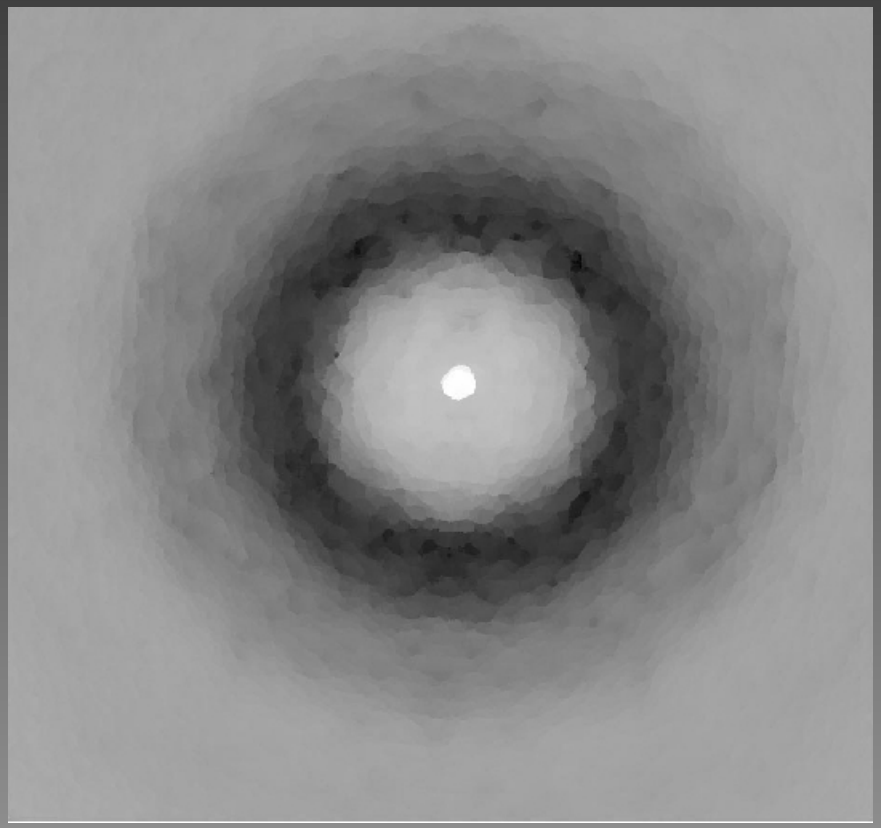
Staph. nuclease

Wall et al., PNAS 94 6180 (1997).

Still exposure



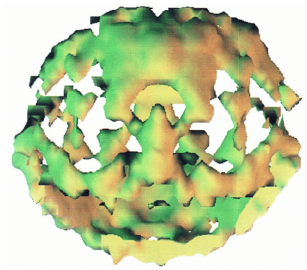
Diffuse scattering after removal of Bragg peaks

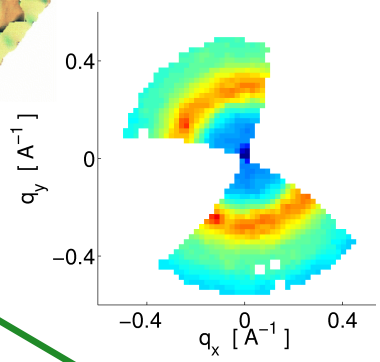


SNase diffuse scattering calculations

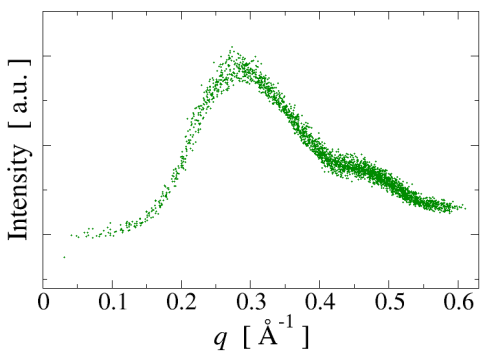
MD simulations

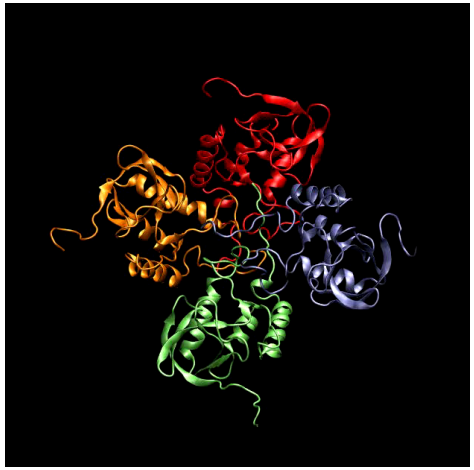
- unit cell: 15993 atoms
  4 proteins
  2115 *TIP3P* + 48 Cl^-
- CHARMM (param:22)
- PME
- Nose-Hoover (300K,1bar)
- 4 ×10*ns*, Δt =1*fs*



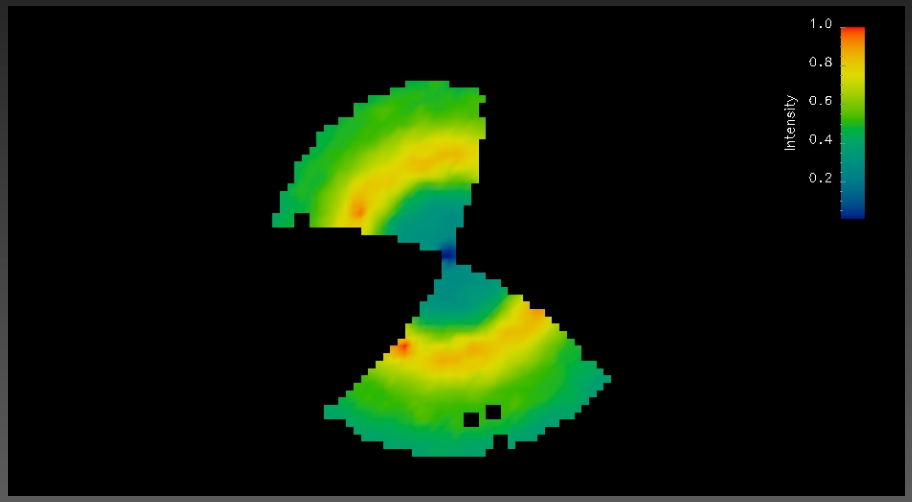


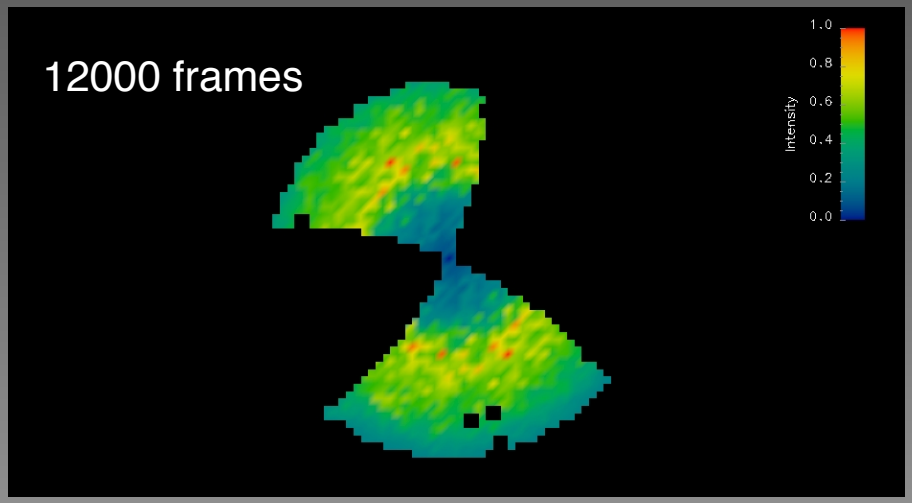
data reduction
3D – 2D – 1D





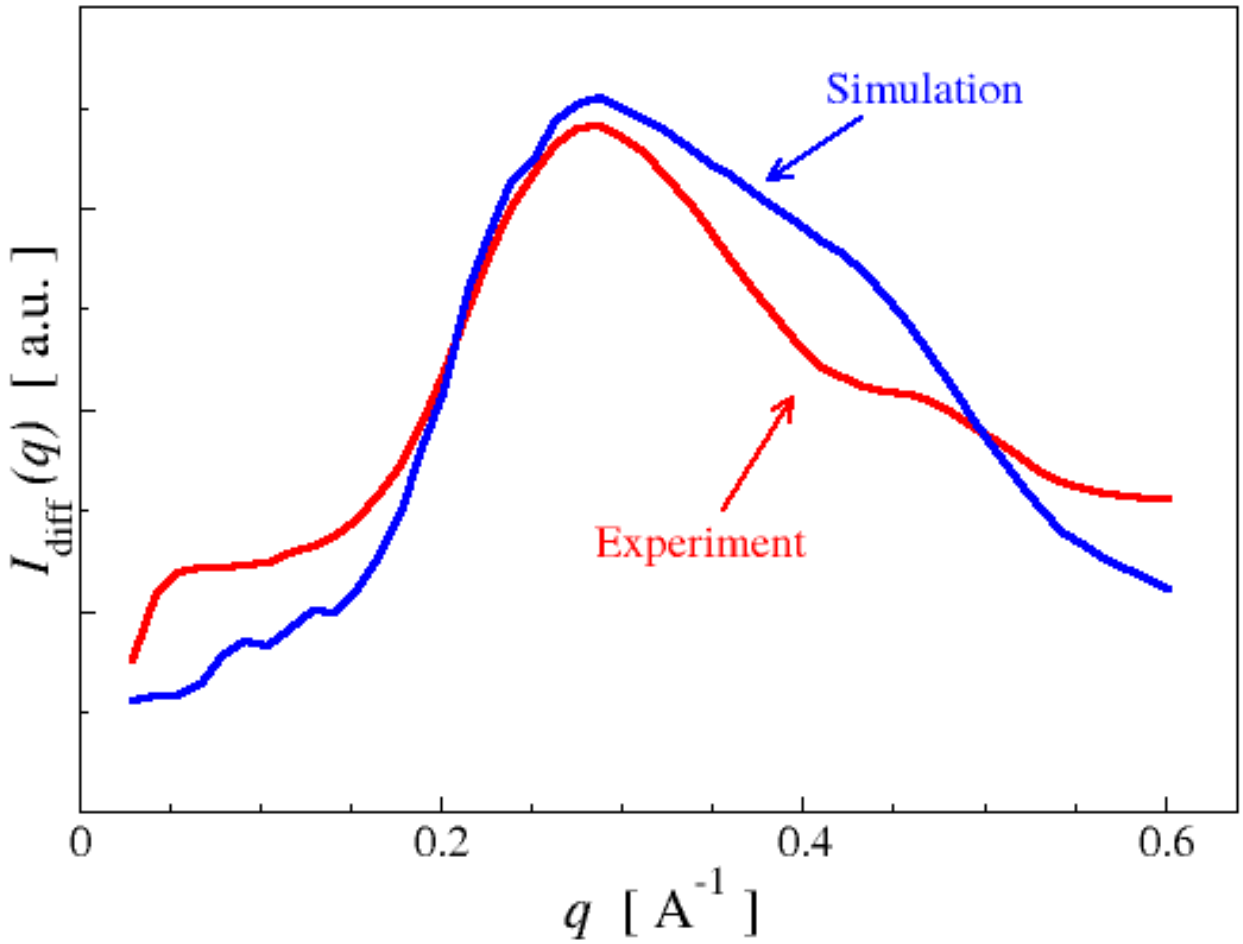
Intensity in hk0 plane



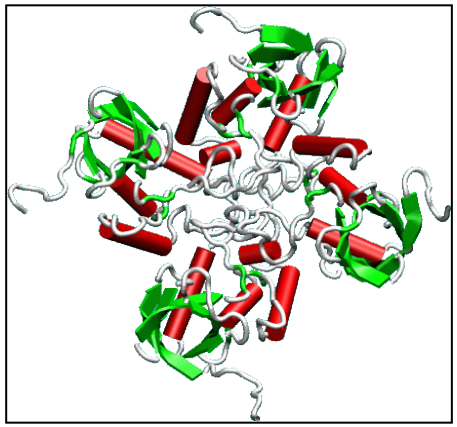


Physica B *350* 127 (2004)

