



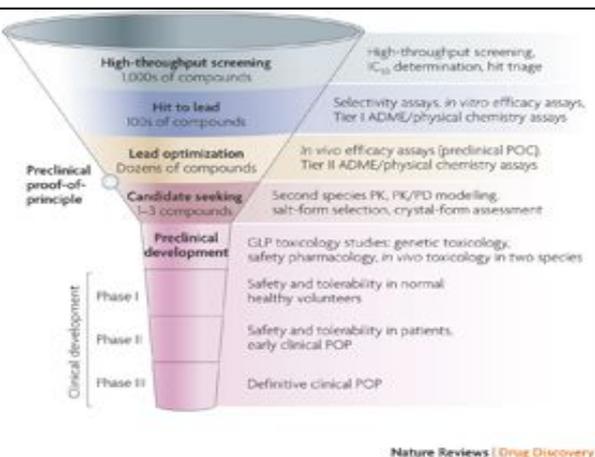
Emptying Hg flasks at the dumping shed (1955)

Environment

Energy



Disease





Cloud Gate, Anish Kapoor, Chicago

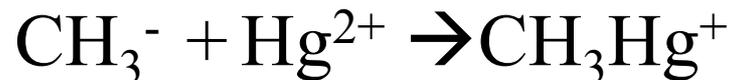


Emptying Hg flasks at the dumping shed (1955)



Solving the
METHYLMERCURY PUZZLE

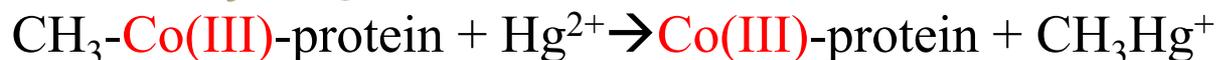
Chemistry of mercury methylation



Generate carbanion, CH_3^- :



Transfer CH_3^- to Hg^{2+} :



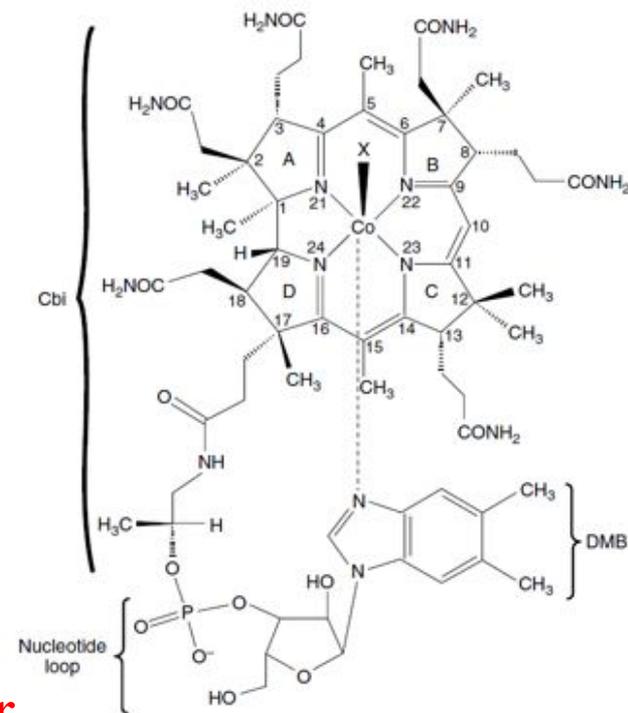
Regenerate Co(I):



Need to find protein(s) that can:

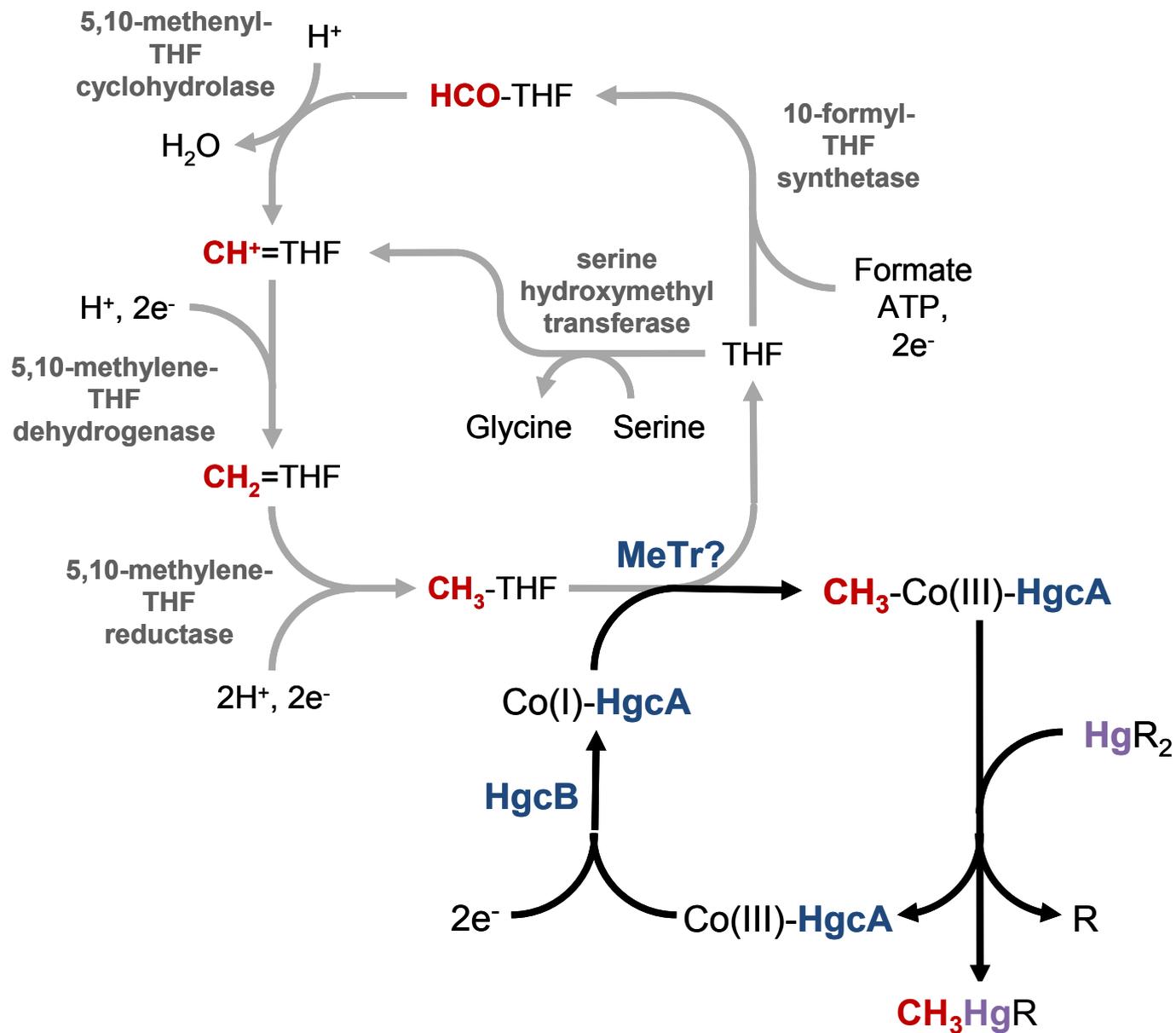
1. Stabilize Co(III) for carbanion transfer
2. Provide 2 electrons to generate Co(I)

Jerry
Parks



cobalamin

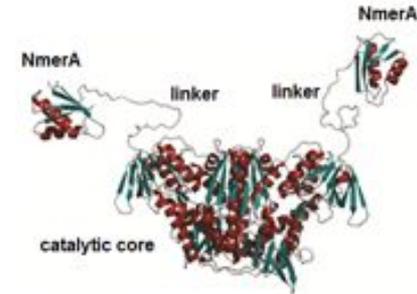
Proposed mercury methylation pathway



Good Bacteria!
Mer Operon



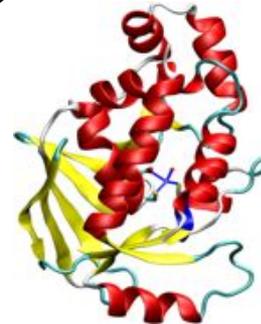
$\text{Hg}(0)$



Reduction
- Mer A

$\text{Hg}(\text{II})$

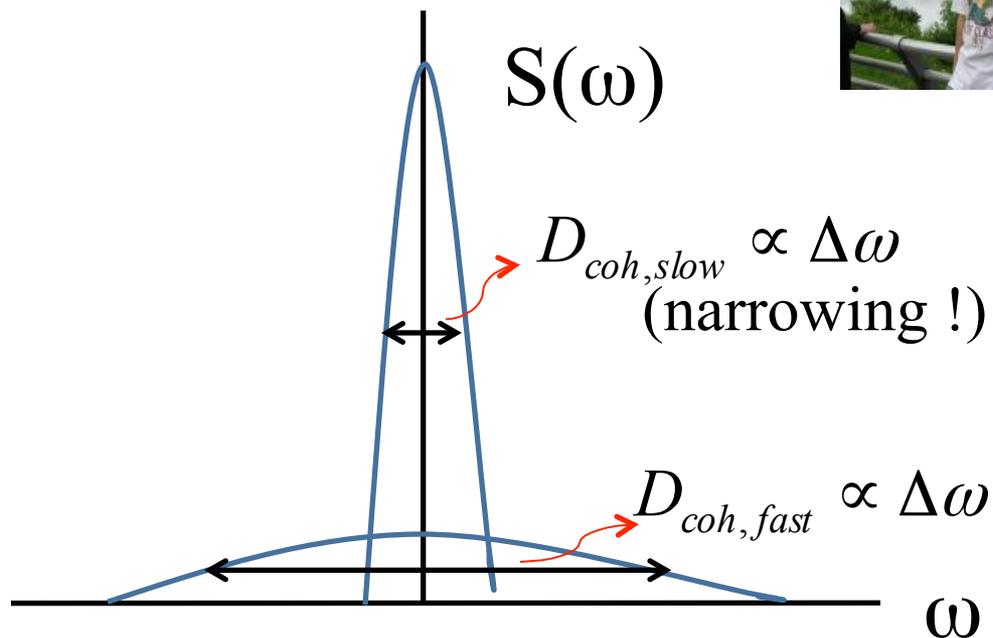
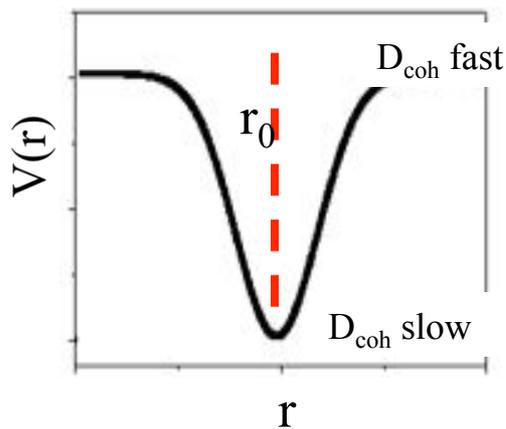
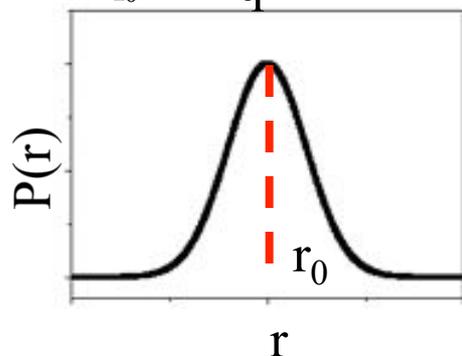
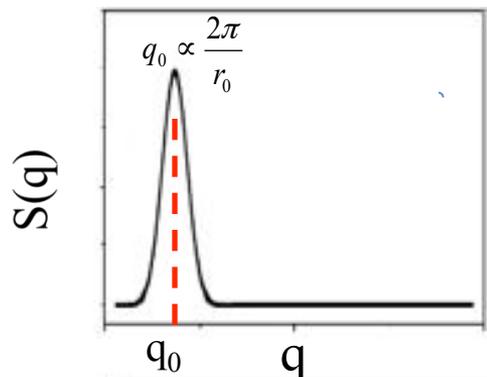
Demethylation
-Mer B



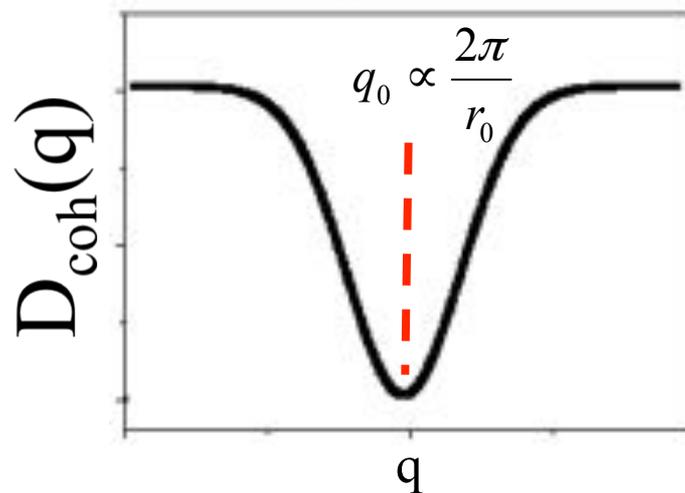


De Gennes Narrowing

Liang
Hong

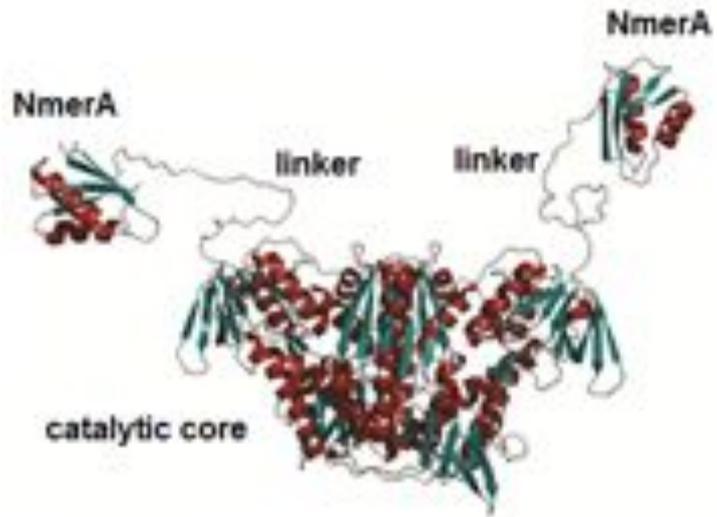


$$D_{coh} \propto \Delta\omega$$

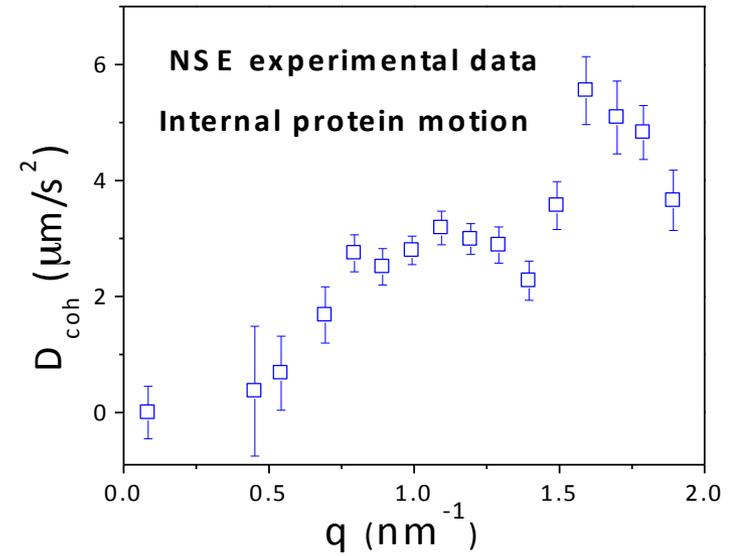


$$D_{coh}(q) = \frac{const}{S(q)}$$

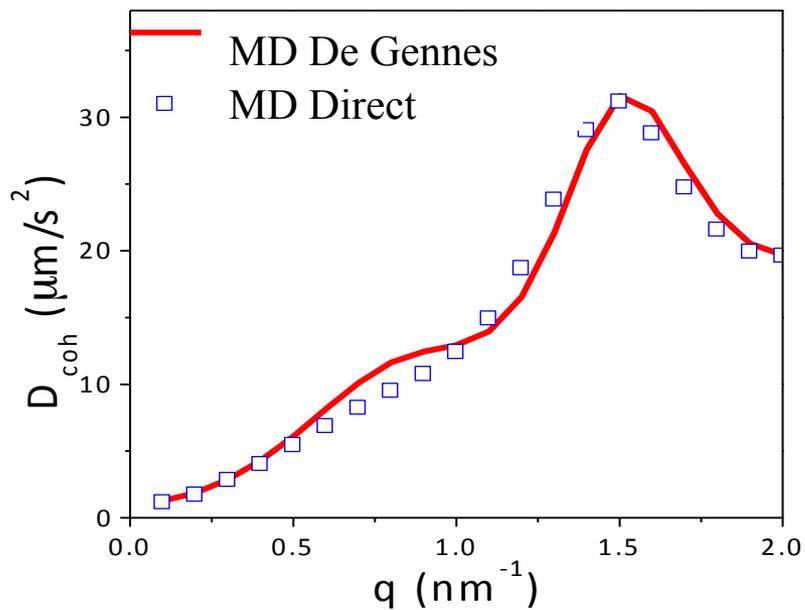
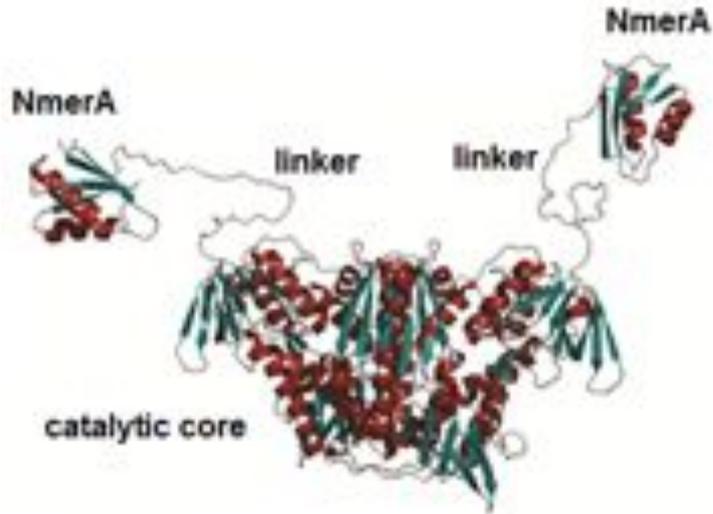
Interdomain Motion in Mer A