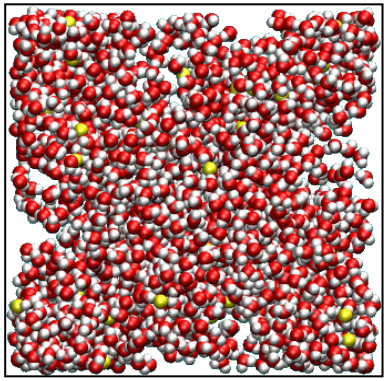
X-Ray Diffuse Scattering



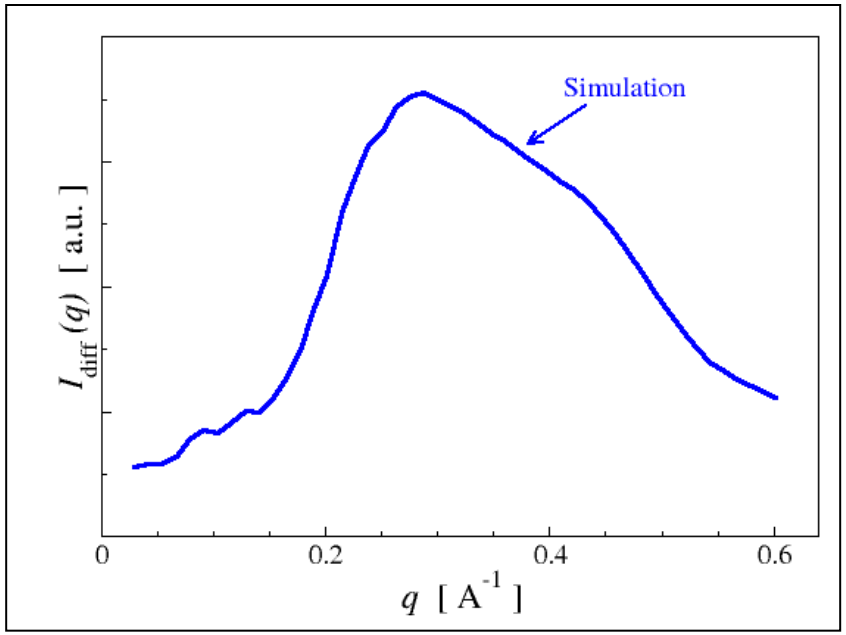
Protein Scattering



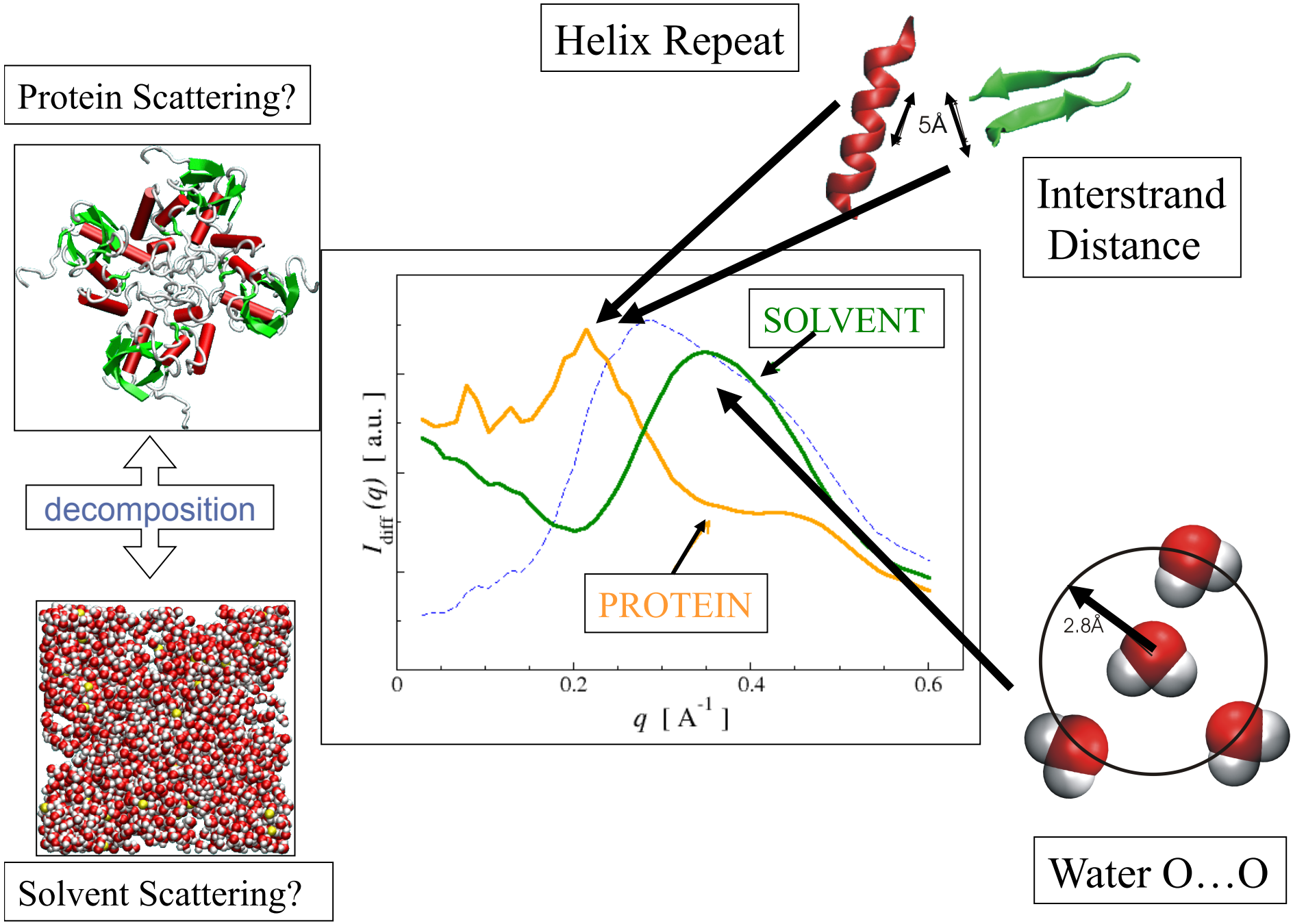
decomposition



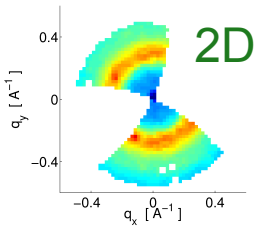
Solvent Scattering



PRL **95**:218103 (2005)



PRL **95**:218103 (2005)



$$I_{\text{diff}} \propto \sum_{kk'} f(k,k')\left[e^{\mathbf{q}^T \langle \mathbf{u}_k \mathbf{u}_{k'}^T \rangle \mathbf{q}} - 1\right]$$

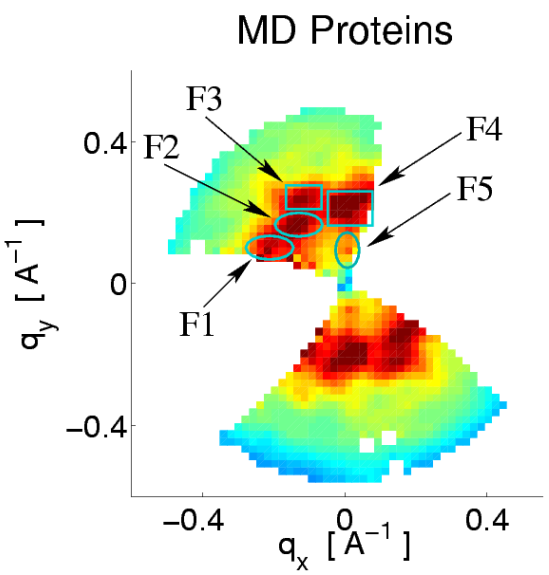
variance-covariance matrix

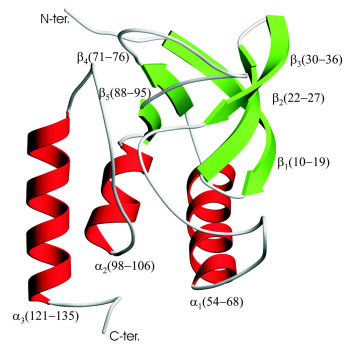
$\langle u_k u_{k'}{}^T \rangle$

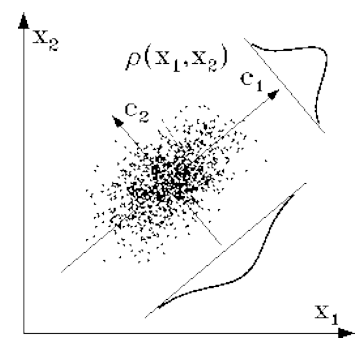
decomposition

pairs (k,k')

PCA

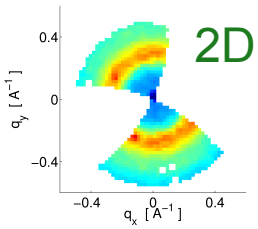




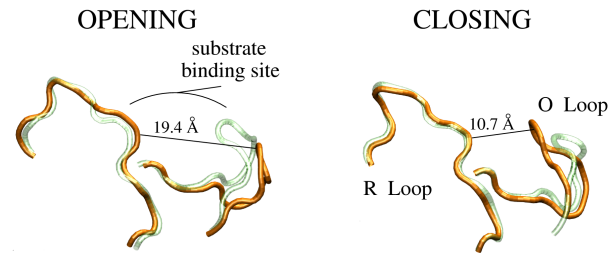


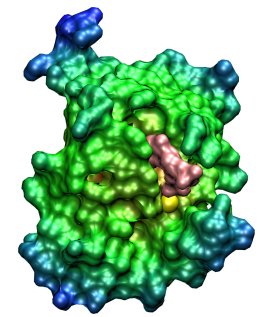
Which parts of the protein and which types of motion cause the intense scattering features?

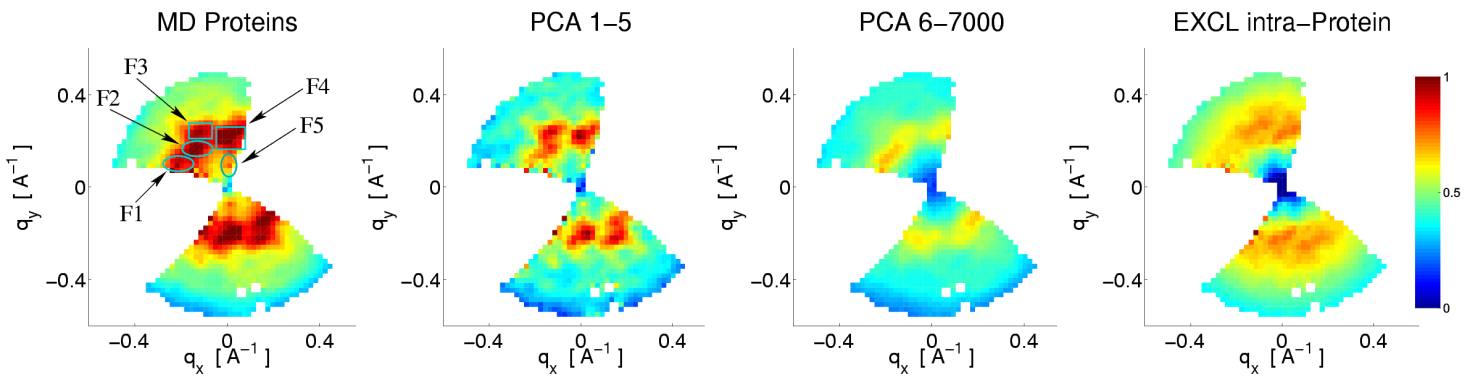
PRL **95**:218103 (2005)