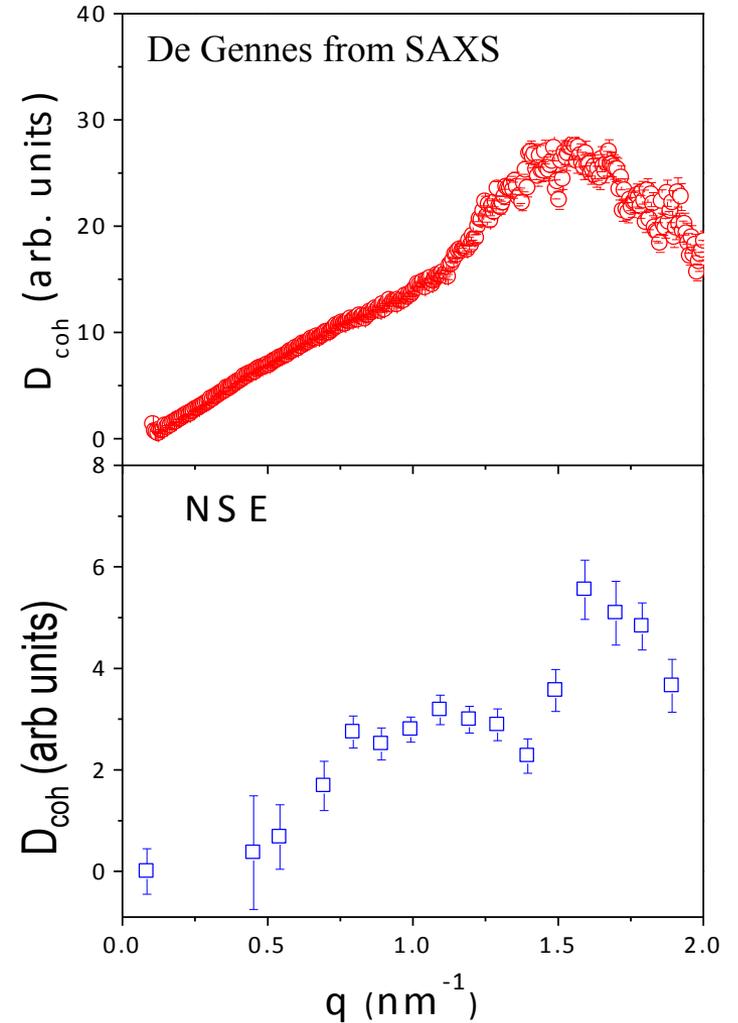
Neutron Spin Echo



De Gennes Narrowing



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

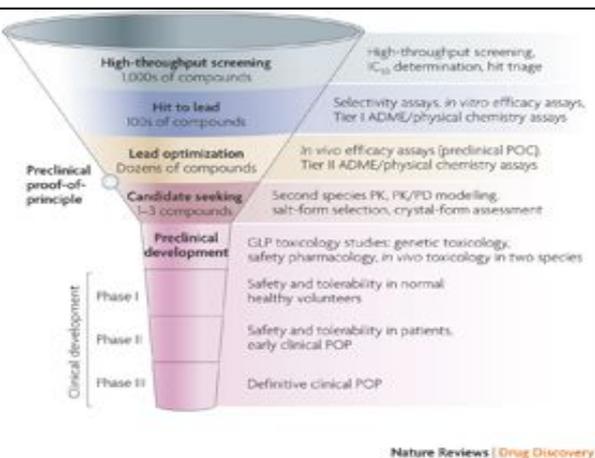




Emptying Hg flasks at the dumping shed (1955)

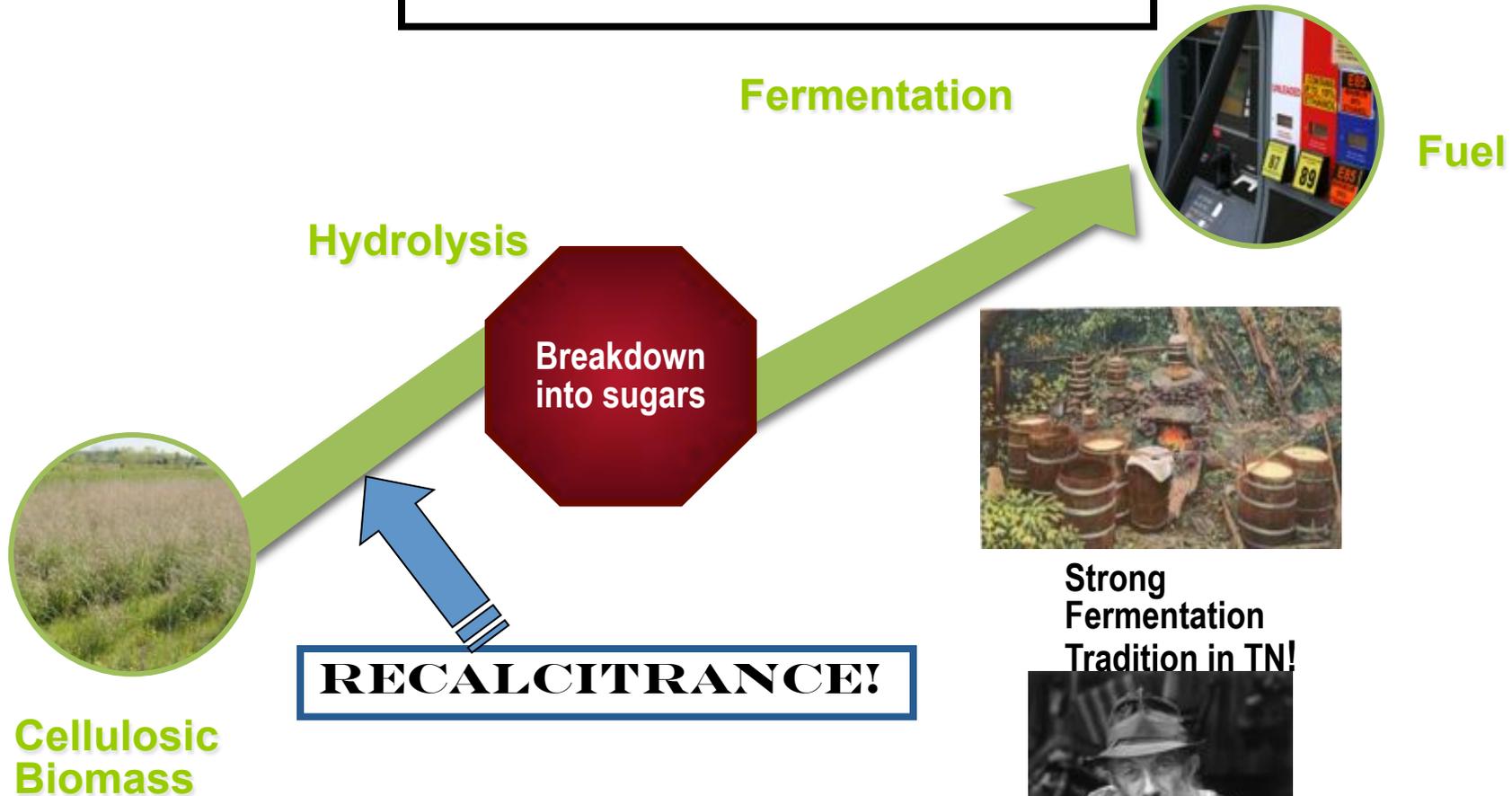
Environment

Energy



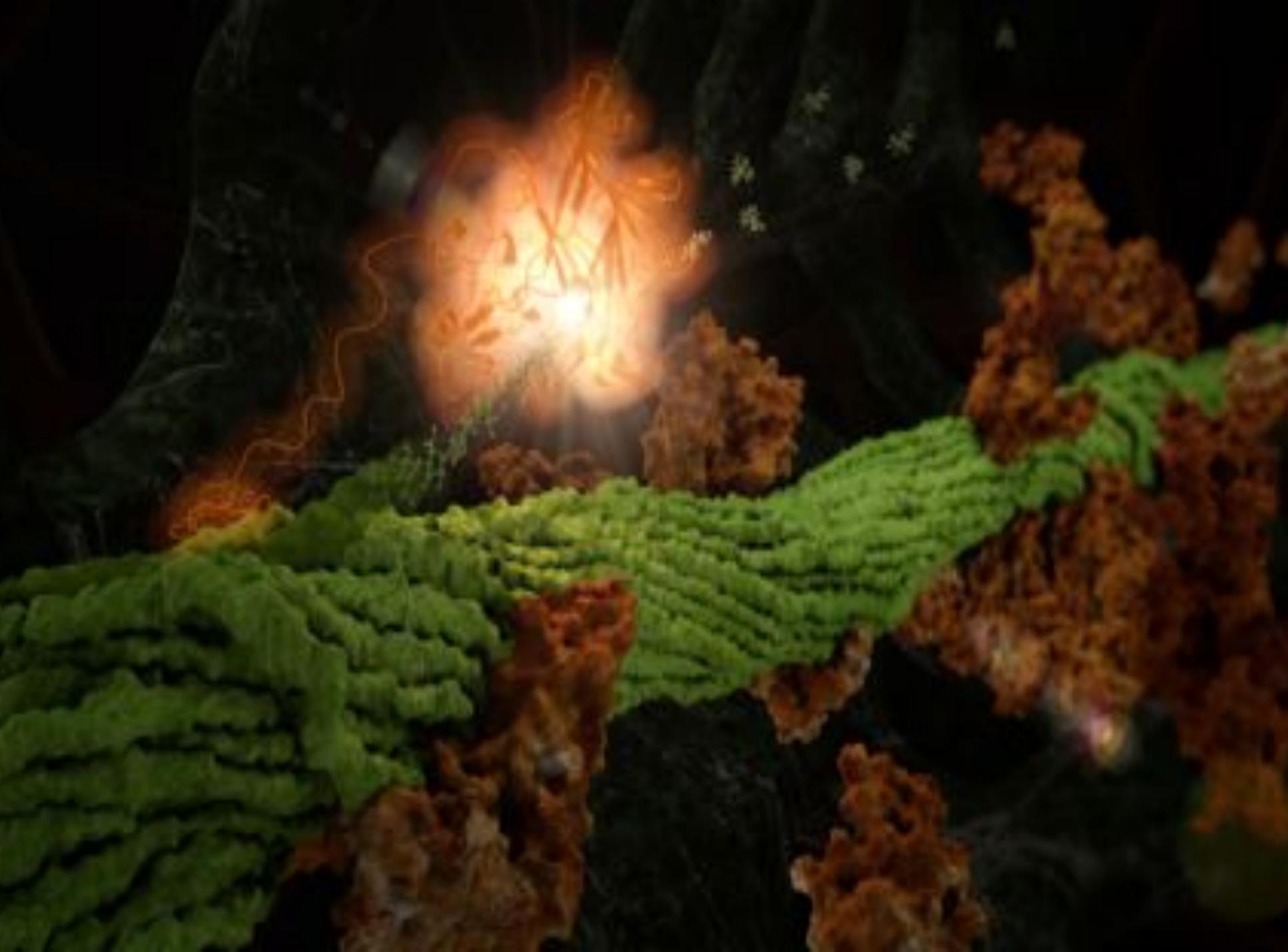
Disease

Cellulosic Ethanol

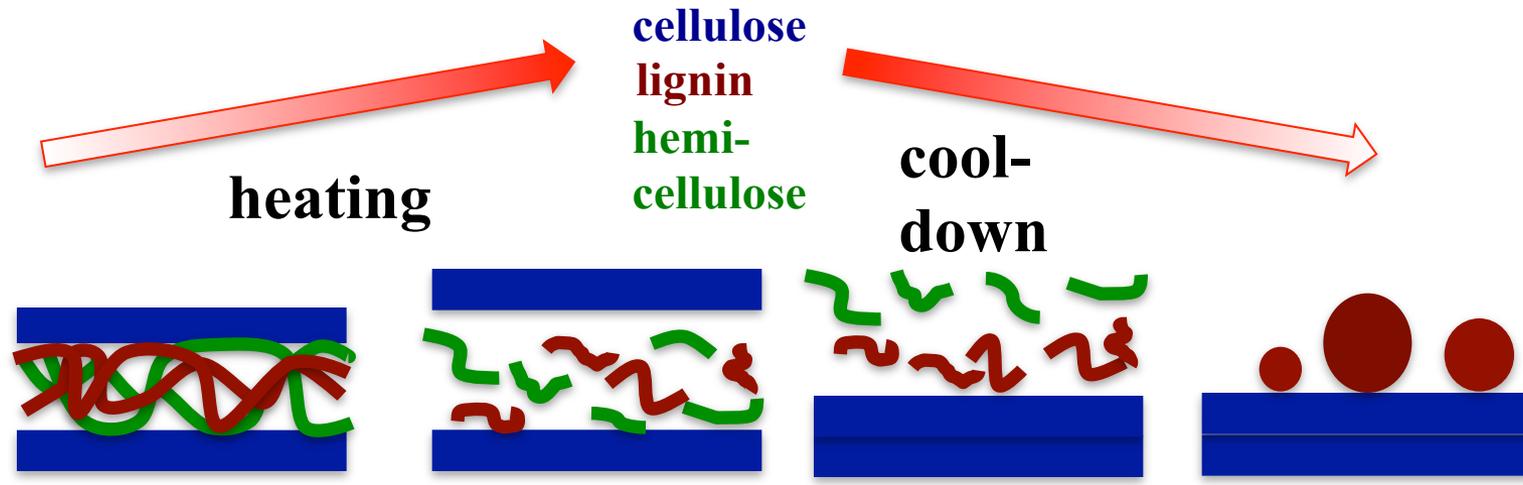


Strong
Fermentation
Tradition in TN!





Lignin Aggregation During Heating Phase of Dilute-acid Pretreatment

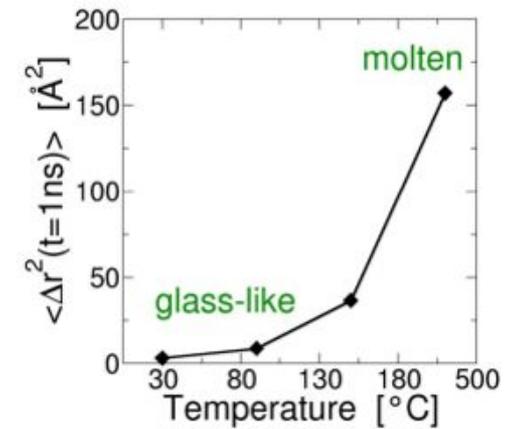
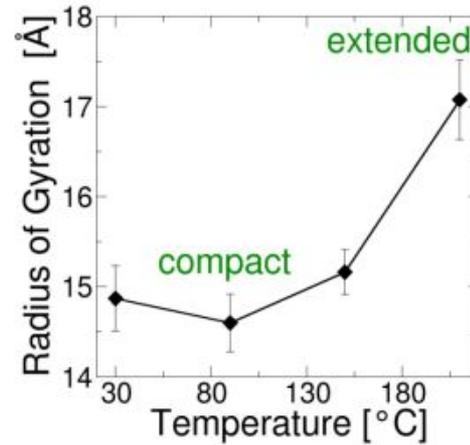
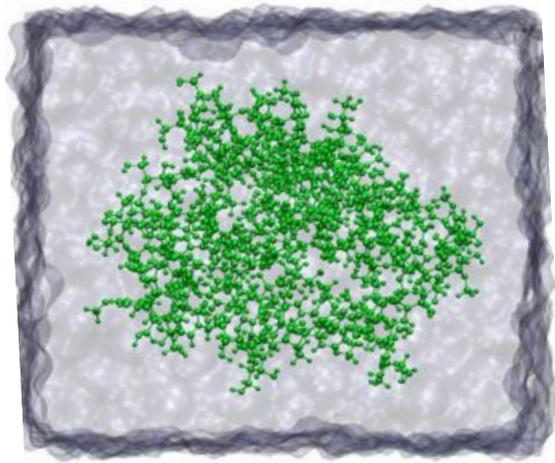


aggregation occurs during cool-down

Loukas Petridis

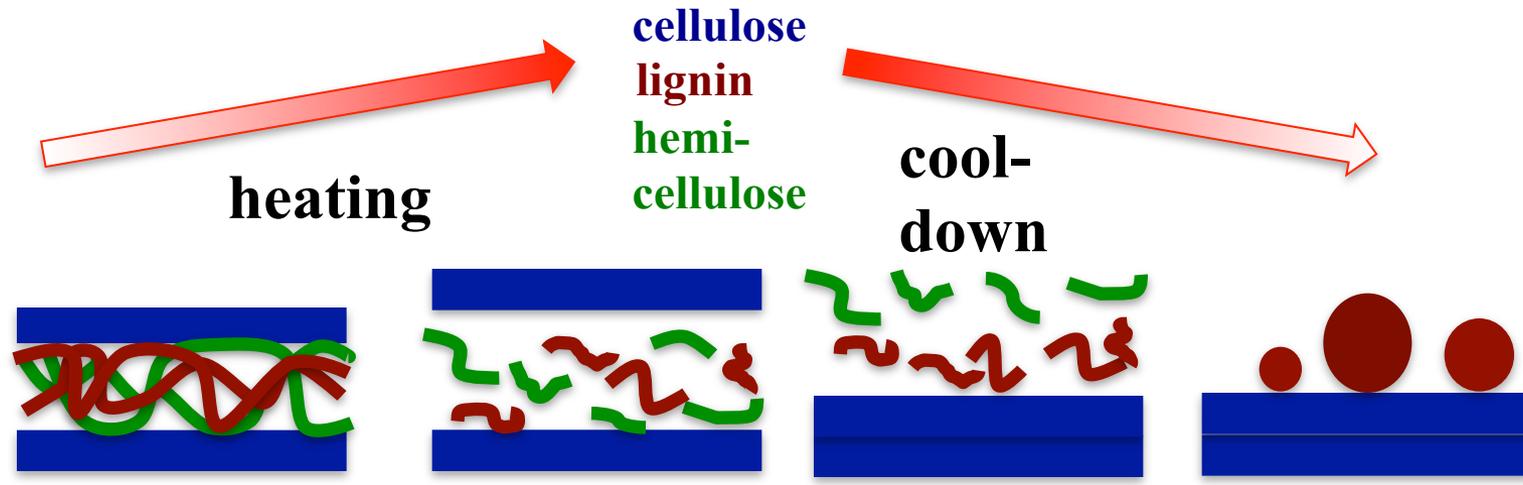


MD Simulation of Softwood Lignin

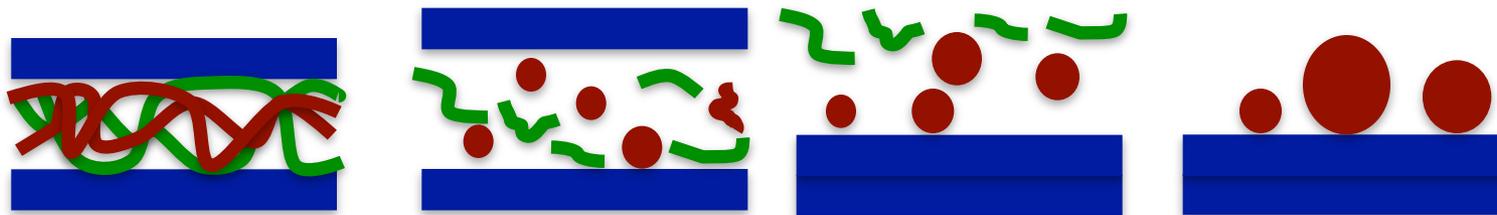


JACS 133 20277 (2011)

Lignin Aggregation During Heating Phase of Dilute-acid Pretreatment



aggregation occurs during cool-down



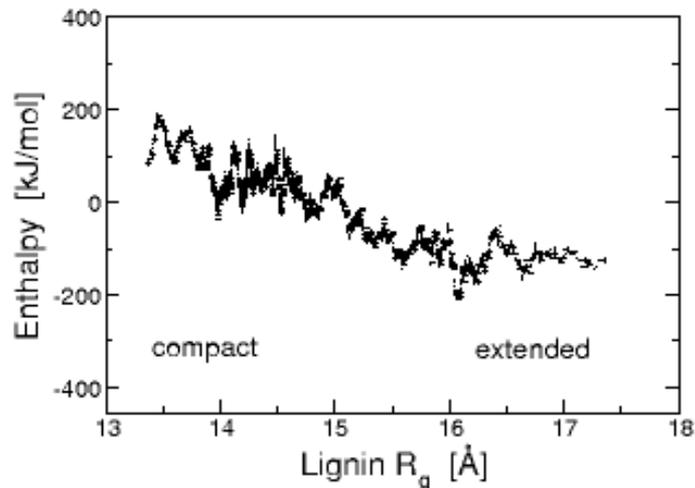
aggregation occurs during heating

Why does Lignin Collapse at Room Temperature?

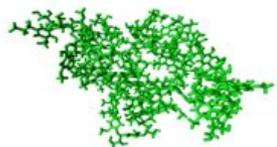
Loukas Petridis



- Enthalpy
- $\Delta H \approx +200$ kJ/mol **Unfavorable**

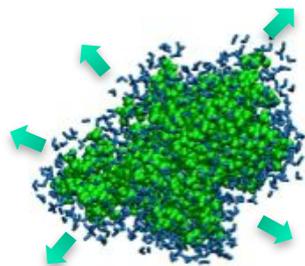
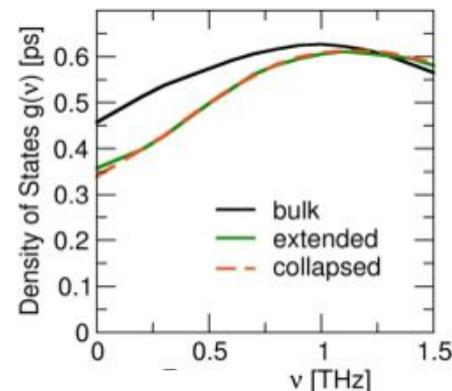


- Lignin configurational entropy
- $-T\Delta S_{\text{conf}} \approx +10$ kJ/mol **Unfavorable**



JACS 133 20277 (2011)

- Hydration water translational & rotational entropy
- $-T\Delta S_{\text{t+r}} \approx -100$ kJ/mol **Favorable**



- Hydration water compressibility
- $-T\Delta S_{\text{fluc}} \approx -300$ kJ/mol **Favorable**

Collapse Driven by Removal of Entropically Unfavorable Water Molecules from Lignin Surface to Bulk

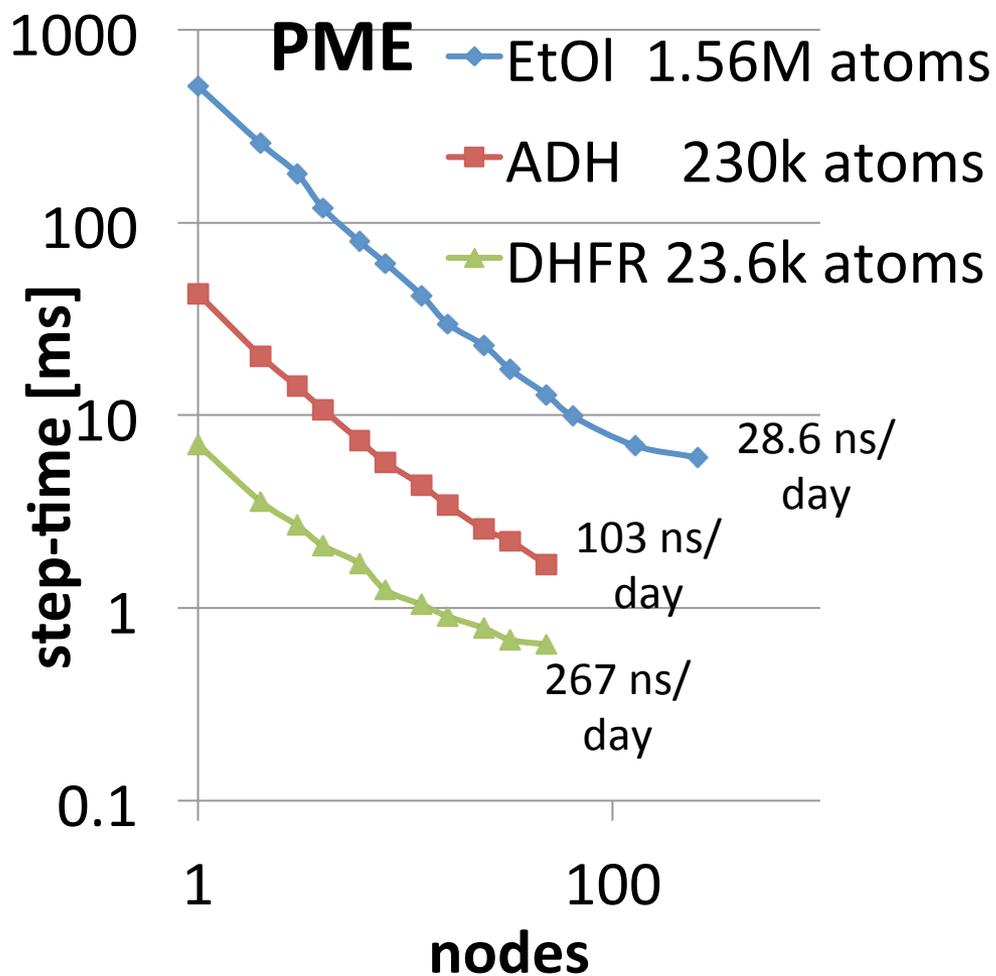


ROLAND
SCHULZ



TITAN

- Reaction Field
23M atoms, 3750 nodes (60k cores):
40ns/day
- OpenMP for all kernels
- Larger number of threads for PME
- AMD AVX intrinsic

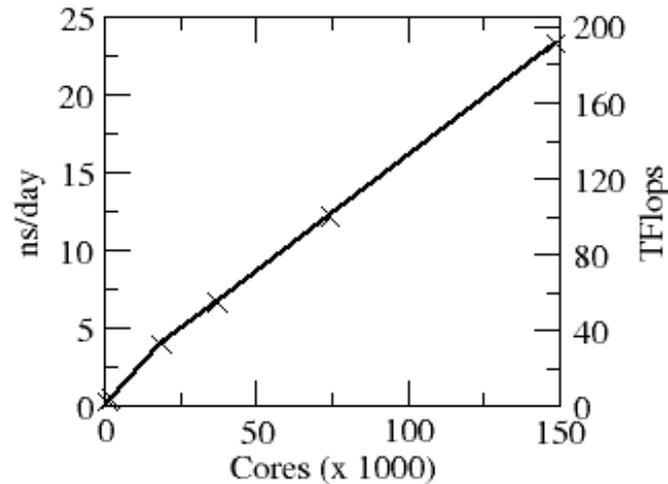




**ROLAND
SCHULZ**



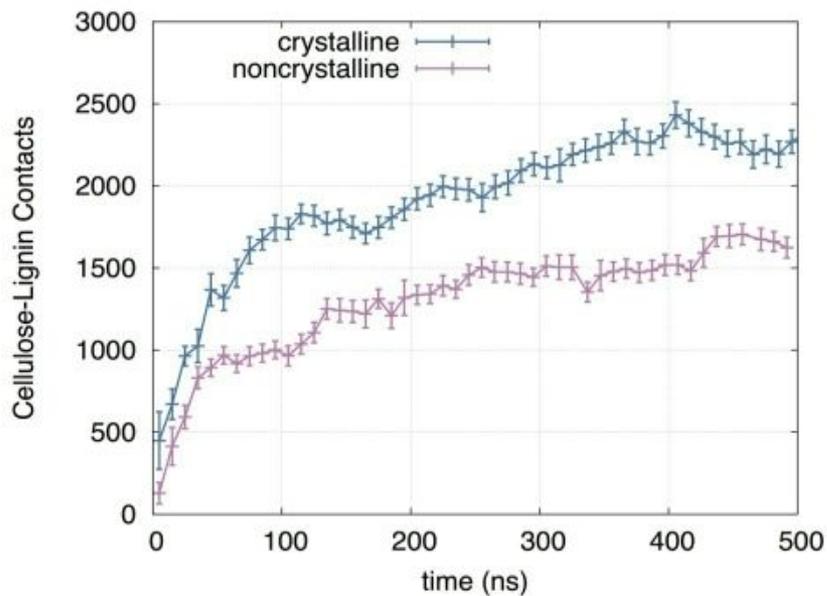
Molecular Dynamics Supercomputer Scaling



~ 100 million atoms.

- **Scales to 150,000 cores**

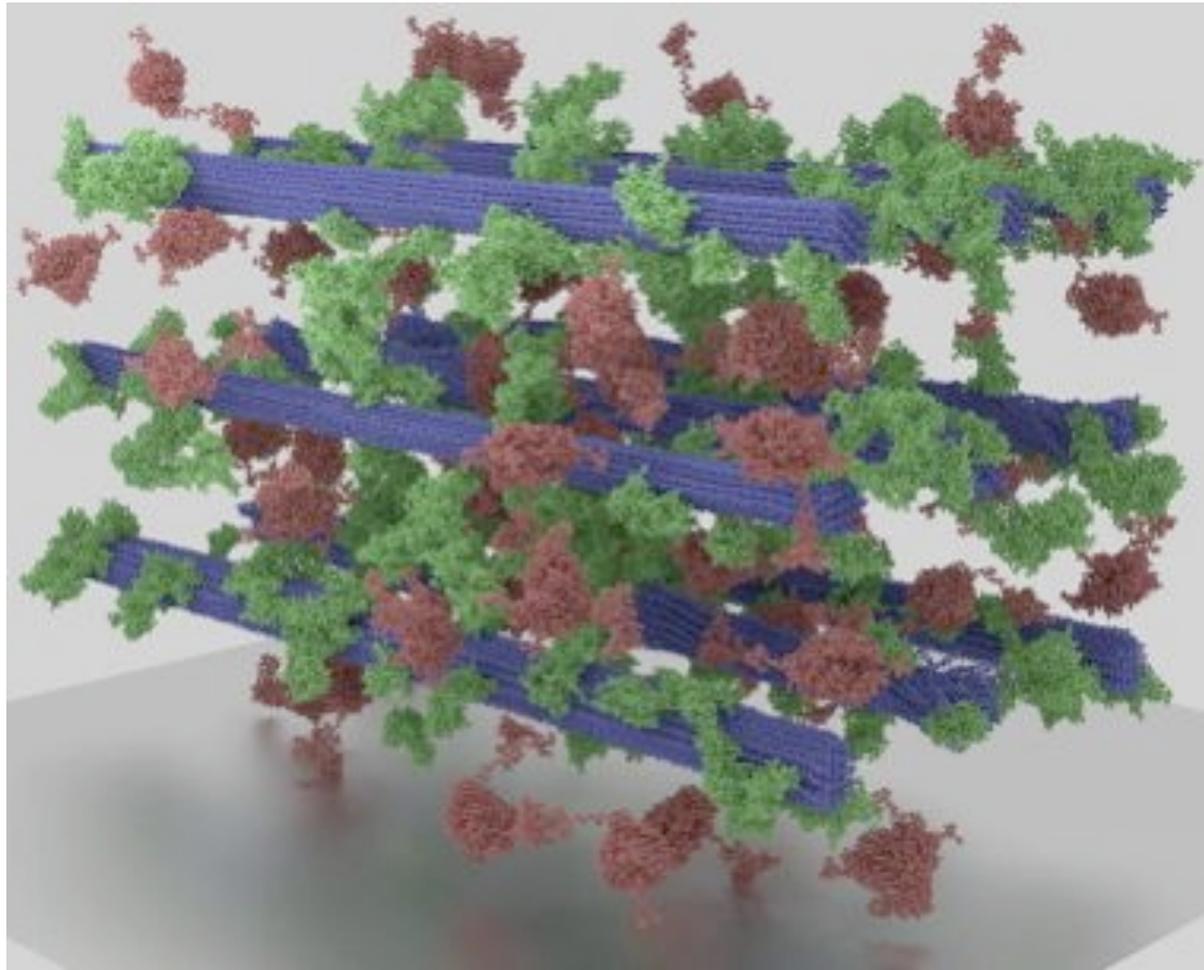




Interface	Interaction Energy Density (kJ/mol/nm ²)
lignin: crystalline cellulose	-49±2
lignin: non-crystalline cellulose	-50±2
water : crystalline cellulose	-94±2
water : non-crystalline cellulose	-107±2

Solvent-Driven Preferential Association of Lignin with Crystalline Cellulose

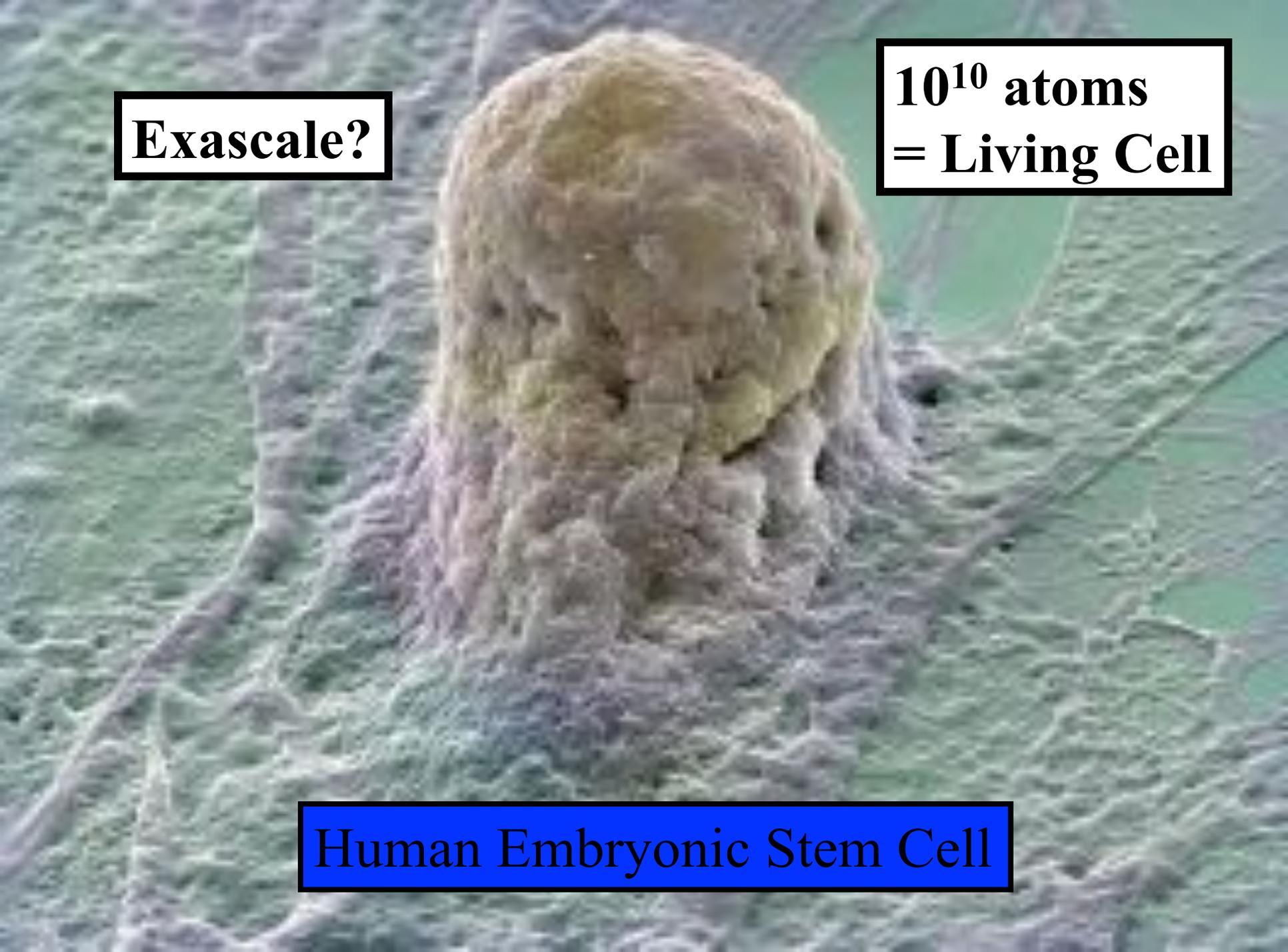
**24M-atom capability-class
simulation
of enzyme binding
to pretreated lignocellulose**



Exascale?