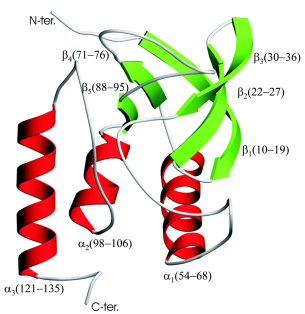


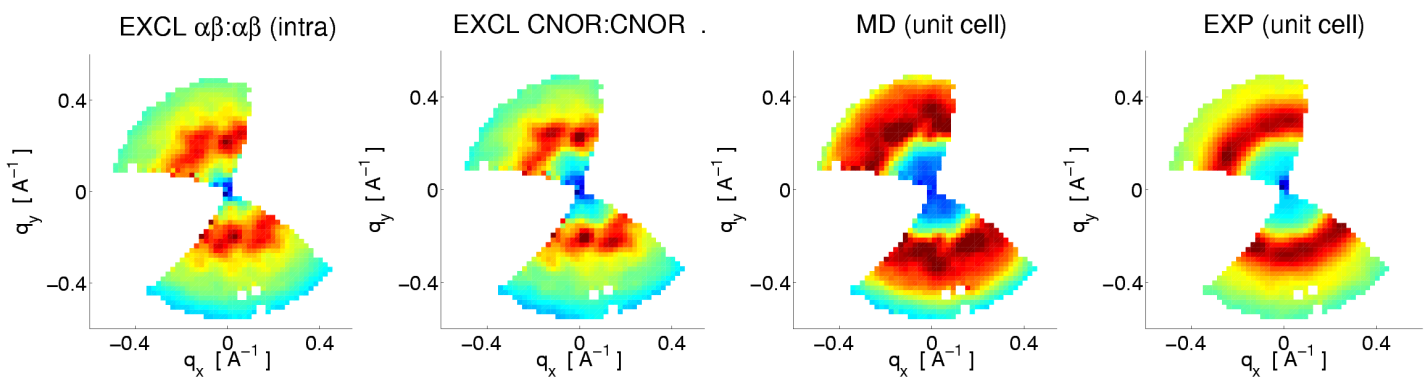
$$I_{\text{diff}} \propto \sum_{kk'} f(k,k')\left[e^{\mathbf{q}^T \langle \mathbf{u}_k \mathbf{u}_{k'}^T \rangle \mathbf{q}} - 1\right]$$





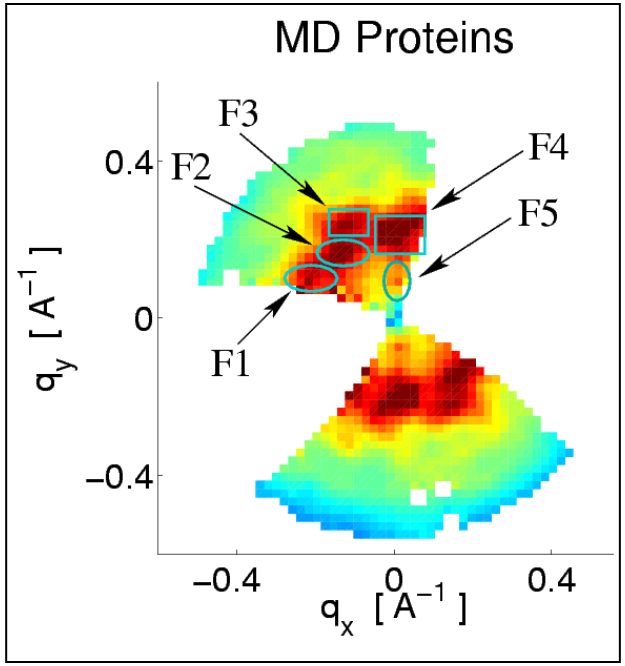




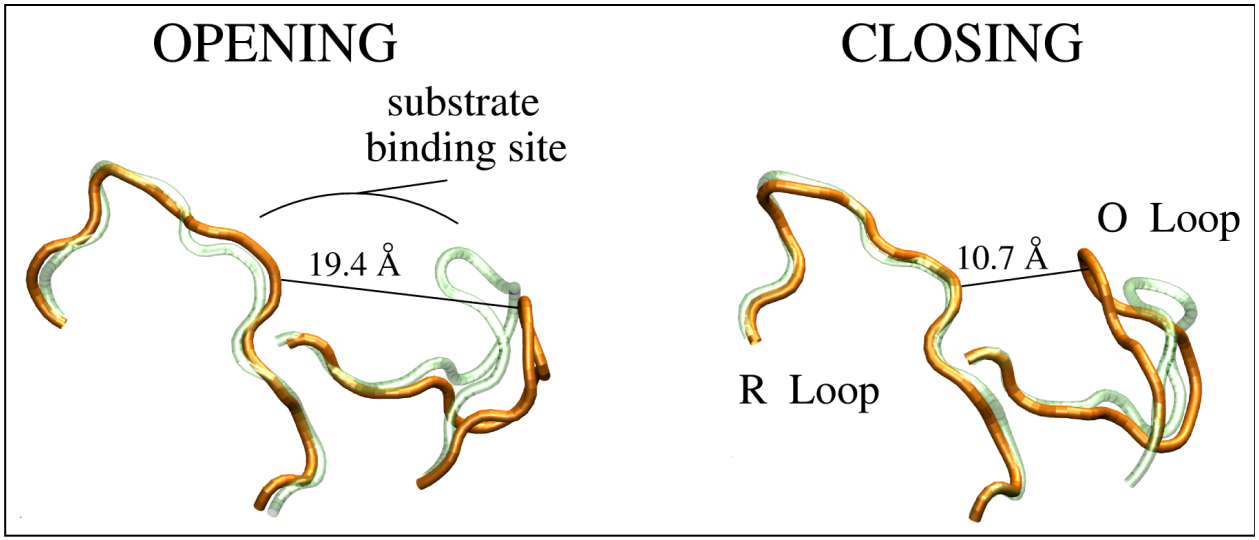


PRL **95**:218103 (2005)

Specific Motions in Diffuse Scattering Pattern

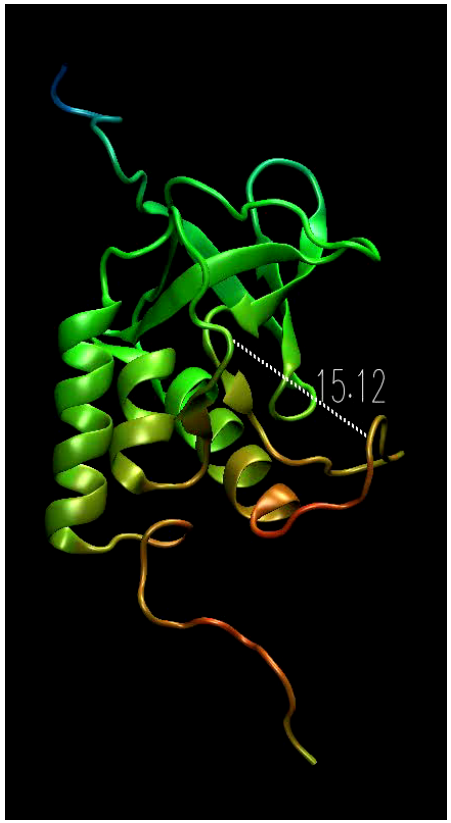


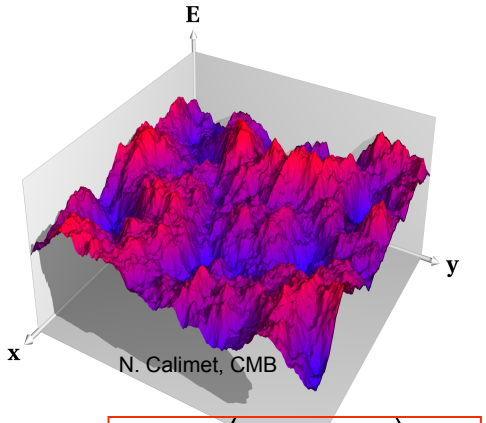
Feature F2



PRL **95**:218103 (2005)

Dynamical Characterization of PCA modes



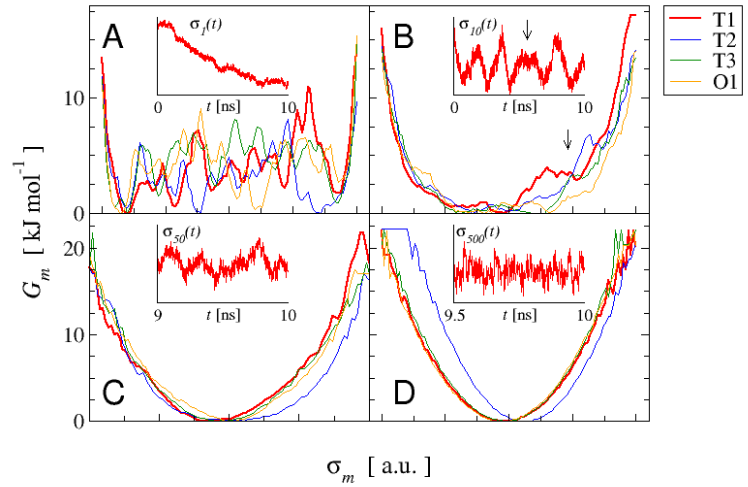


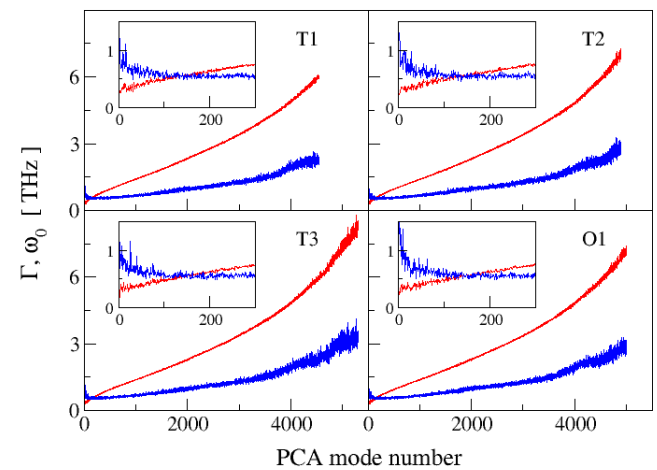
$$\sigma_m = \left(M^{1/2}\,\mathrm{u}^T\right)\cdot \mathrm{v}_m$$

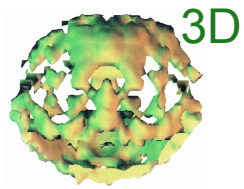
$$G_m = -k_B T \ln p_{\sigma_m}$$

$$\dot{\sigma} = v$$

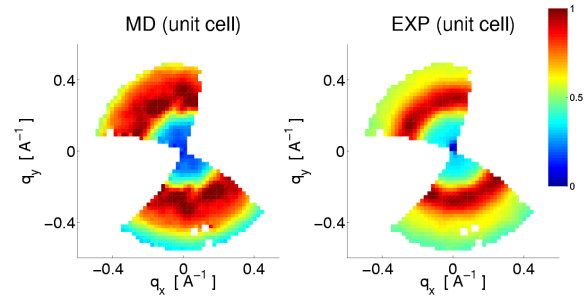
$$\dot{v} = -\Gamma v - \omega_0^2 \sigma + \xi$$