**10^{10} atoms
= Living Cell**

Human Embryonic Stem Cell



But...

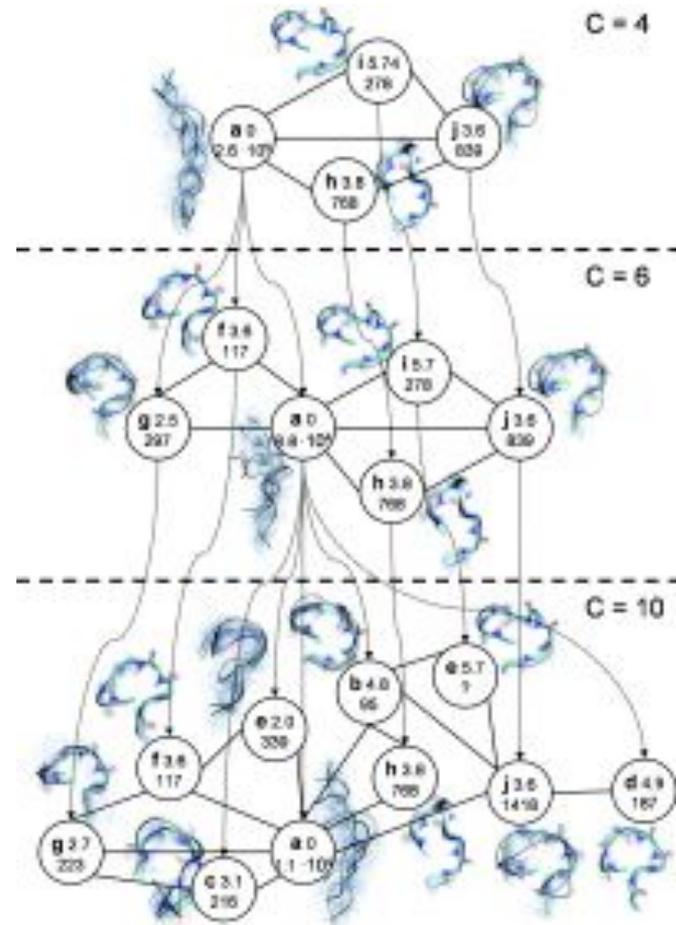
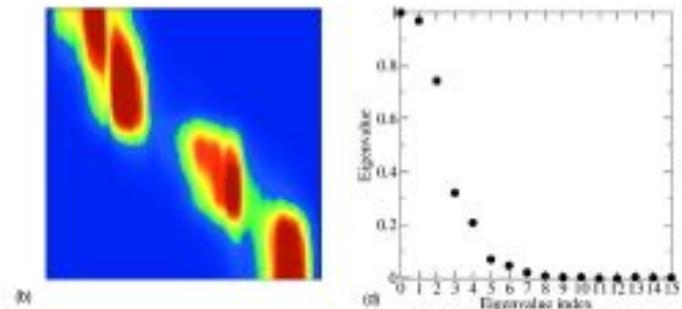
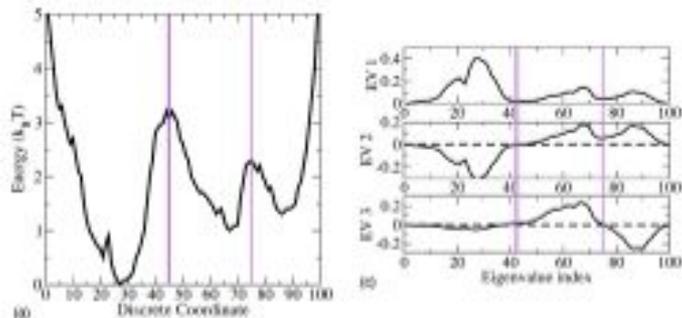
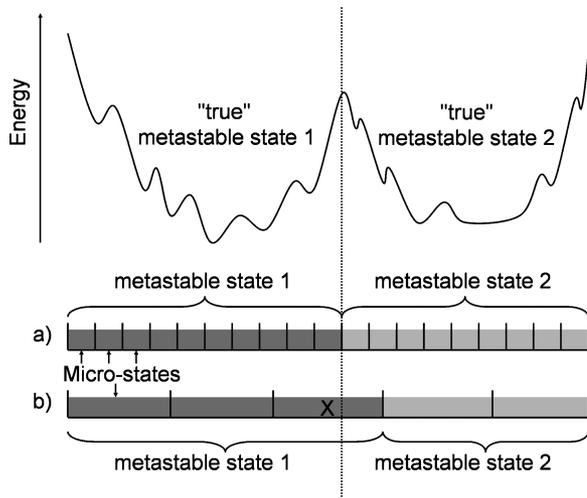
Microsecond Timescale Limitation!

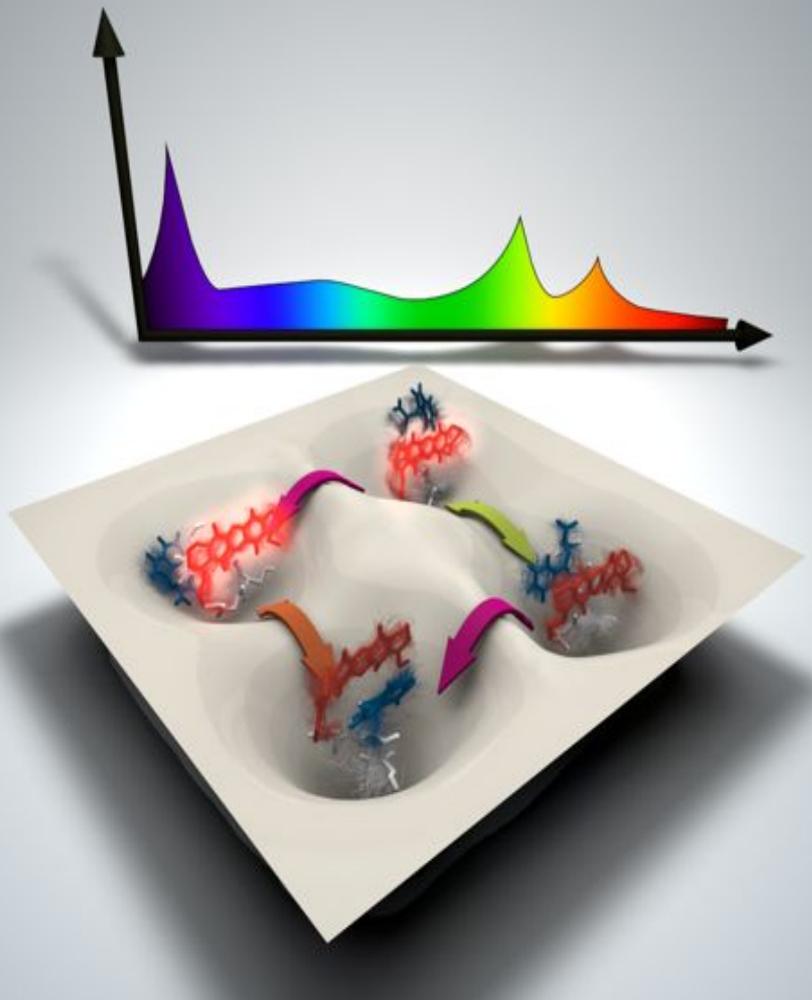
New Concepts Needed....



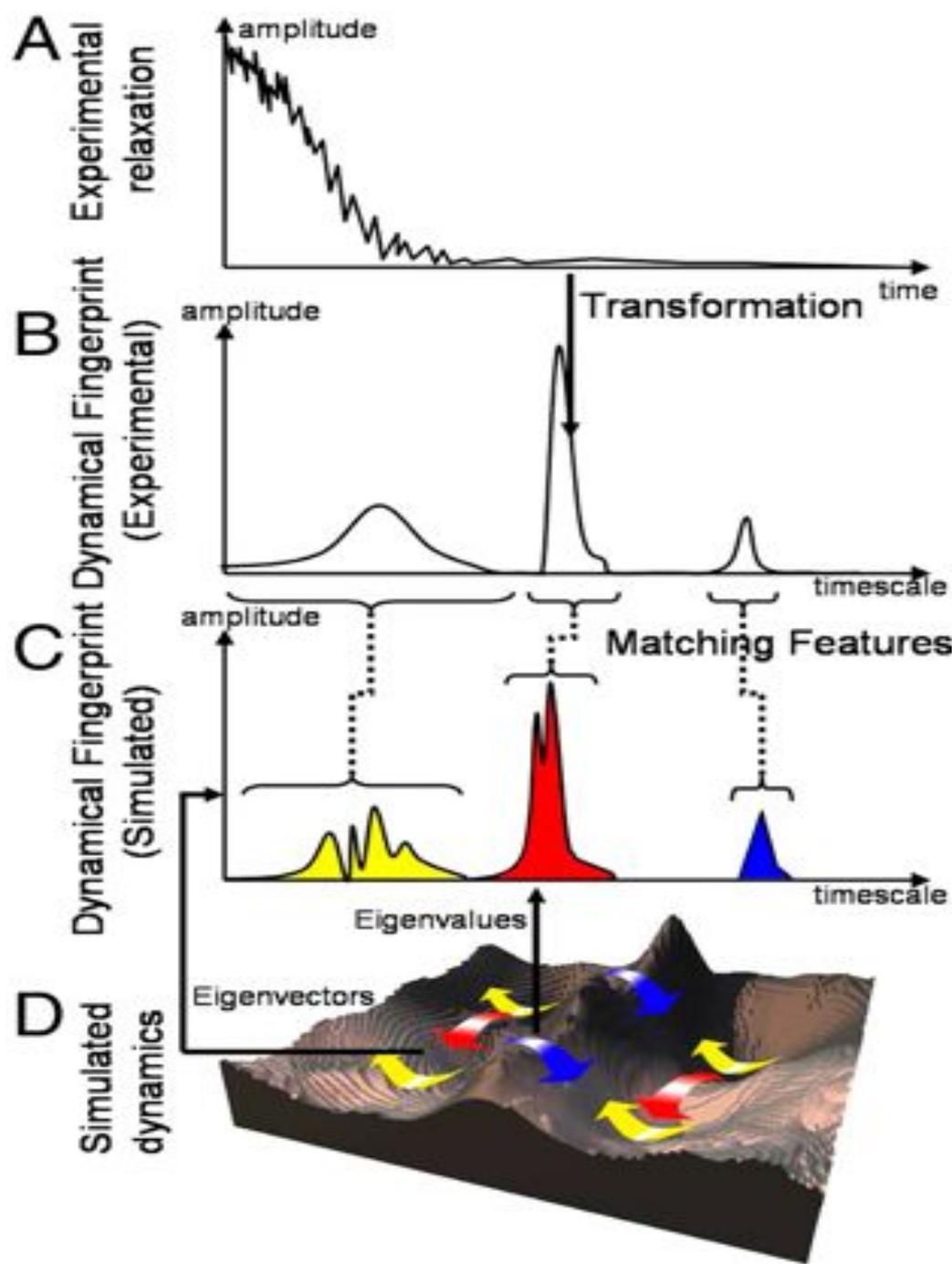
Transition Networks Of Metastable States

Frank
Noe





Dynamical Fingerprints

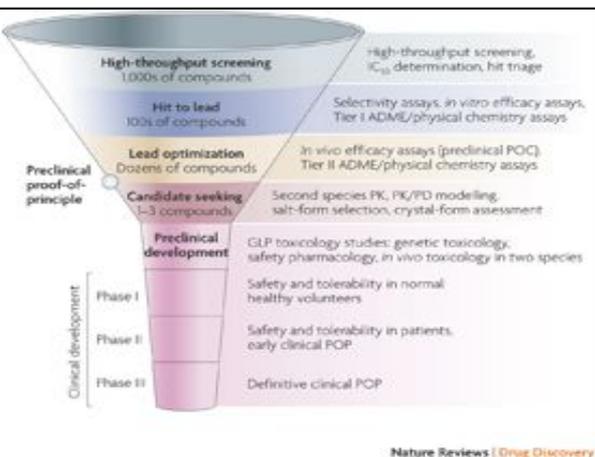




Emptying Hg flasks at the dumping shed (1955)

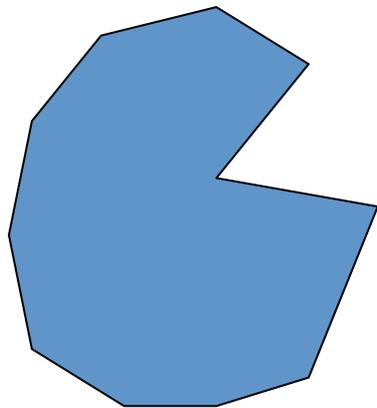
Environment

Energy

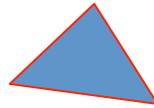


Disease

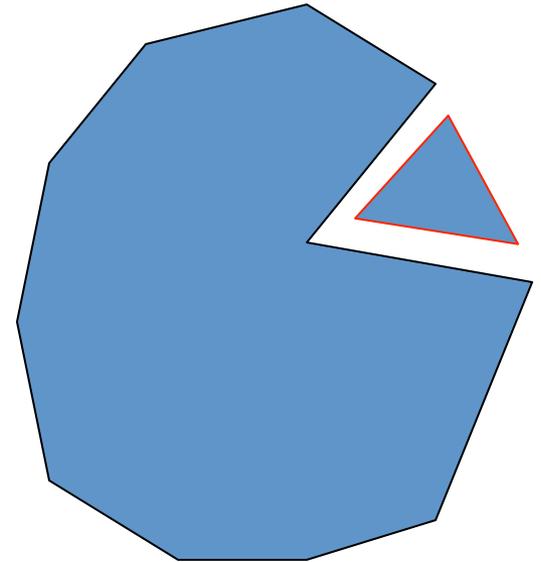
Ligand Binding



Protein



Ligand



Complex

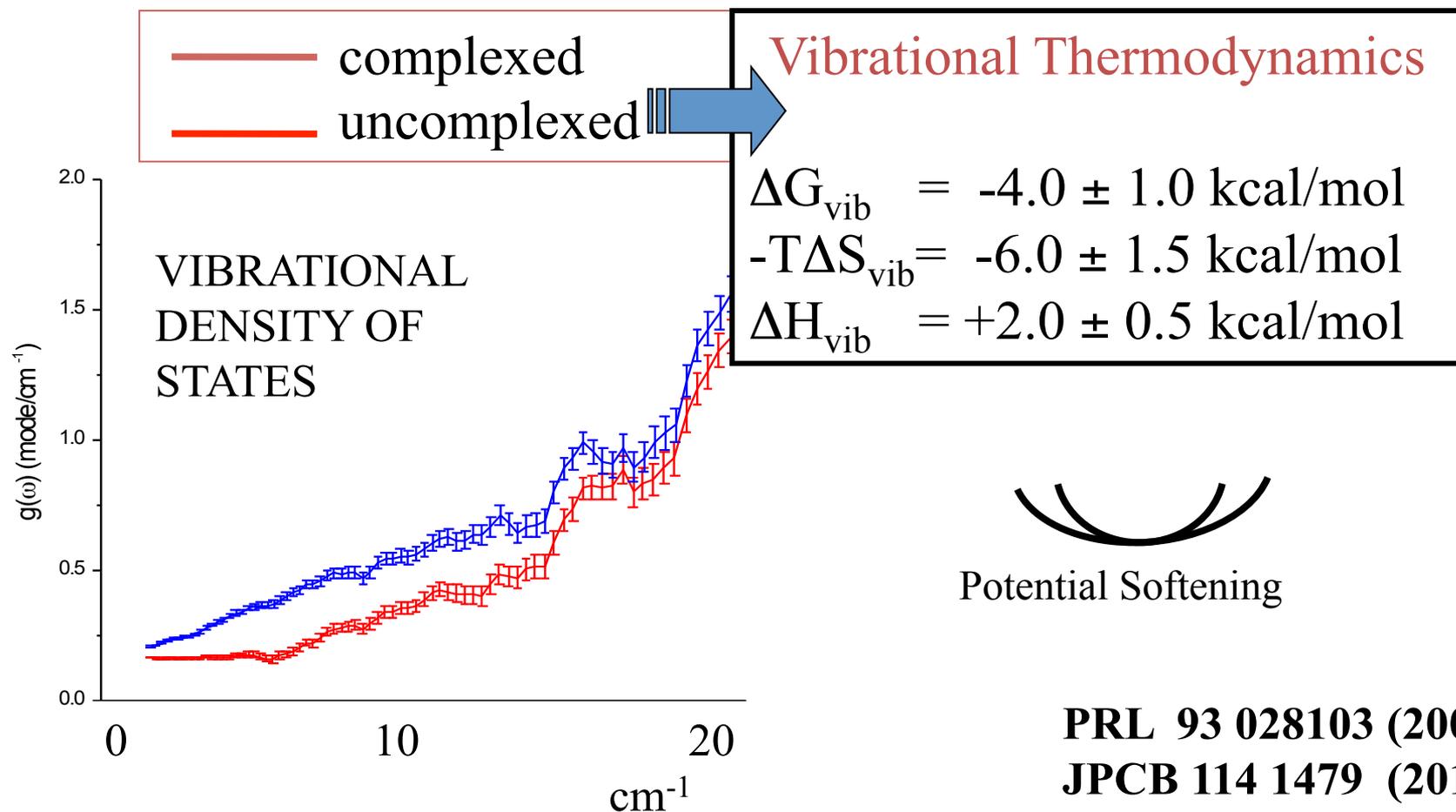
physical understanding

vibrational changes?