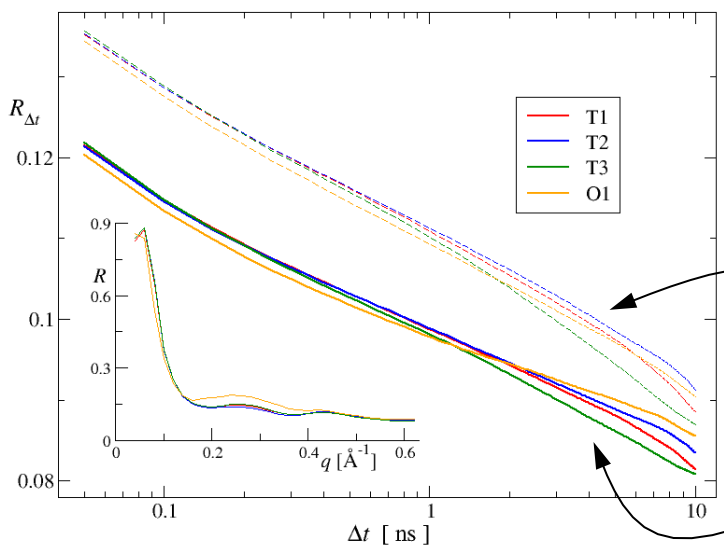
Convergence of Diffuse Scattering



MD scattering not converged

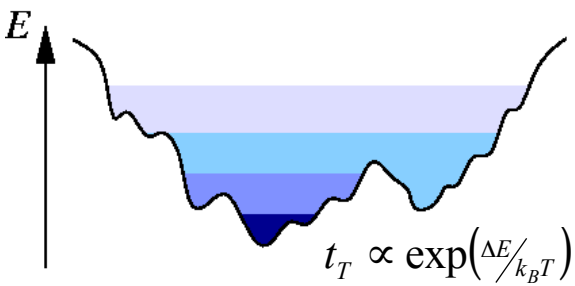
Agreement factor: EXP - MD

$$R = N_q^{-1} \sum_q \frac{I_q^{Exp} - I_q^{MD}}{I_q^{Exp}}$$



without hydrogens including

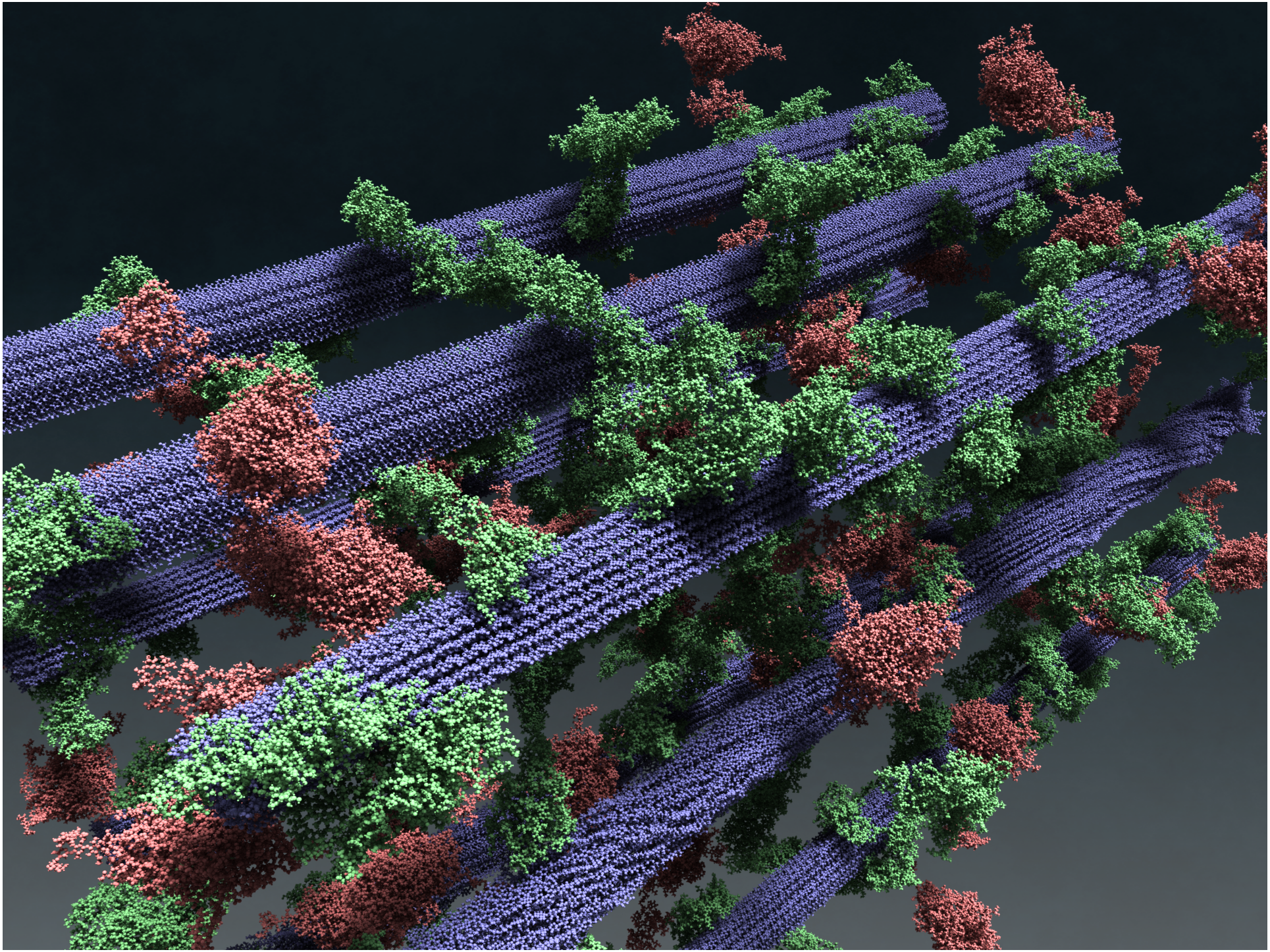
$$R_{\Delta t} \propto \log \Delta t \quad \Rightarrow \quad \Delta t^* \approx 1\mu s$$



BiophysJ **88**:2554 (2005)

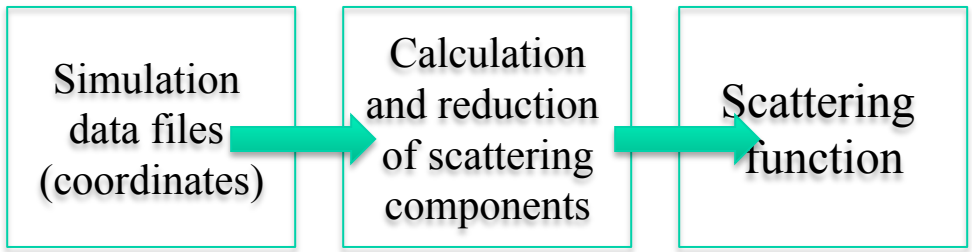
MAN HATE !
WOMAN LOVE !
BURT LANCASTER'S toughest portrayal topping "The Killers" for thrills!
Mark Hellinger
TELLS IT THE "KILLERS" WAY !
BRUTE FORCE
with the men on the "inside"
BURT LANCASTER
HUME CRONYN
CHARLES BICKFORD
SAM LEVENE HOWARD DUFF ART SMITH JEFF COREY
and as the women on the "outside"
YVONNE DeCARLO
ANN BLYTH
ELLA RAINES
ANITA COLBY

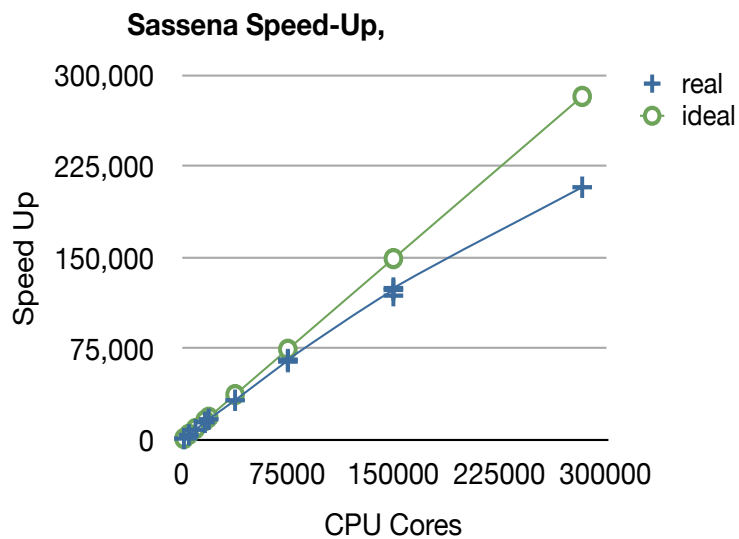
TITAN



SASSENA: Calculating Scattering Profiles on Massively Parallel Supercomputers

$$\vec{r}(n,t) \mapsto f(\vec{q},n,t) \mapsto F(q,\tau)$$



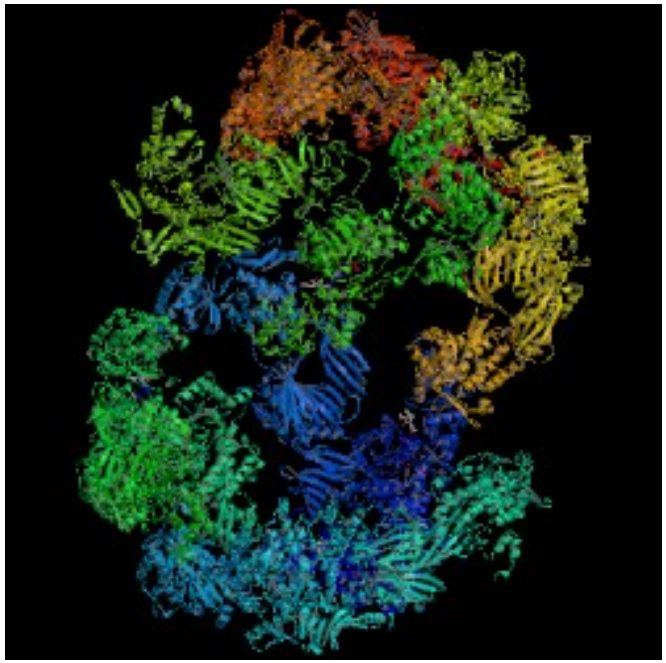


Sassena solves computational performance problems, e.g. :

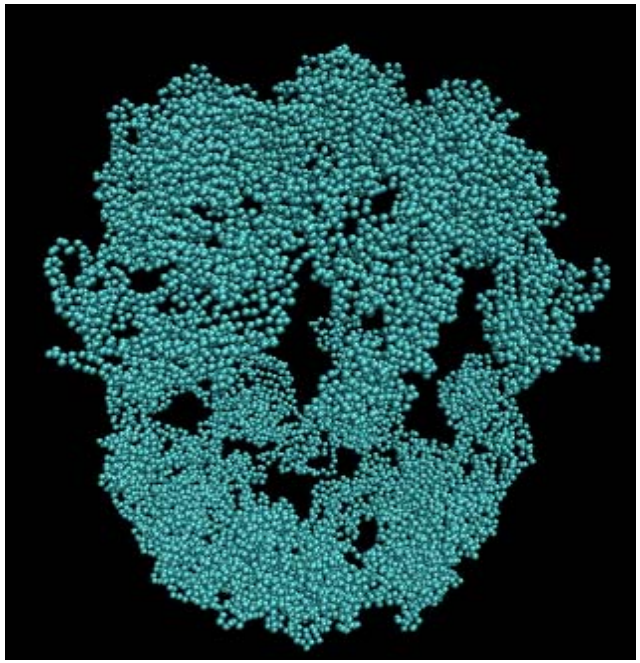
- Optimal placement of simulation data in memory
- Minimal IO requirements (no redundant reads)
- Utilization of optimized parallel partitioning
- Calculation and storage of results is asynchronous (buffered)

(www.sassena.org)

Self-Consistent Multiscaling



Mapping

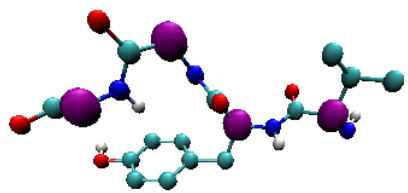


Atomic-Detail Model

Coarse-Grained Model

REACH
(Realistic Extension Algorithm via Covariance Hessian)

All-Atom (AA) Model



(CG) Model

$$E_{AA} = \frac{1}{2}\sum_{bonds} K_b (b-b_0)^2 + \frac{1}{2}\sum_{angles} K_\theta (\theta-\theta_0)^2 + \frac{1}{2}\sum_{dihedrals} K_\varphi [1+\cos(n\phi-\delta)] + \sum_{nonbonds}\left[\frac{A}{r^{12}} - \frac{B}{r^6} + \frac{q_1 q_2}{Dr}\right]$$

$$E_{CG} = \frac{1}{2}\sum_{i<j} k_{ij}(r_{ij}-r_{ij}^0)^2$$

$$E_{CG}(x_{CA}) = \int P(\mathbf{x}) E_{AA}(x_{CA}, x_N, x_C, \mathrm{L})\, dx_N dx_C \mathrm{L}$$

$$C_{ij} = \left\langle \left(x_i - \langle x_i \rangle\right)\left(x_j - \langle x_j \rangle\right)\right\rangle$$