$$g_{\text{exp}}(\omega) = \lim_{q \rightarrow 0} \frac{6\omega}{\hbar q^2} (e^{\hbar\omega/kT} - 1) S(q, \omega)$$

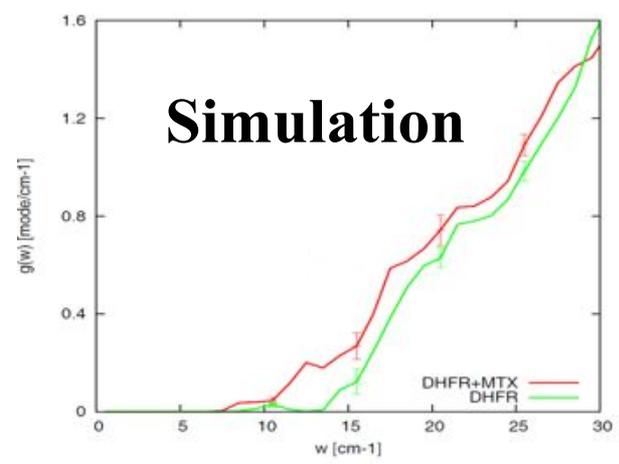
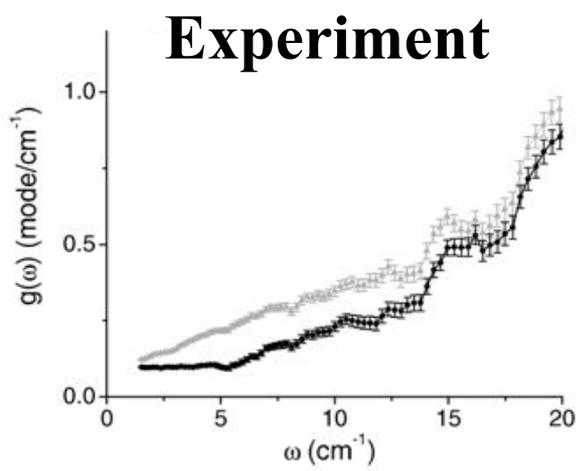
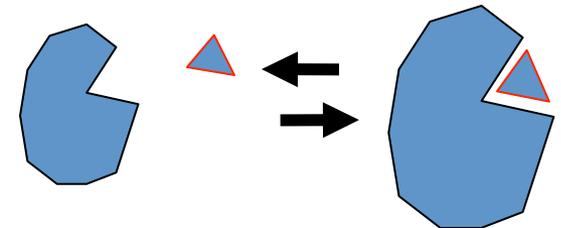
$g(\omega)$ = vibrational density of states (probability distribution of frequencies)

Vibrational Change on Methotrexate Binding to Dihydrofolate Reductase

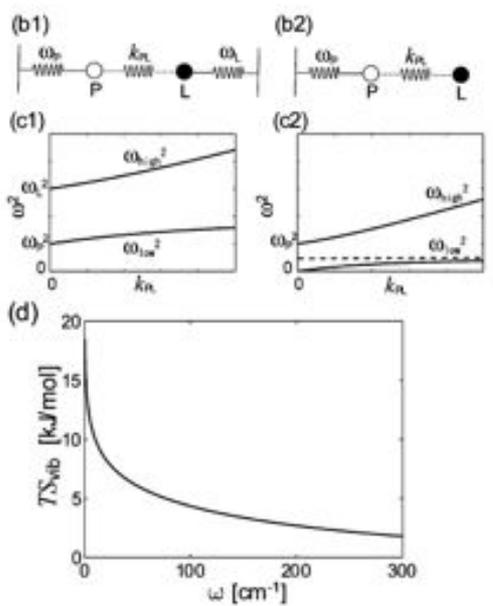


PRL 93 028103 (2004)
JPCB 114 1479 (2010)
JPCB 115 6811 (2011)

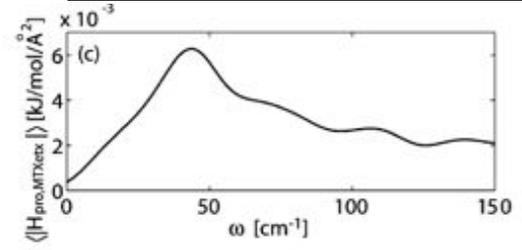
Kei Moritsugu



(b) calculation

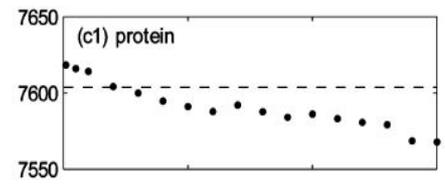


Coupling constant of ligand external motion



Entropy gain from coupling between protein and ligand external motion

Entropy loss on progressive formation of interactions

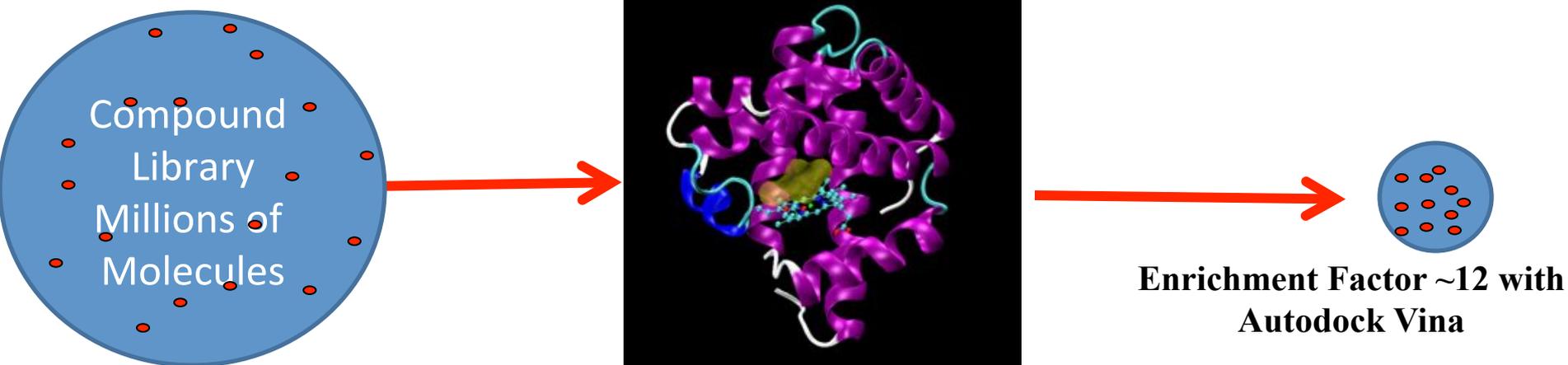


Entropy loss on formation of interactions within bound complex

\gg



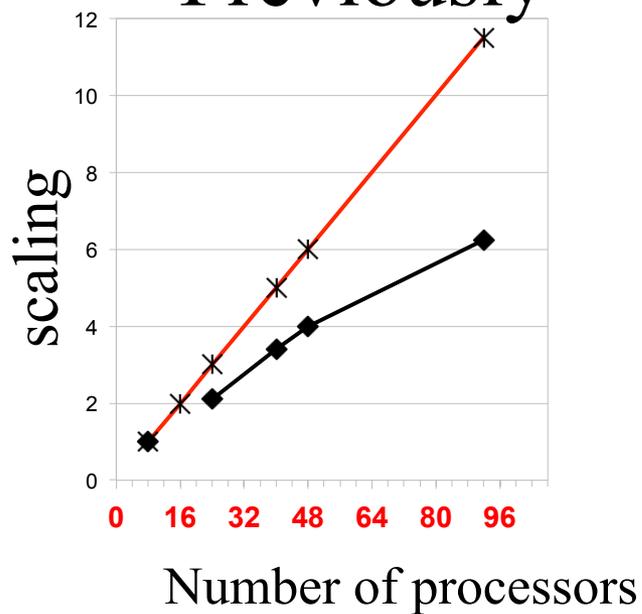
Structure-Based Computational Drug Discovery



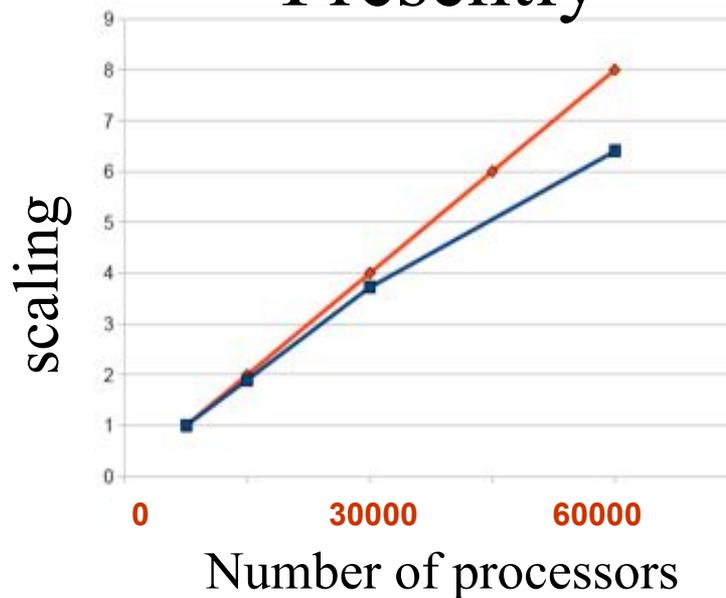
Enrich a collection of compounds with molecules most likely to bind
to the drug target(s)

→ much faster, much more affordable hit & lead discovery

Previously



Presently



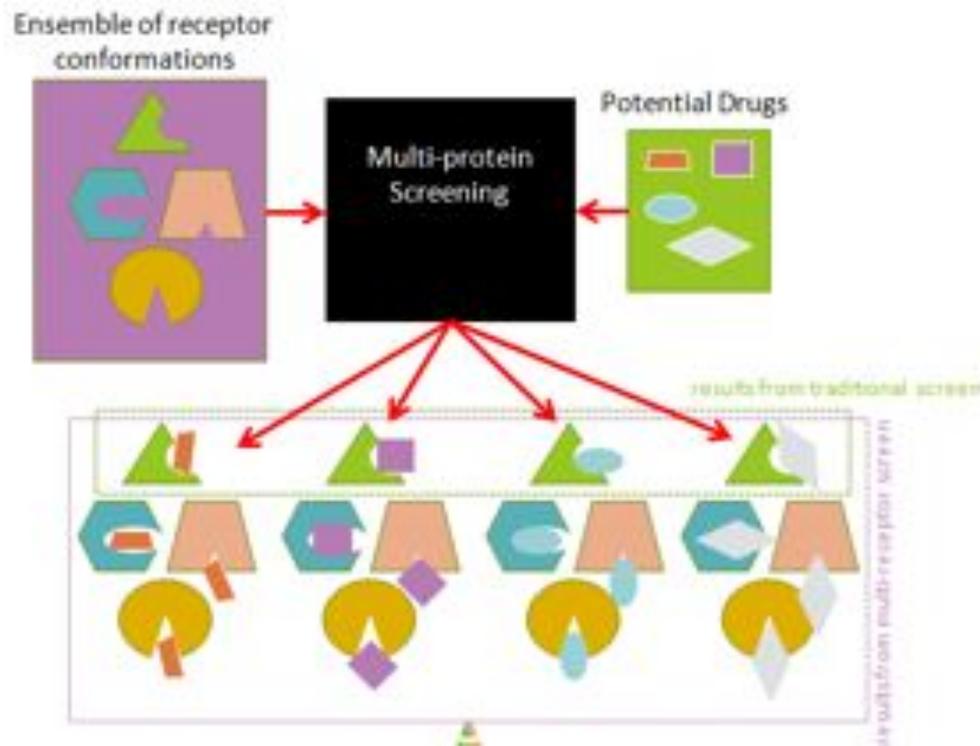
Previously :	1 protein	10^4 ligands	~days
Presently :	1 protein	10^8 ligands	1 day

Ensemble-Based Docking

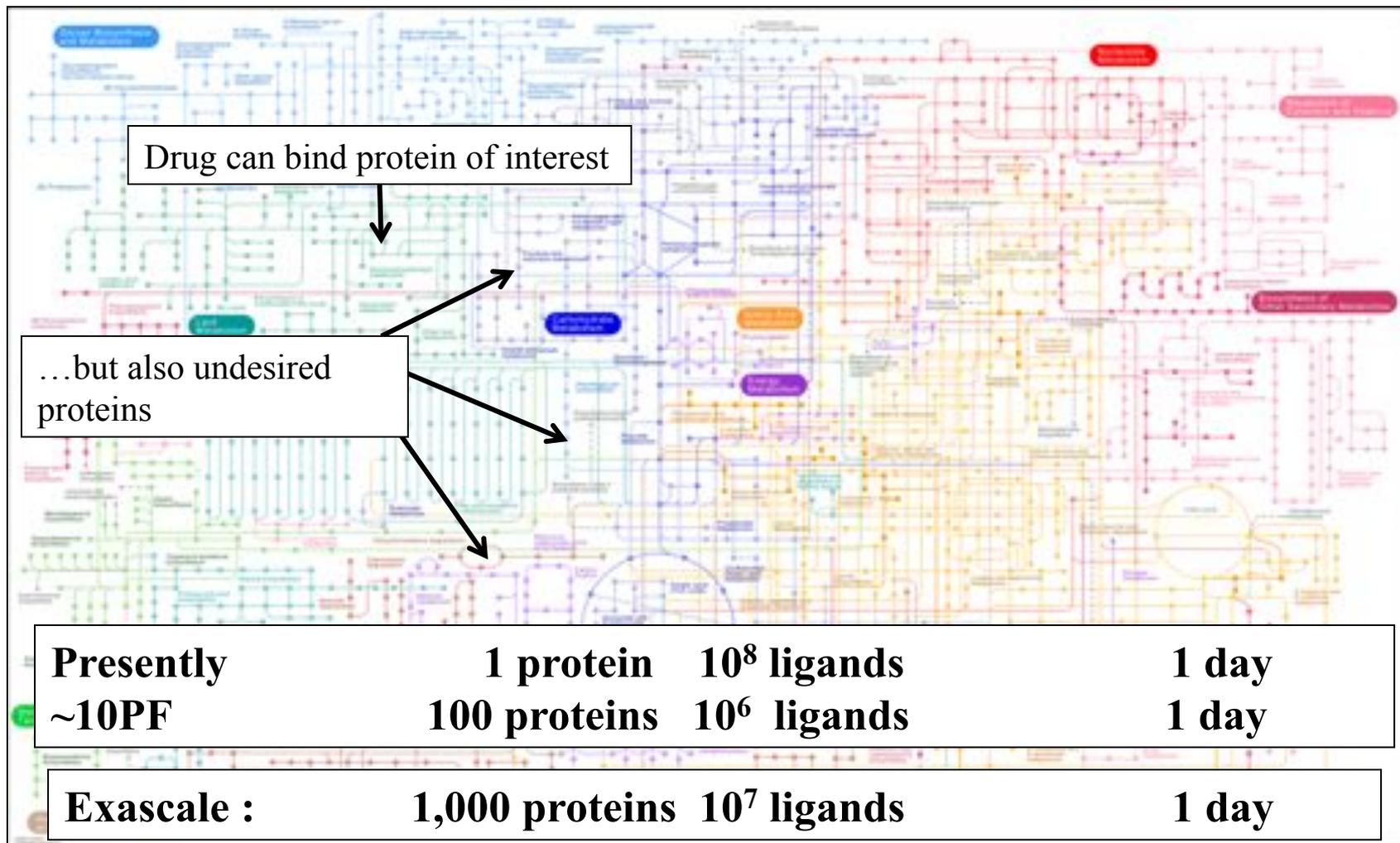
1) MD of each protein: identify permanent and transient binding pockets



2) HTS *in silico* on each structure of interest



10-100 Petaflops: Drugome Exploration, Drug Toxicity, Repurposing



Co-workers

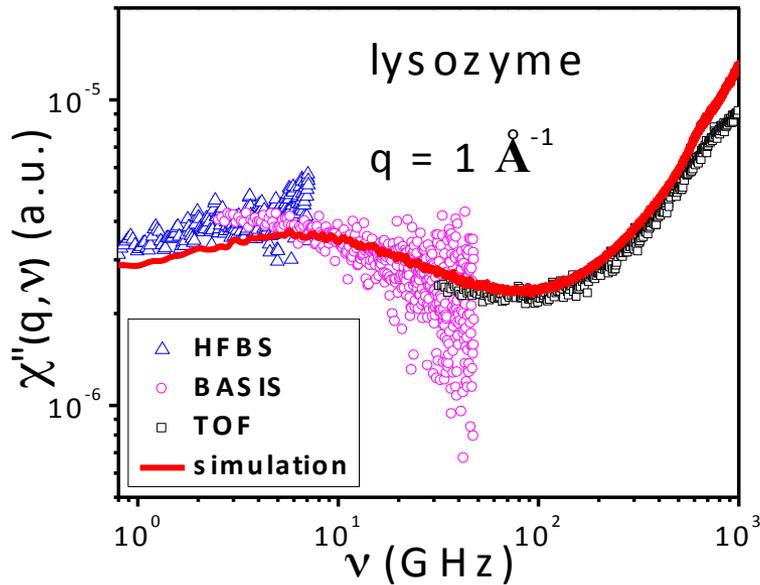
Torsten Becker
Barbara Collignon,
Sally Ellingson,
Jerome Baudry
Loukas Petridis ,
Roland Schulz
Benjamin Lindner
Dennis Glass
Xiaohu Hu
Barmak Mostofian
Amandeep Sangha
Liang Hong
Yinglong Miao
Yi Zheng
Jerry Parks

Collaborators

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Erika Balog (U. Budapest)
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Liyuan Liang, Alexei Sokolov, Barbara
Evans, Hugh O' Neill, Venky Pingali,
William Heller (ORNL)
Judy Wall (U. Missouri)
Anne Summers (U.Ga)
Sue Miller (UCSF)
Ahmed Zewail (CalTech)
Akio Kitao (U. Tokyo)
Dieter Richter, Ralf Biehl, Michael Ohl,
Melissa Sharp (FZ Juelich)

Funding: DOE(BER, BES, ASCR),NSF, NIH,DFG

Dynamic Neutron Susceptibility of a Globular Protein



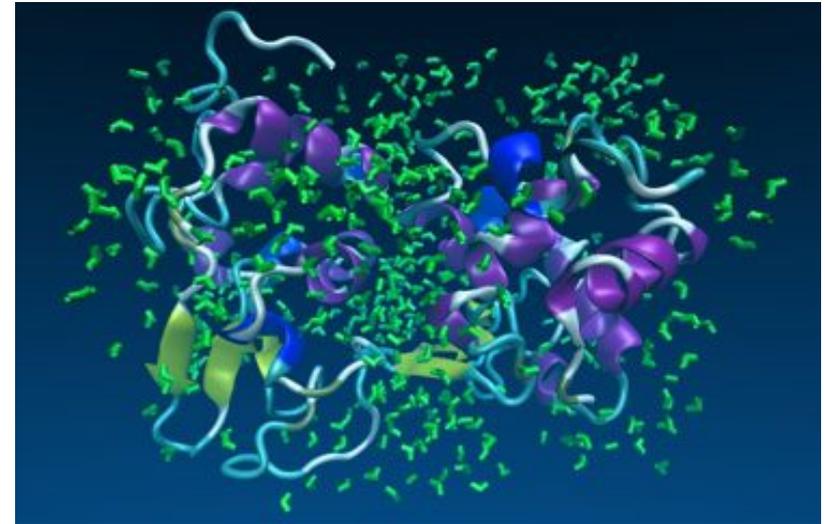
$$\chi''(q, \omega) = S(q, \omega) / n_B(T)$$

$\chi''(q, \omega)$: Dynamic Susceptibility

$S(q, \nu)$: Dynamic Structure Factor

$n_B(T)$: Bose Factor

Liang
Hong



Lysozyme

PRL 107 148102 (2011)

Three Classes of Motion in the Dynamic Neutron Susceptibility

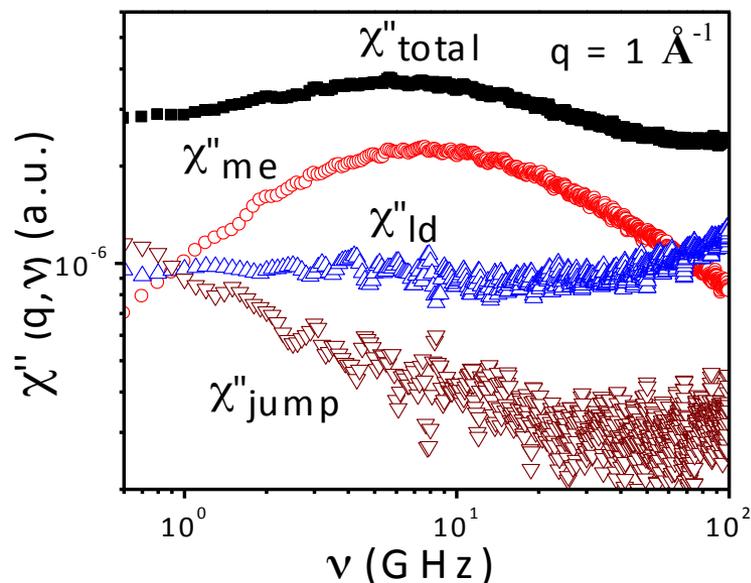
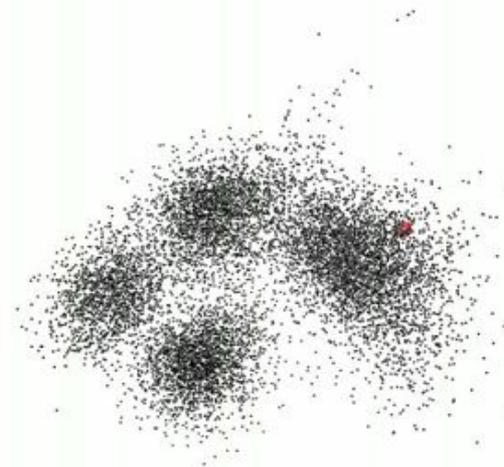
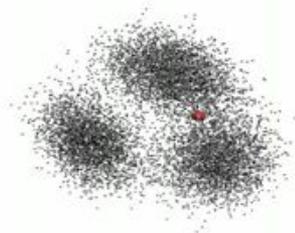
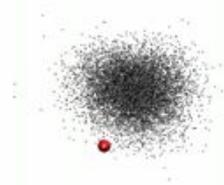
Liang
Hong



Localized diffusion

Methyl rotation

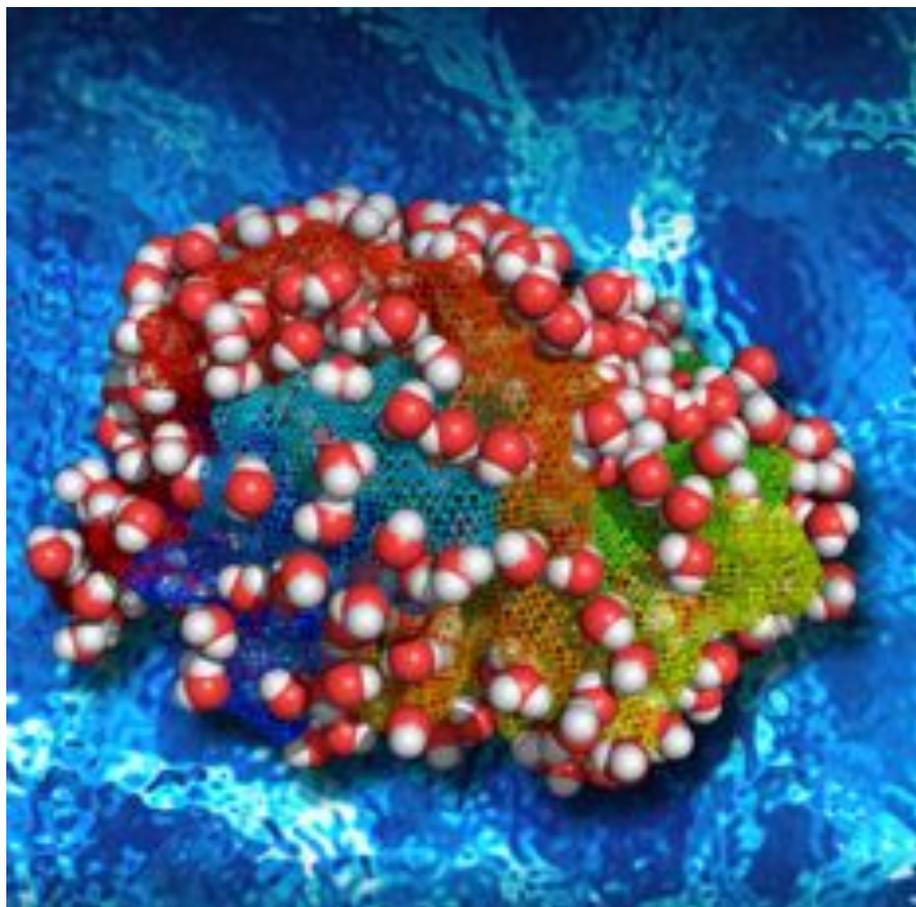
Non-methyl jumps



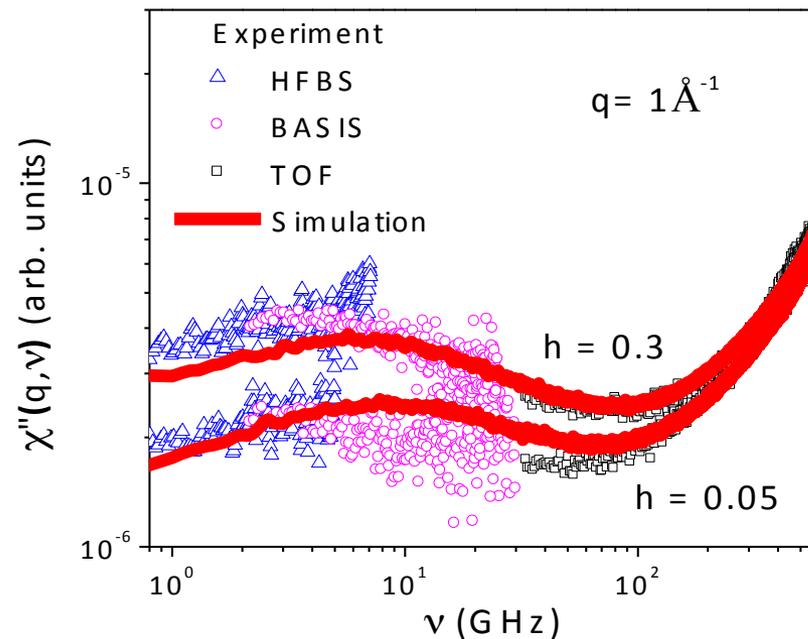
PRL 107 148102 (2011)

Hydration Effect on Protein Dynamics

Liang
Hong



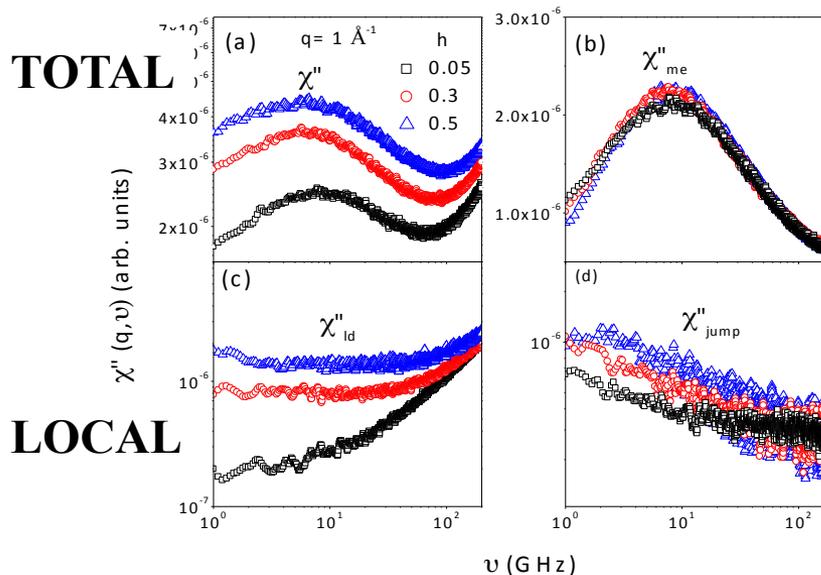
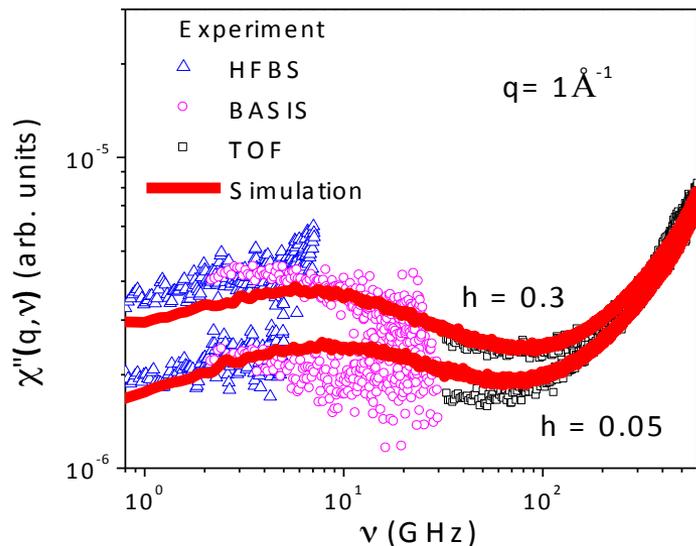
Dynamic Susceptibility



PRL 108 238102 (2012)

Hydration Effect on Dynamic Susceptibility

Liang
Hong



METHYL

JUMP

Localized diffusion

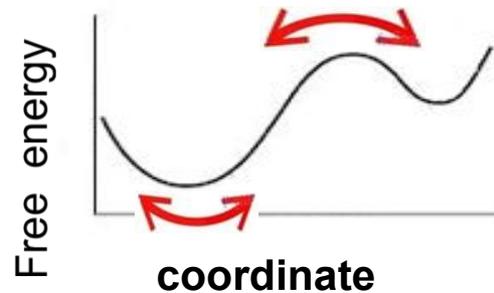


2 Å

Nonmethyl Jumps

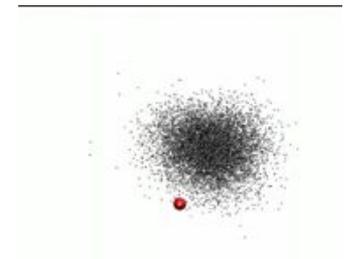
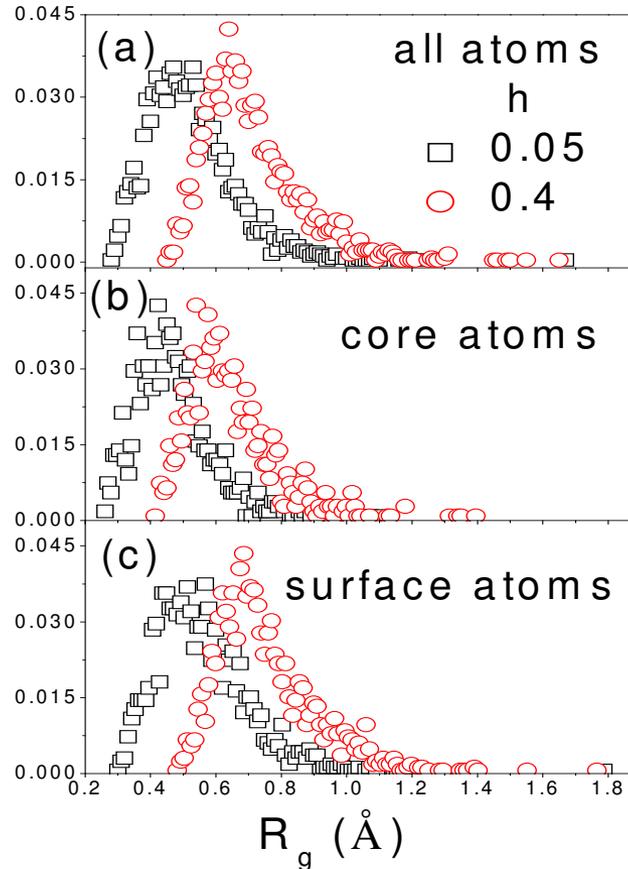
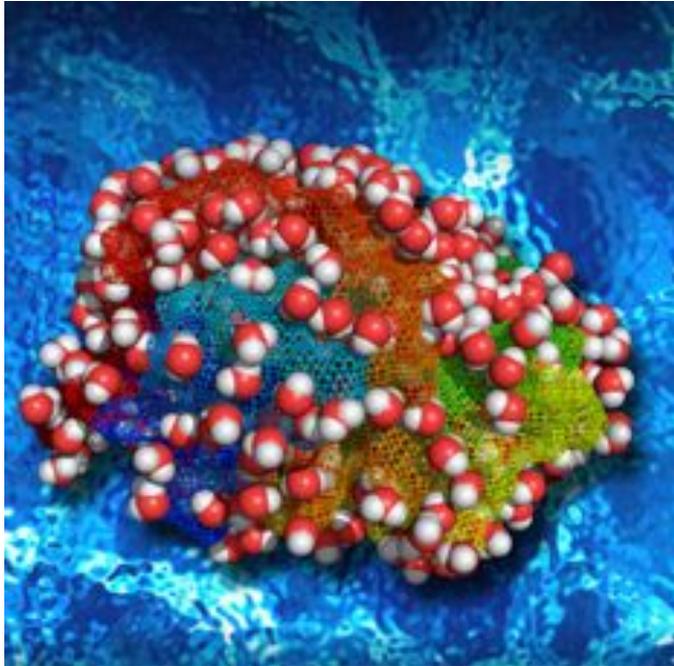


Methyl rotation



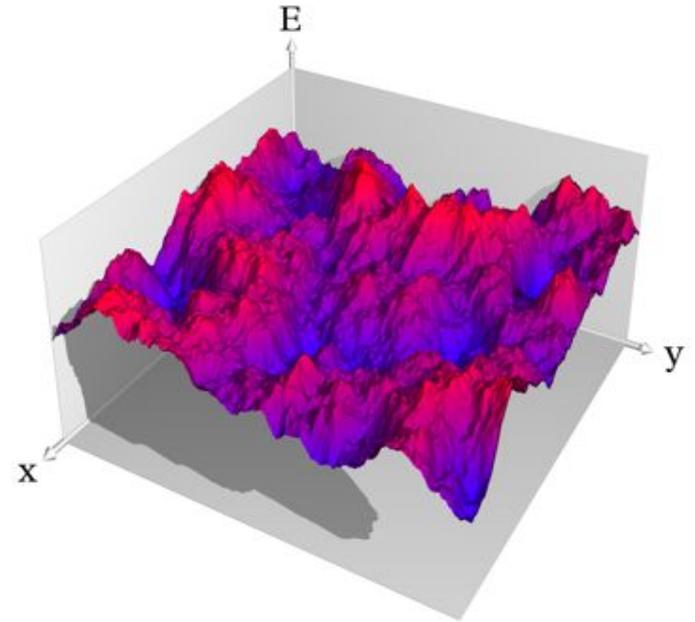
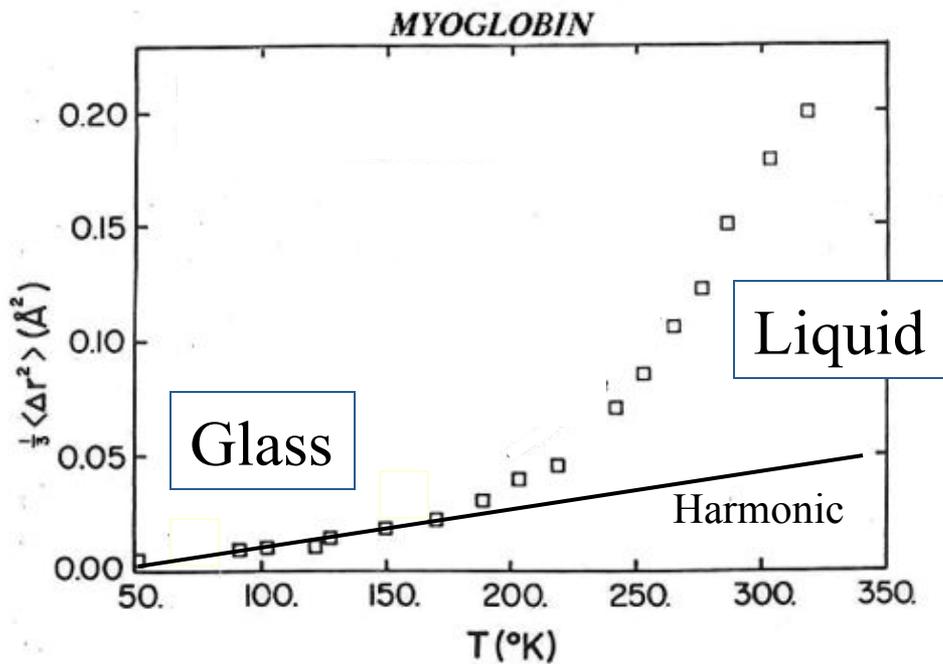


Does hydration affect core dynamics?