S_{AA} S_{CG}

$\langle x^2 \rangle_{AA}$ $\langle x^2 \rangle_{CG}$

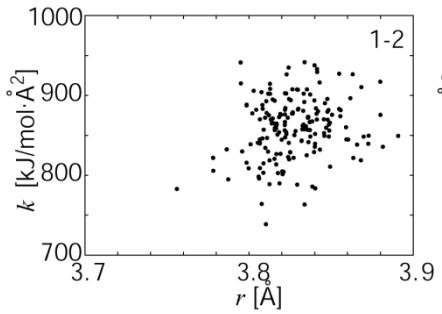
C: covariance matrix

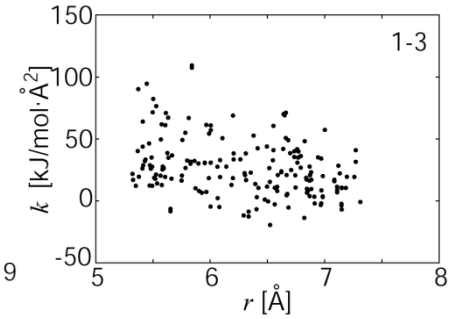
$k_{ij} = -k_B T \, \mathrm{tr}\,(C_{ij}^{-1})$

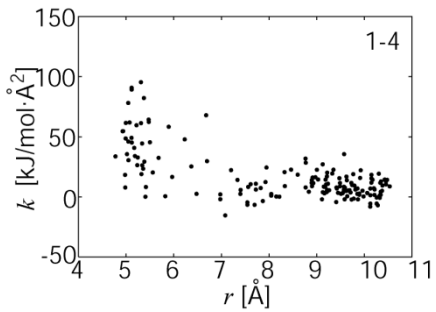
Biophys. J. 93 3460 (2007); 95 1639 (2008).

REACH
Force Constants and Fluctuations
Dihydrofolate Reductase

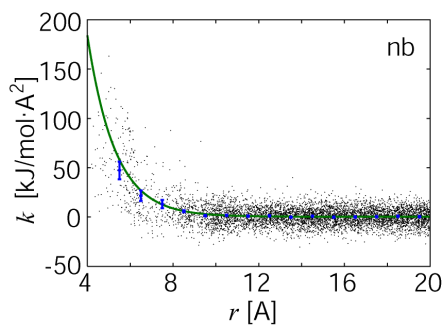
Local Interactions



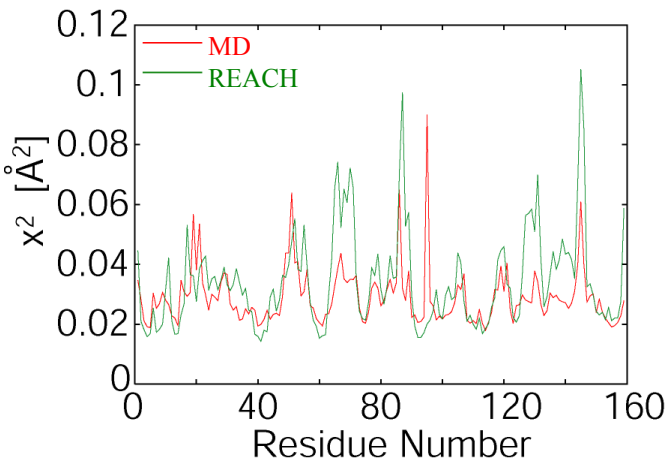




Nonbonded Interactions



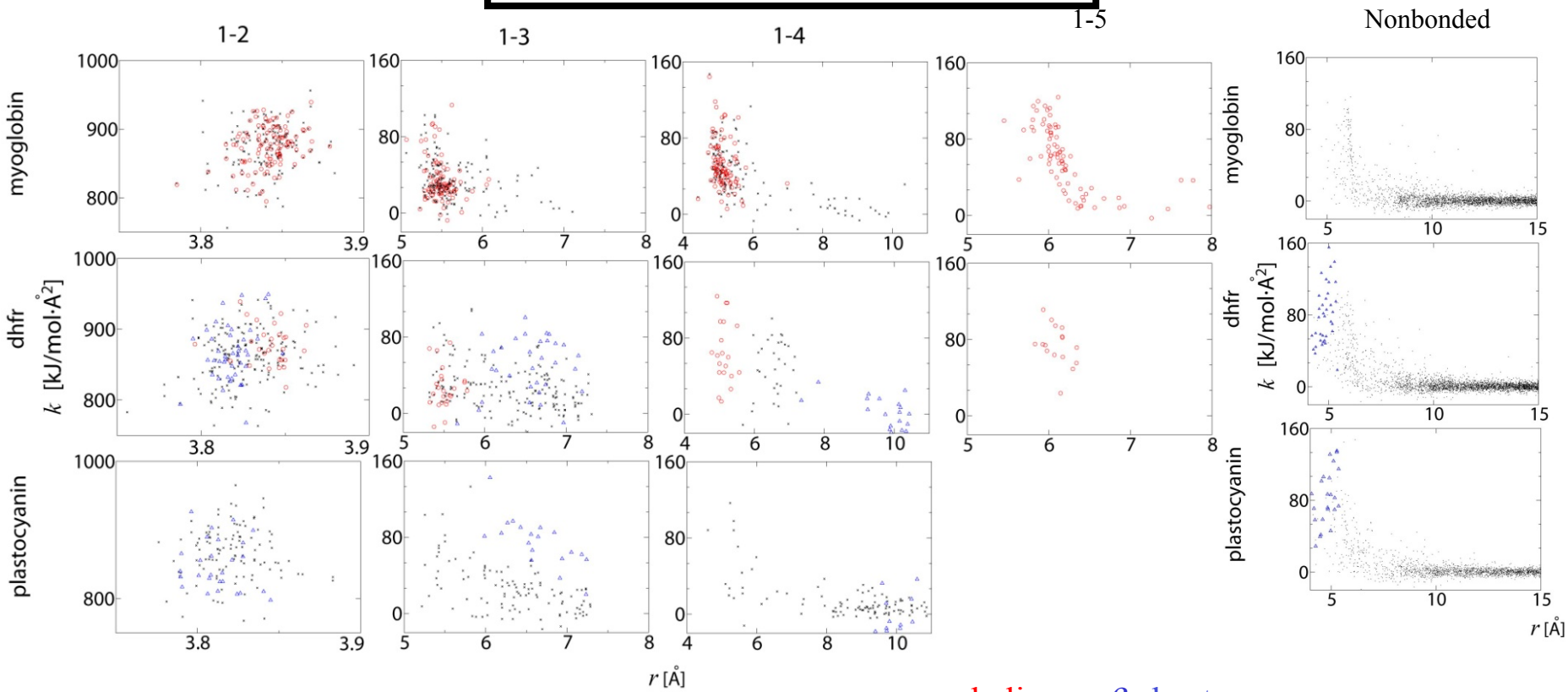
Mean-Square Fluctuations



	$\langle x^2 \rangle$ [Å^2]	corr. coef.
MD	0.0310	
REACH	0.0336	0.54

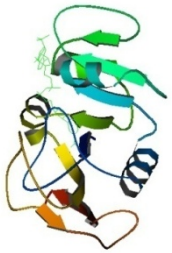
Comp. Phys. Comm. 180, 1188 (2009).

Transferability of *REACH* Force Field



α-helices β-sheets

myoglobin

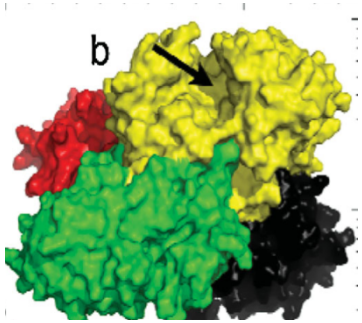


DHFR

plastocyanin

Biophys. J. 97 1158 (2009)

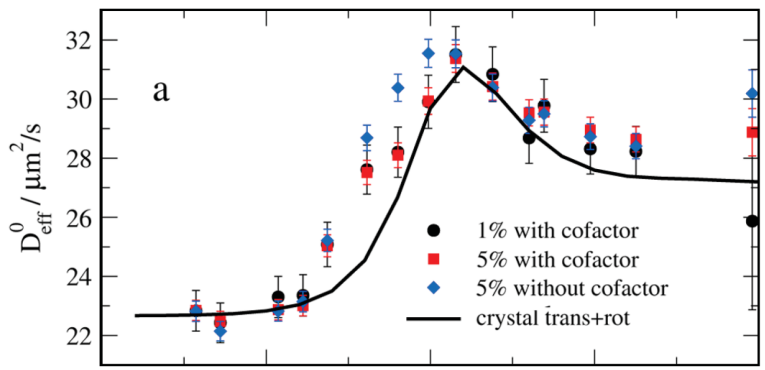
Alcohol Dehydrogenase



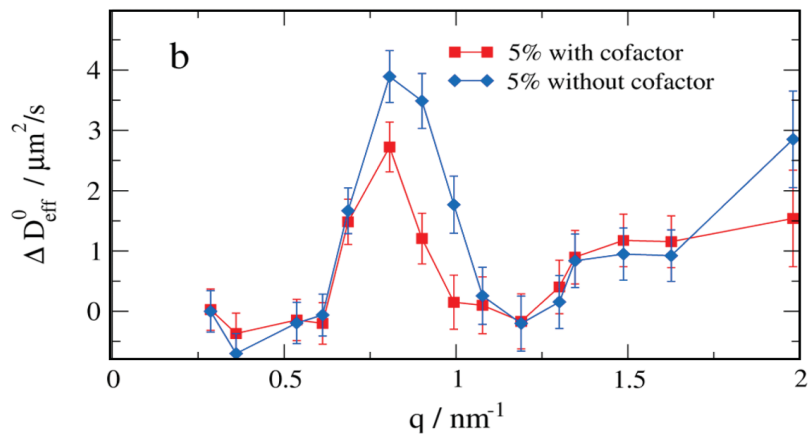
Biophys. J. 102 1108 (2012)

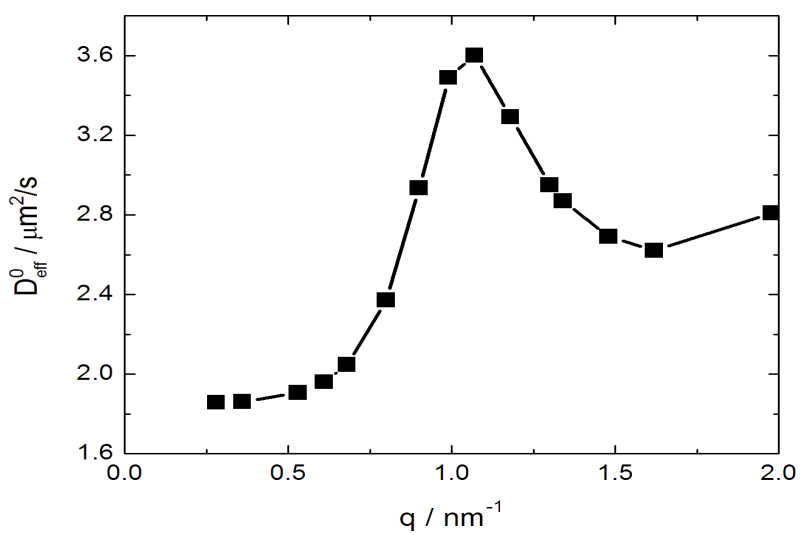
Neutron Spin Echo

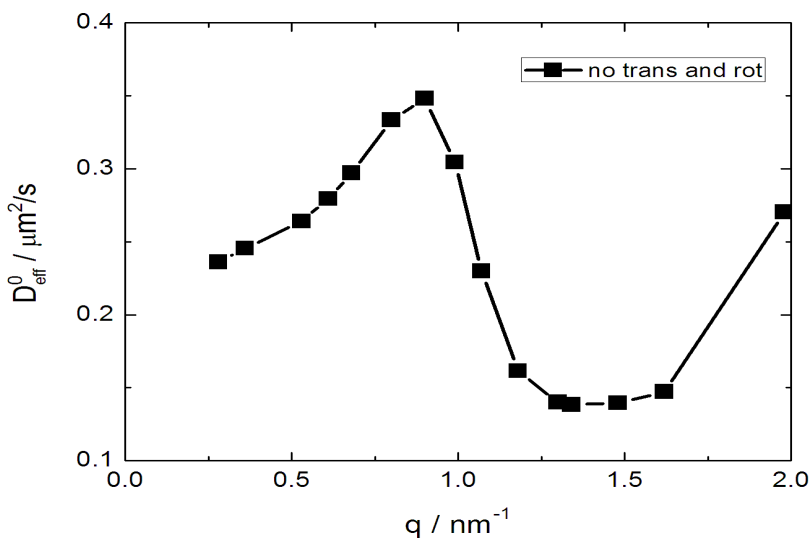
Single tetramer diffusion coefficient



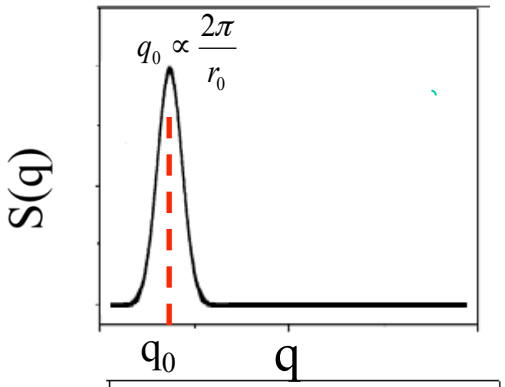
Internal component

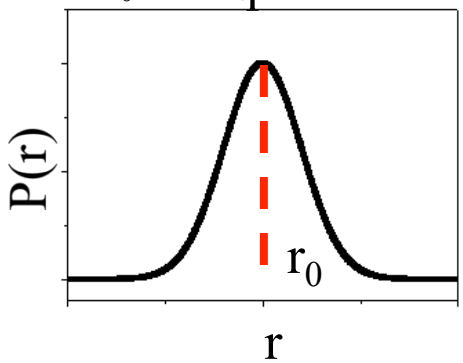


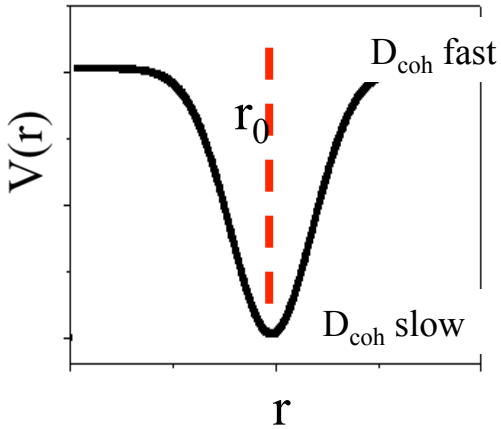


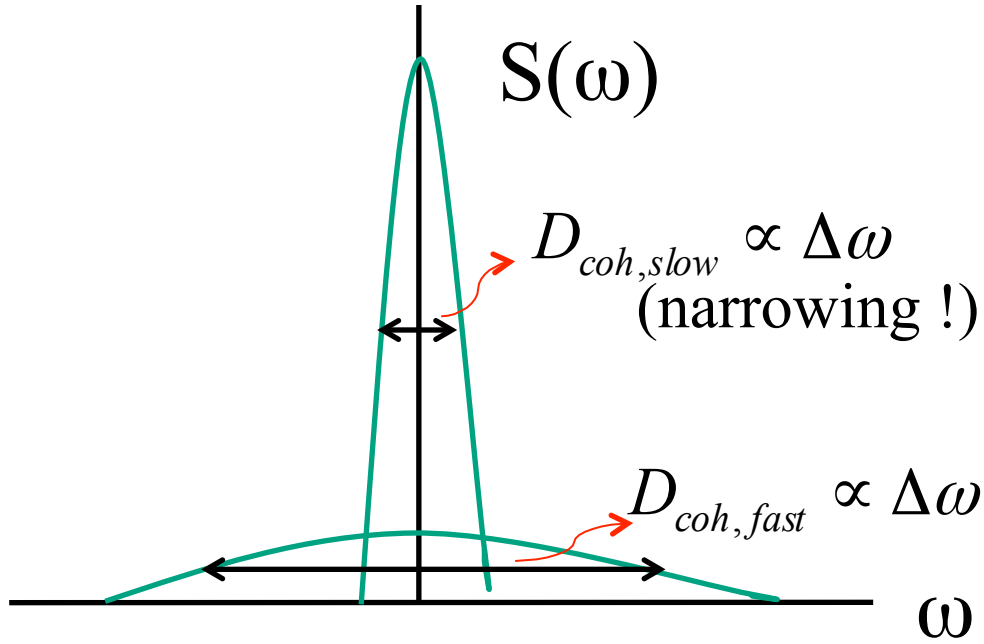


De Gennes Narrowing

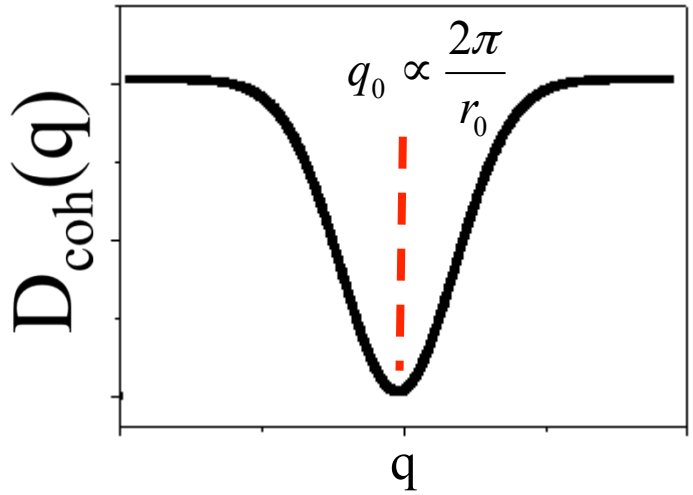






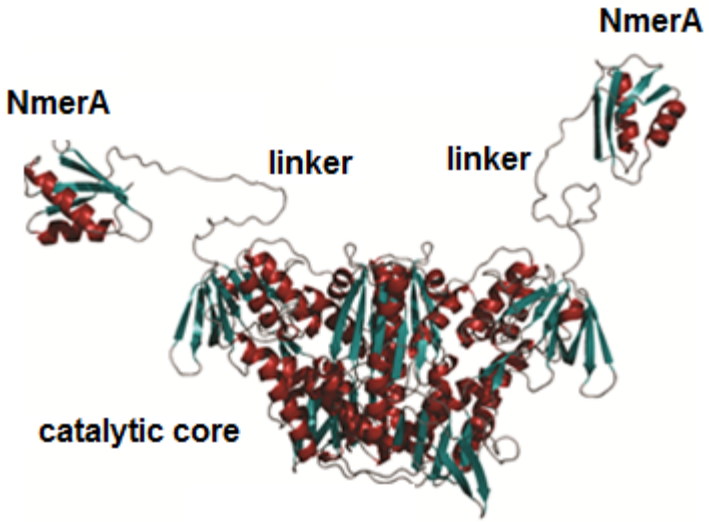


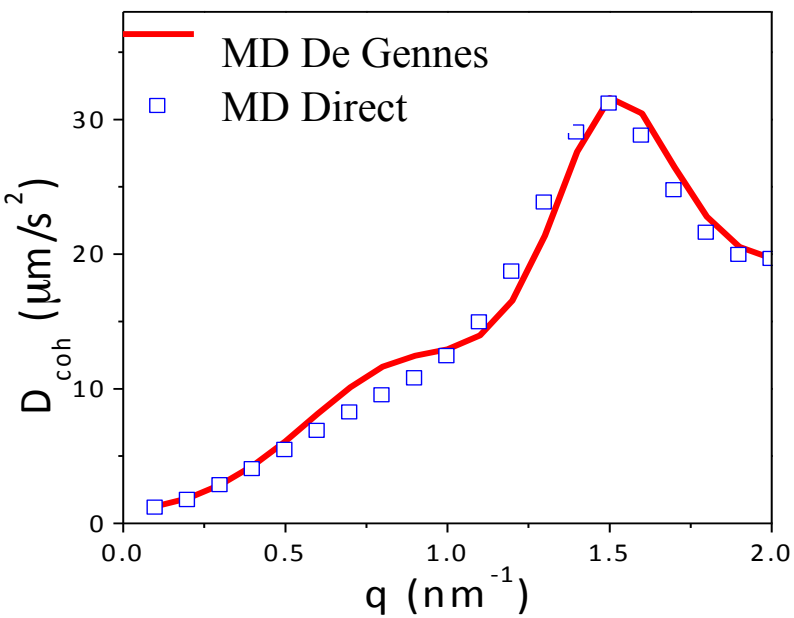
$$D_{coh} \propto \Delta\omega$$



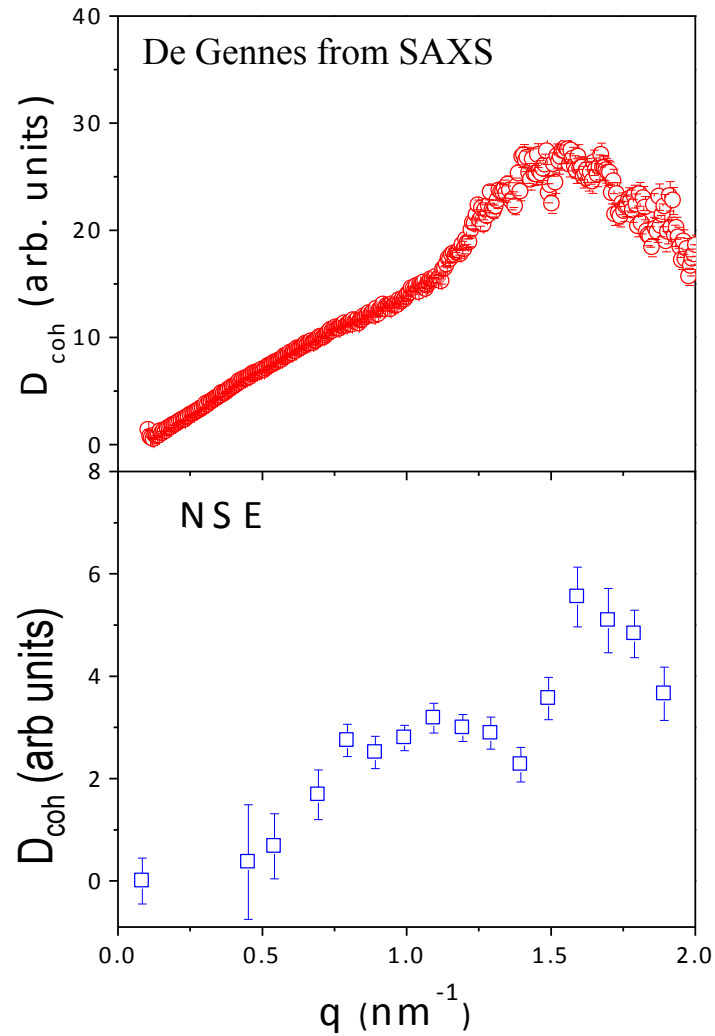
$$D_{coh}(q) = \frac{const}{S(q)}$$

De Gennes Narrowing

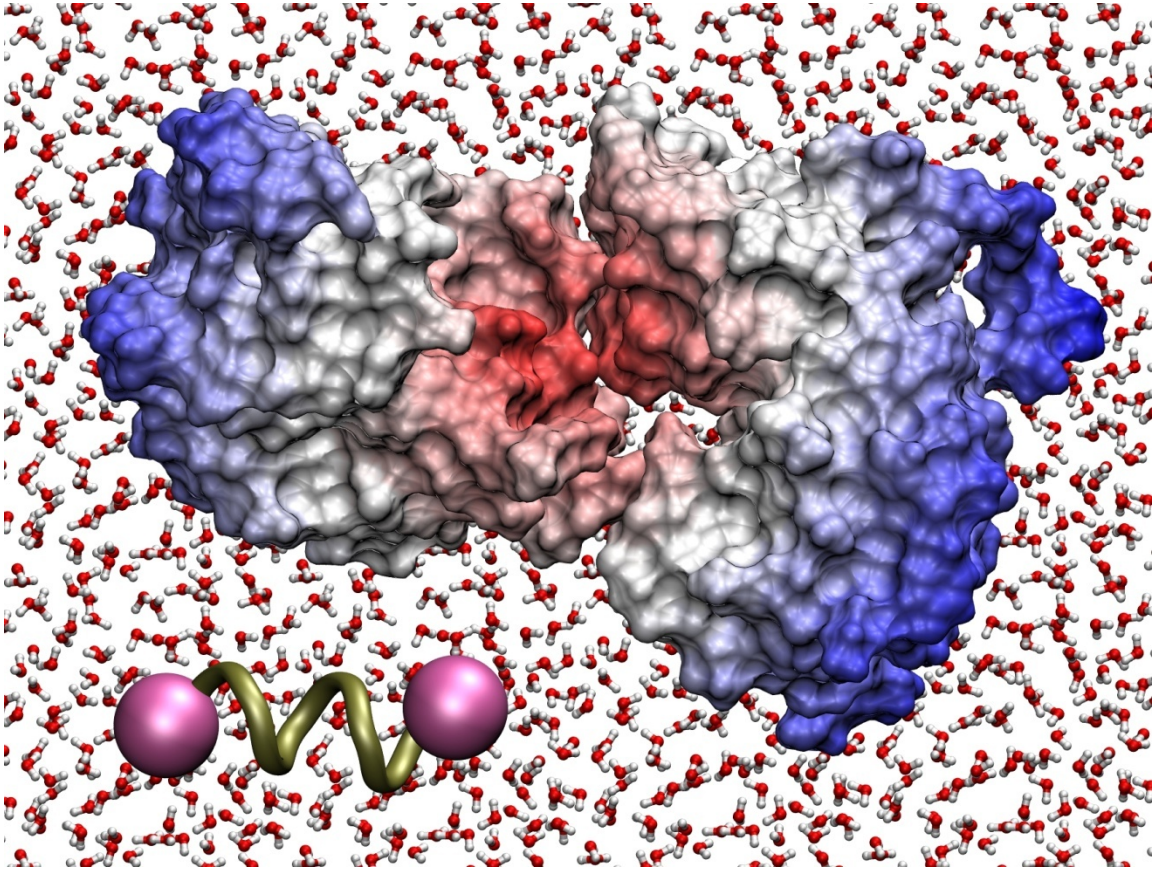