Surface hydration amplifies single-well protein atom diffusion propagating into the macromolecular core

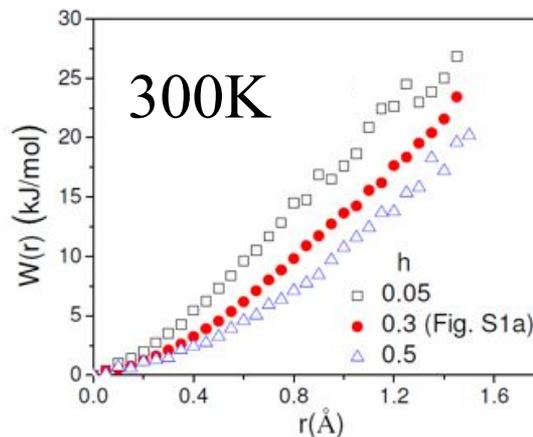
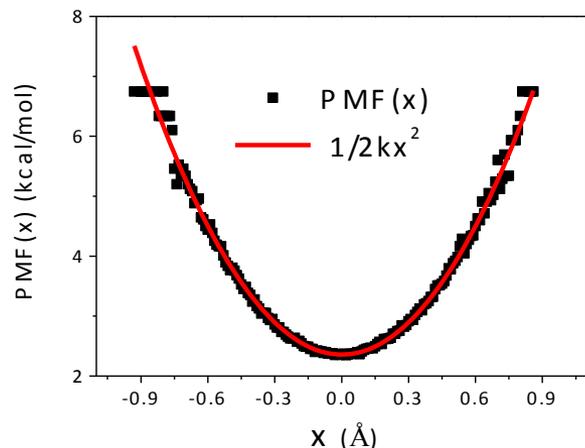
Elastic and Conformational Softness of a Globular Protein



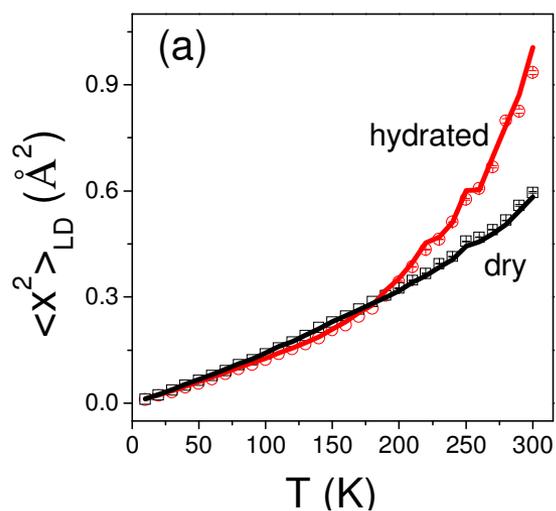
$$\delta T / \delta(r^2) = \text{resilience?}$$



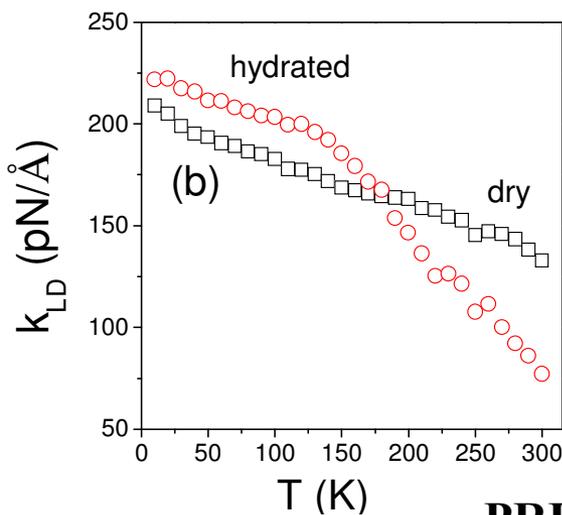
Single-Well Dynamics



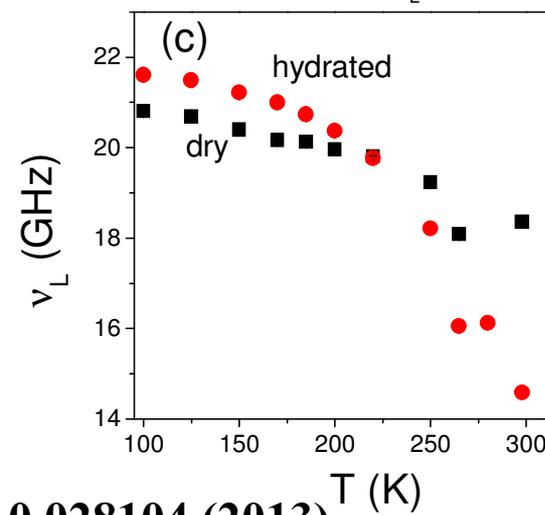
MSD of localized diffusion

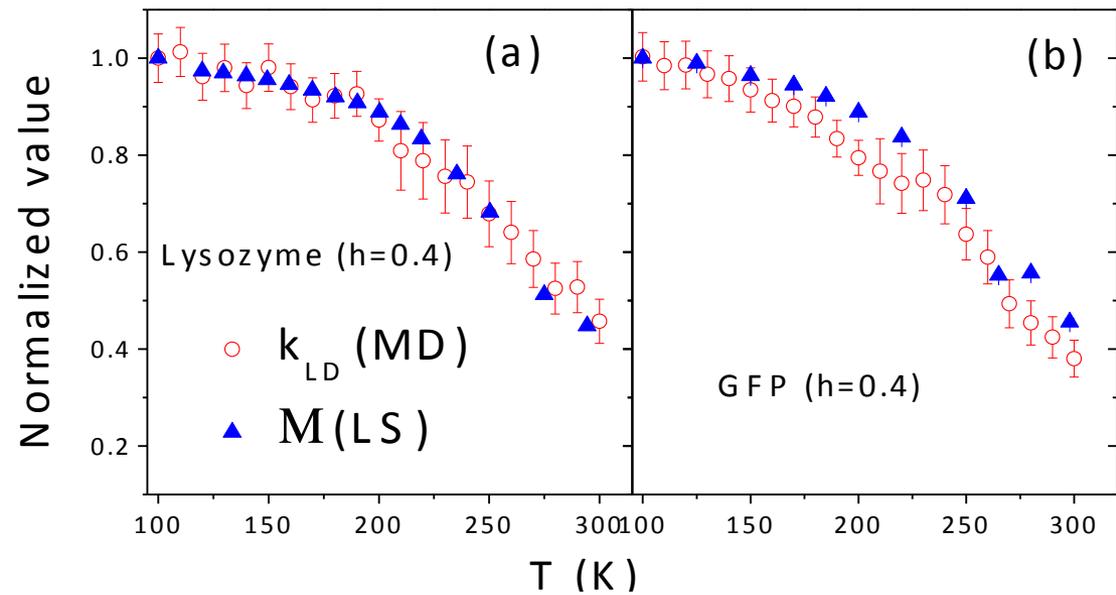
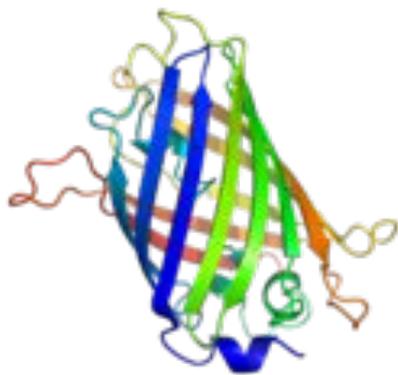
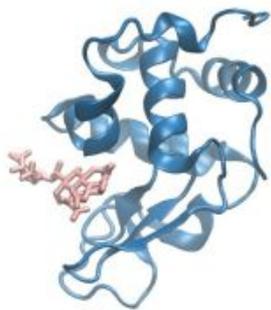


Force constants

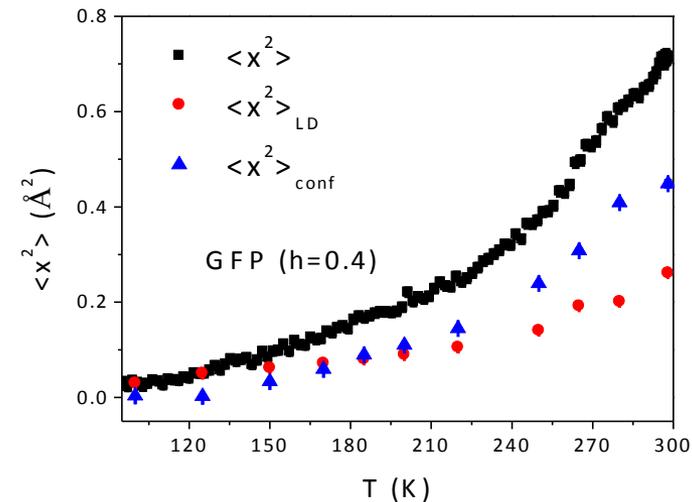
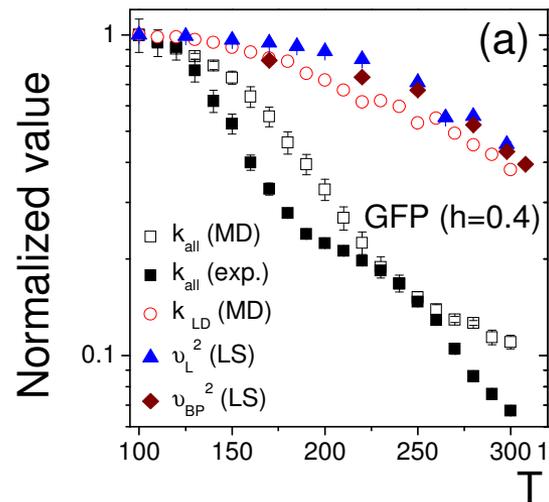


Longitudinal ν_L





$$M \longrightarrow k_{LD} \longrightarrow \langle x^2 \rangle_{LD}$$

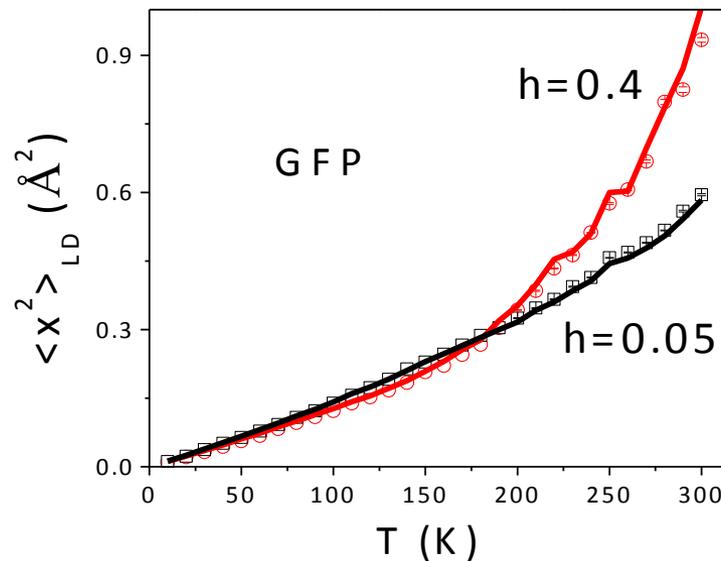
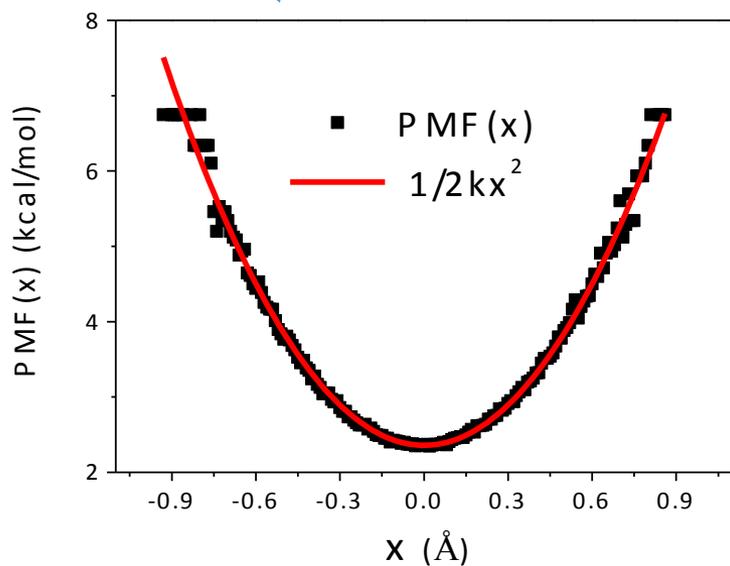
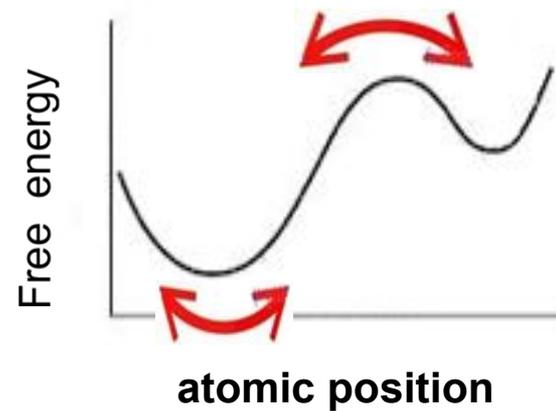
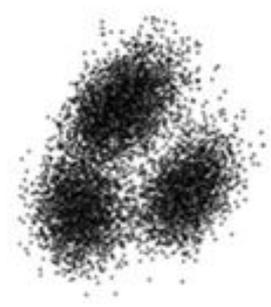
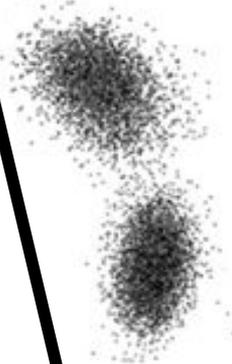


$$\langle x^2 \rangle_{conf} = \langle x^2 \rangle - \langle x^2 \rangle_{LD}$$

Localized diffusion Nonmethyl jump Methyl rotation

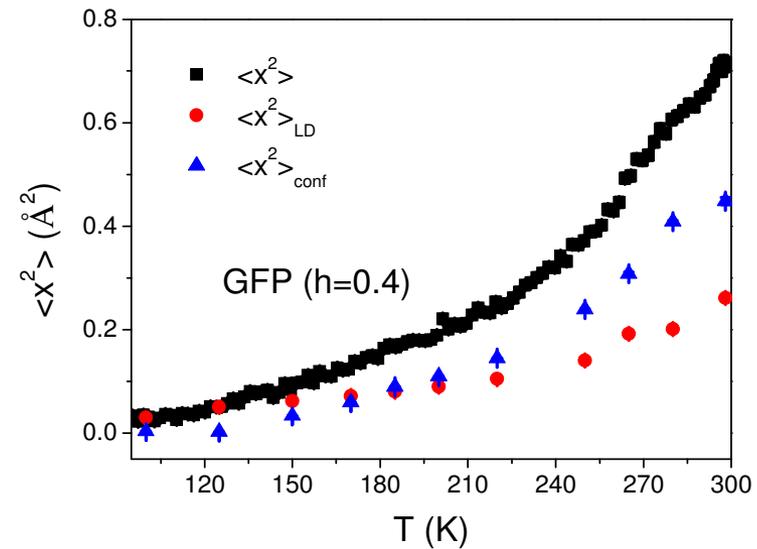
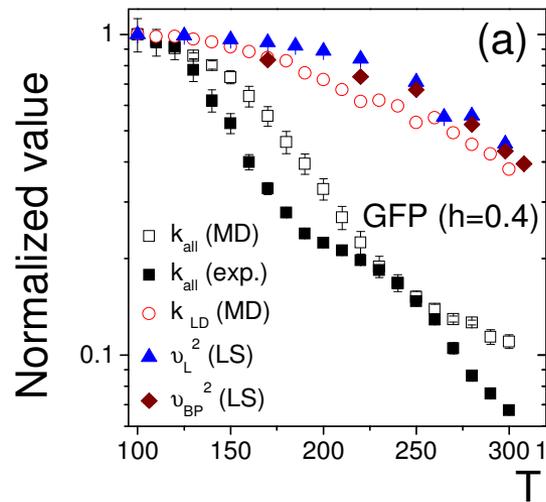