$$D_{coh}(q) = \frac{const}{S(q)}$$

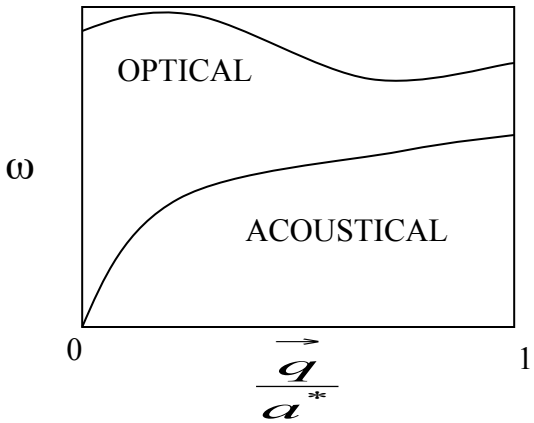


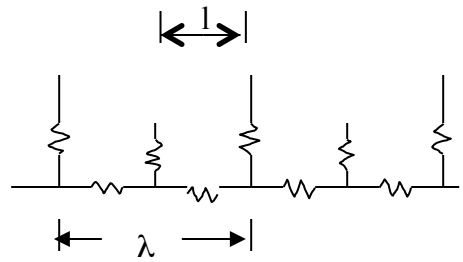
Protein:Protein Interactions



Lattice Vibrations

- PERIODIC in TIME and SPACE.
- DISPERSION RELATIONSHIP between FREQUENCY and WAVEVECTOR

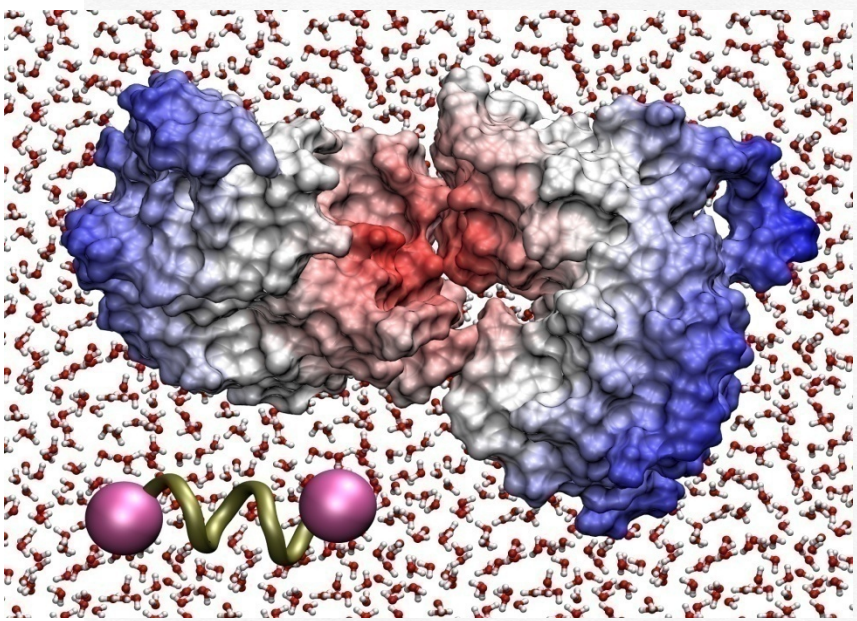


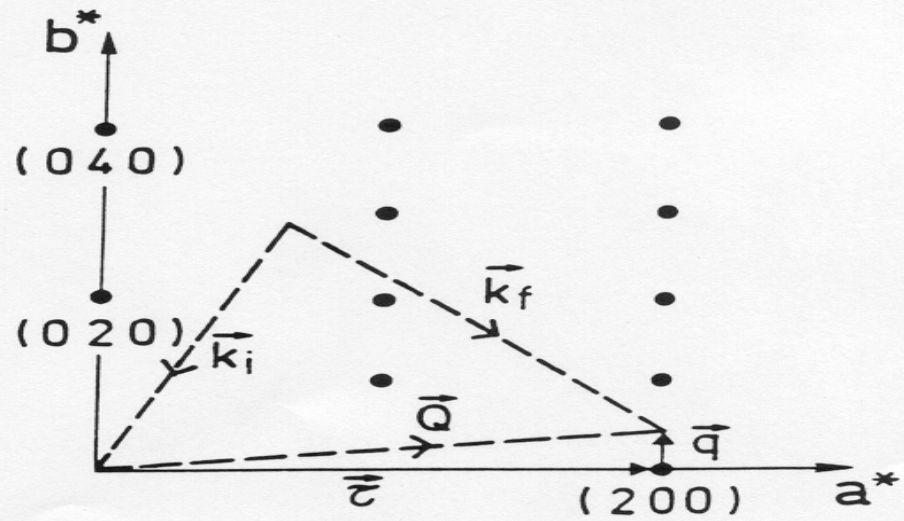


$\Theta = 180^o = \pi$

$\lambda = 2l$

$q = \pi / l$





COHERENT INELASTIC NEUTRON SCATTERING

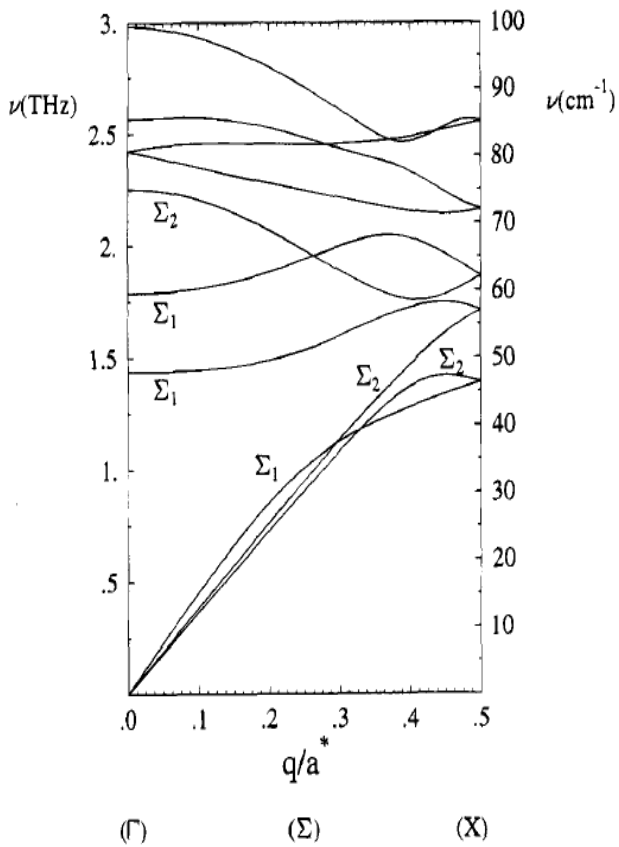
CRYSTALLINE L-ALANINE : LATTICE DYNAMICS

EXPERIMENT - Triple-Axis Coherent Inelastic Neutron Scattering

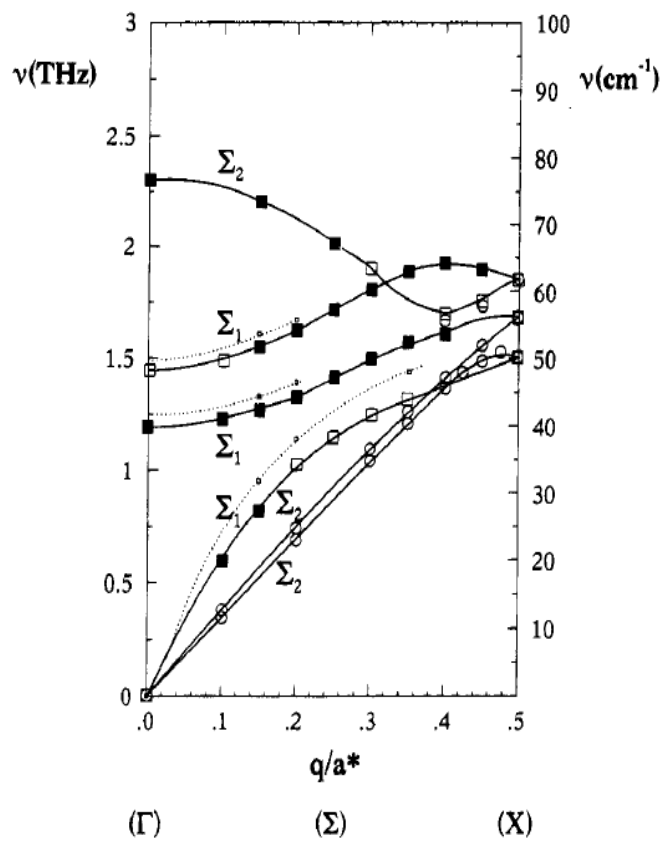
J Phys Chem
99 5645 (1995).

PHONON DISPERSION CURVES

Calculated



Experimental



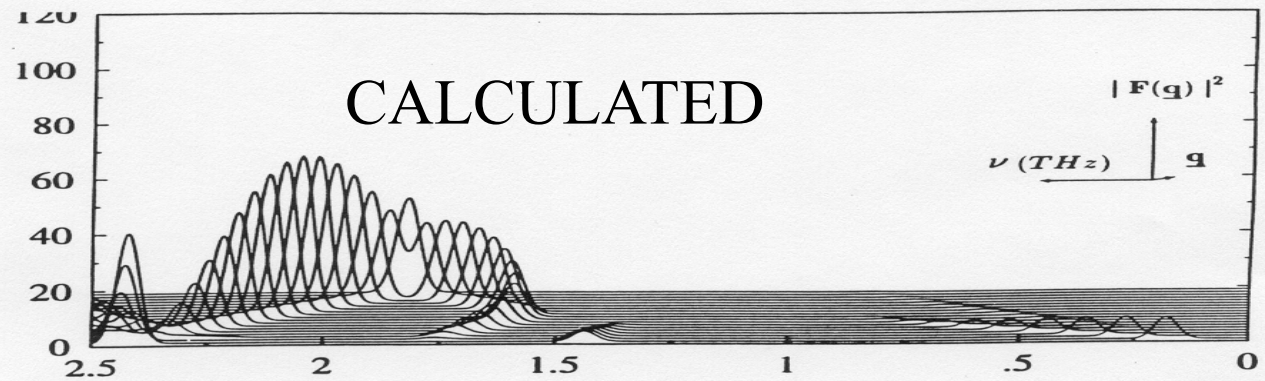
COHERENT INELASTIC NEUTRON SCATTERING INTENSITIES

$$\left|F(\vec{q})\right|^2 \approx \left|\vec{Q}.\vec{e}\right|^2$$

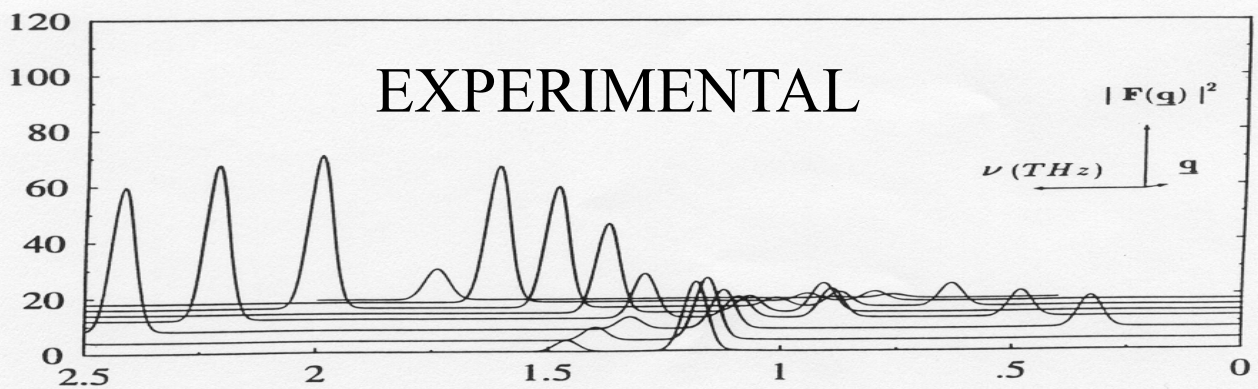
INTENSITY

SCATTERING VECTOR

MODE POLARIZATION VECTOR

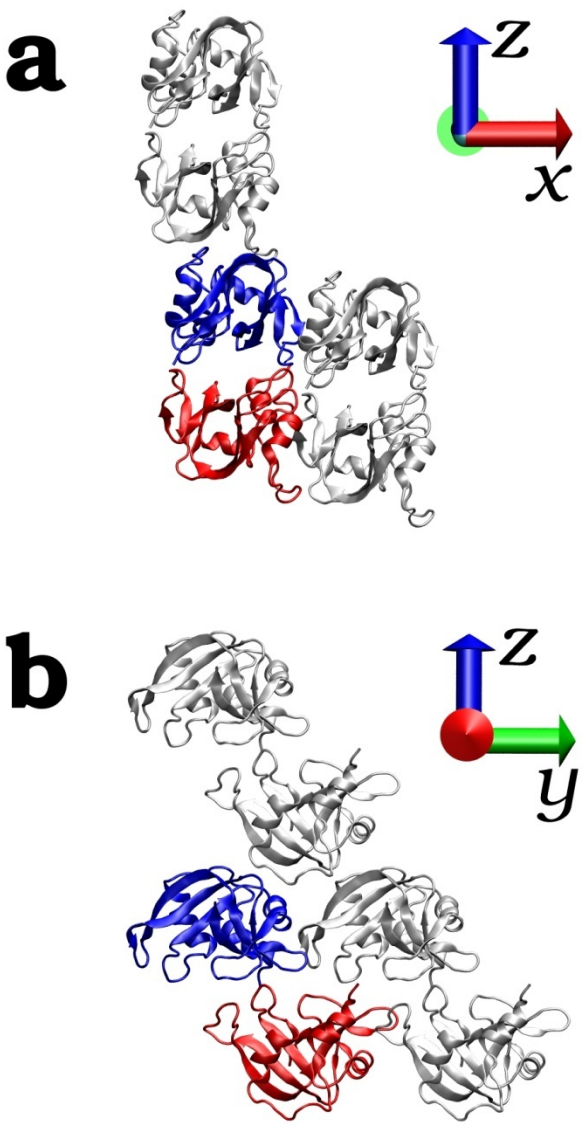


b*direction

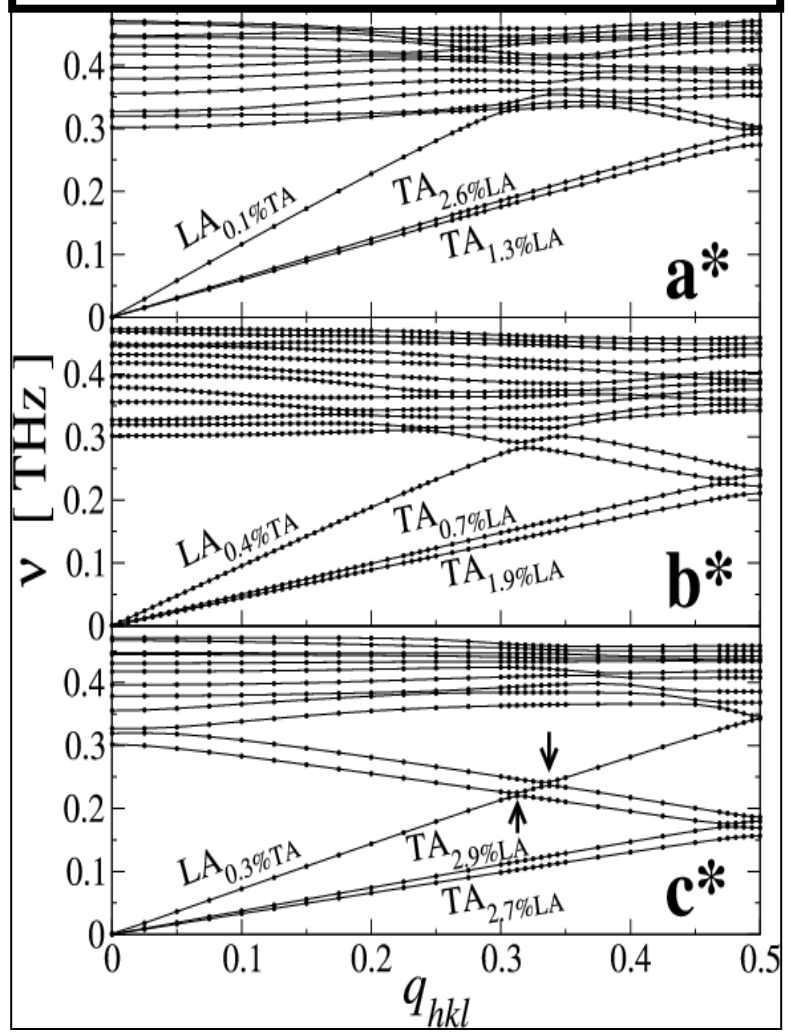


J Phys Chem *99* 5645 (1995).

Monoclinic Ribonuclease A:
6442 atoms

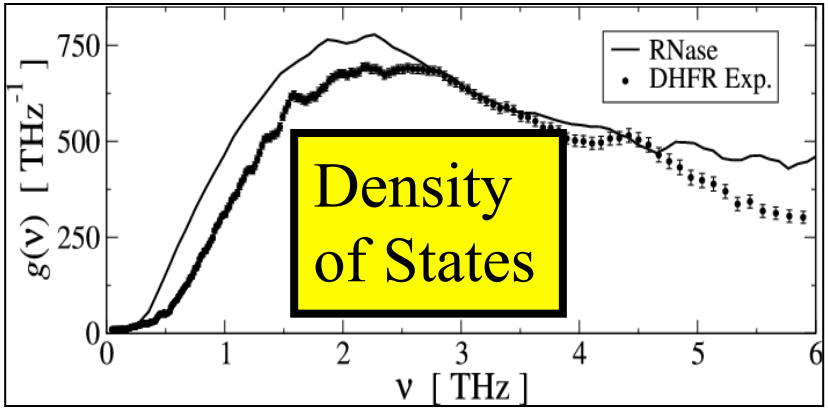


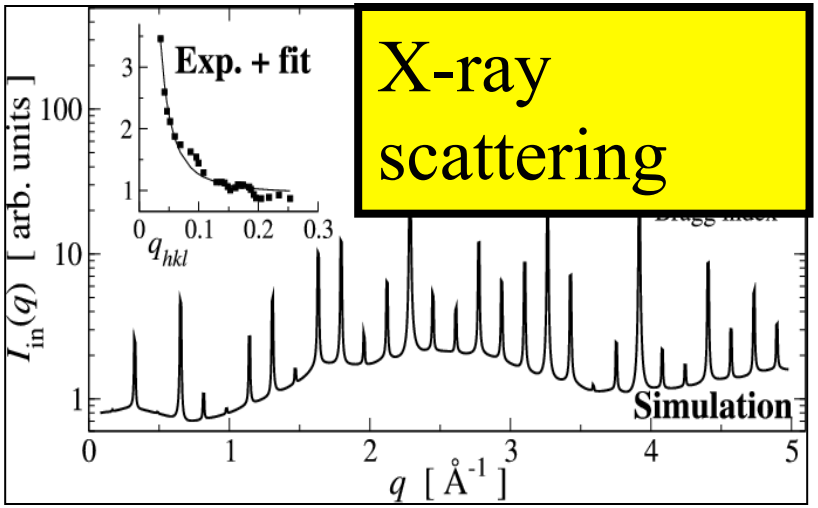
Phonon Dispersion Relations

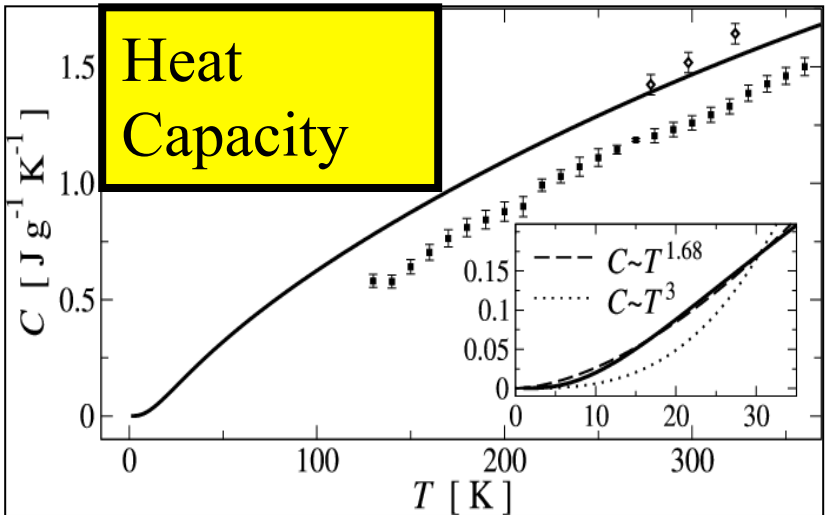


PRL 99 (13):138101 (2007).

Monoclinic Ribonuclease A:
6442 atoms







PRL 99 (13):138101 (2007).

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