2 Å

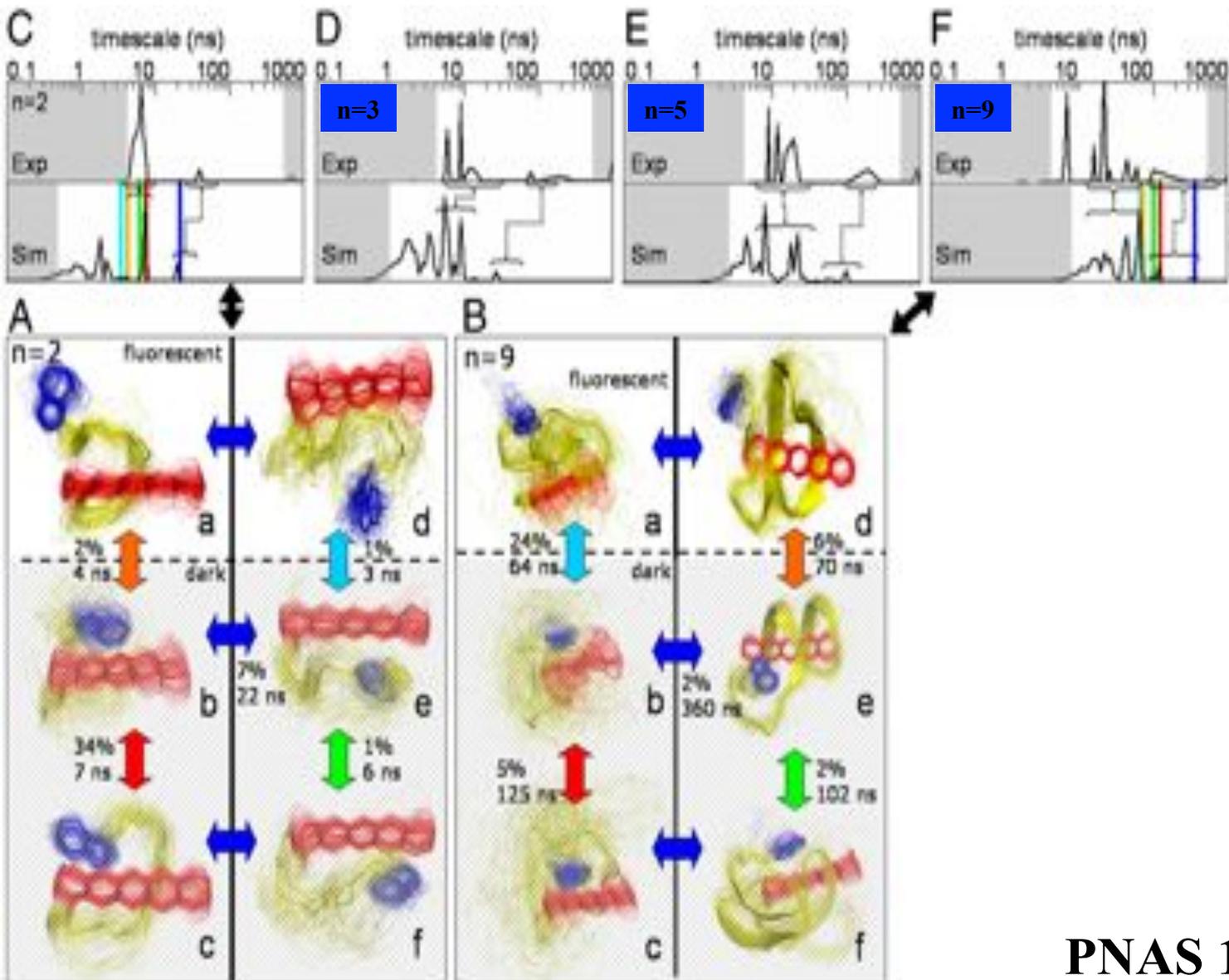




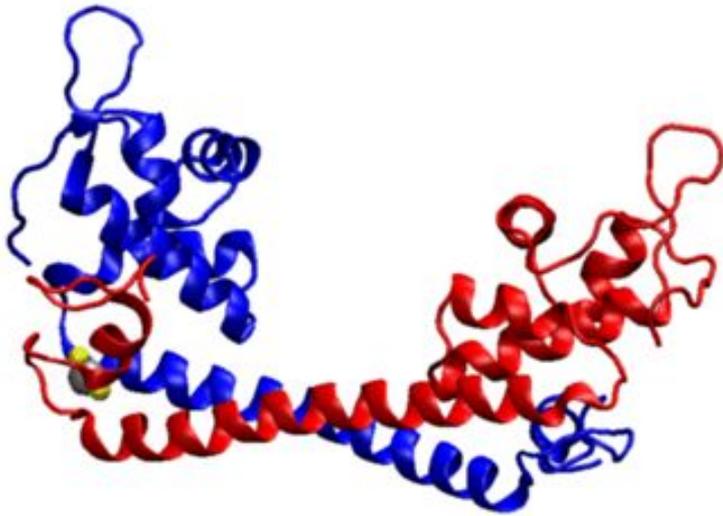
Elastic and Conformational Softness of a Globular Protein



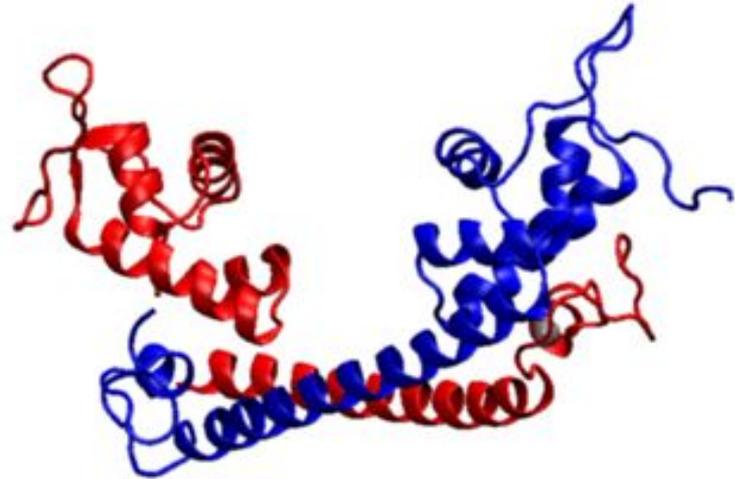
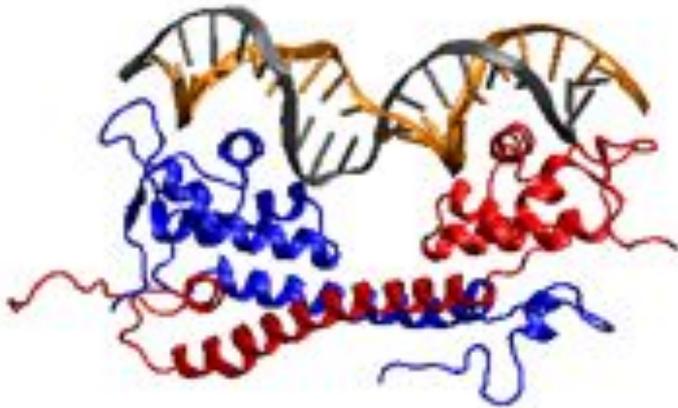
Dynamical Fingerprints of MR121 -(Gly-Ser)_n-Trp



**MerR
Transcriptional
Activation**

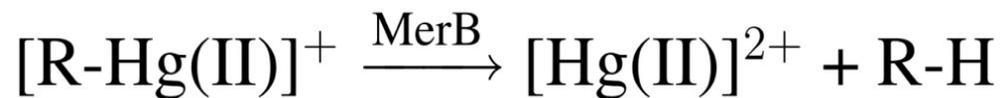
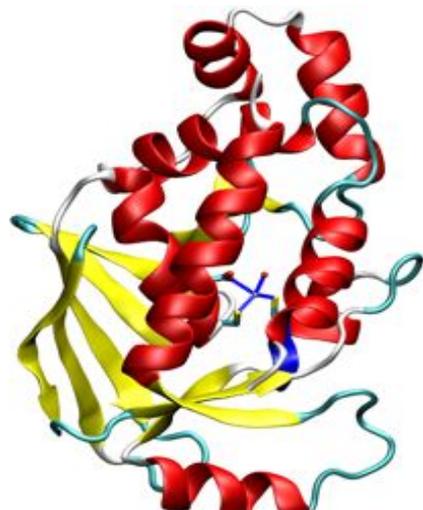


Principal Component Analysis

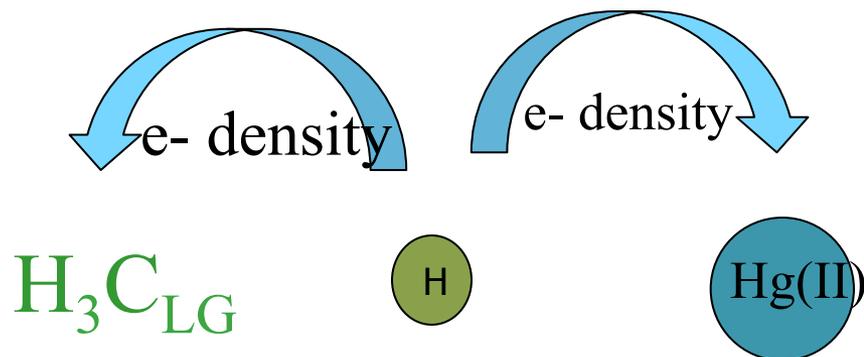
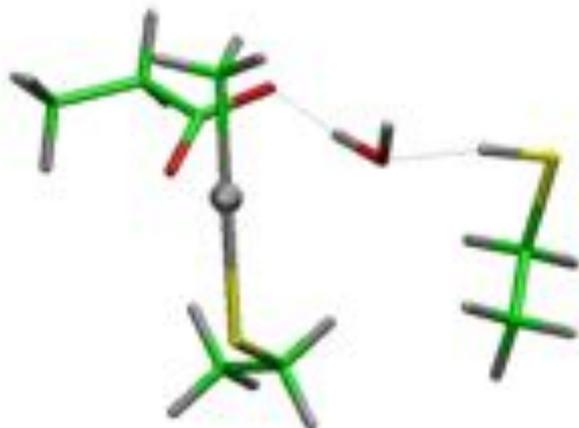


Catalytic Mechanism of MerB

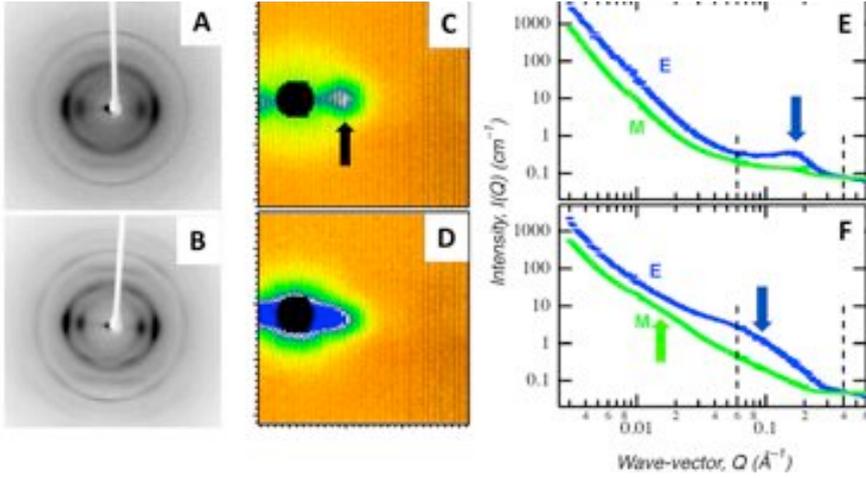
Hg-C Protonolysis



- Thiol *bis*-coordination of Hg at Transition State Polarizes Attacking Proton.

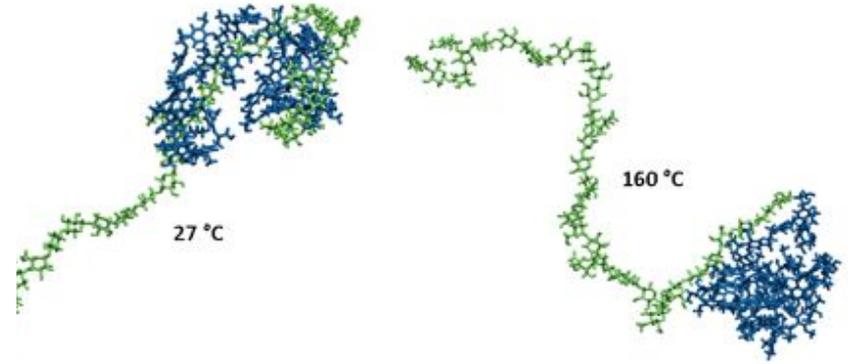
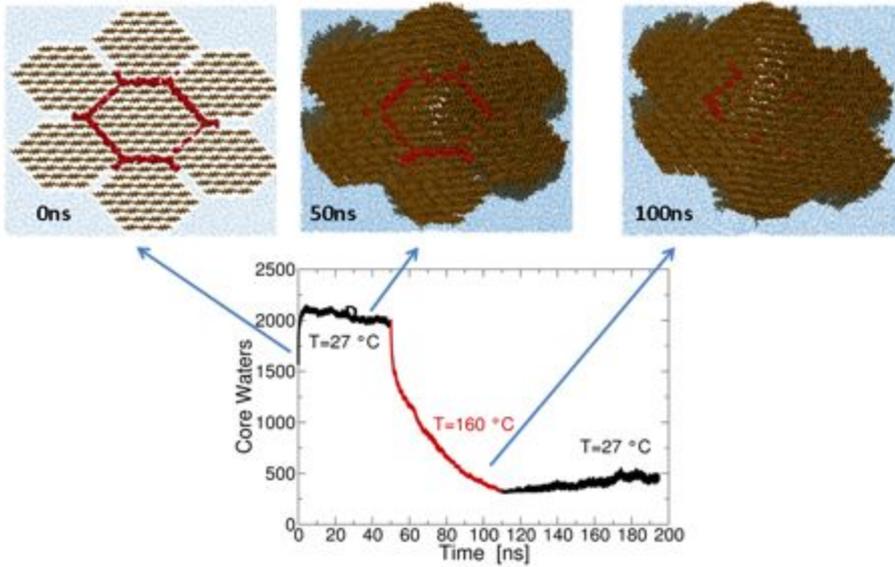


Effect of Pretreatment on Biomass Structure



Untreated

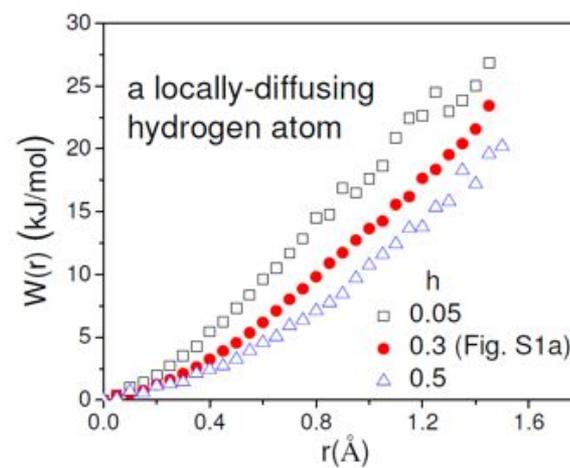
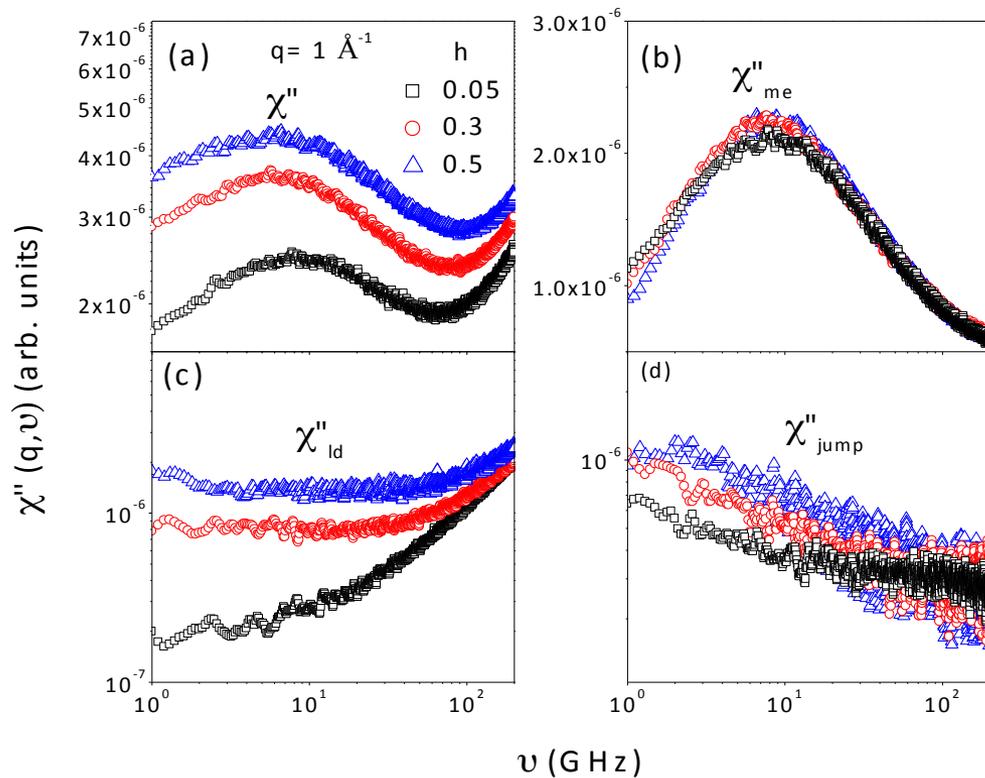
Pretreated



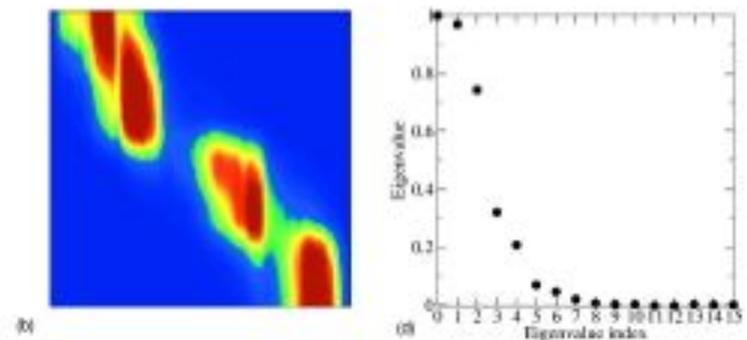
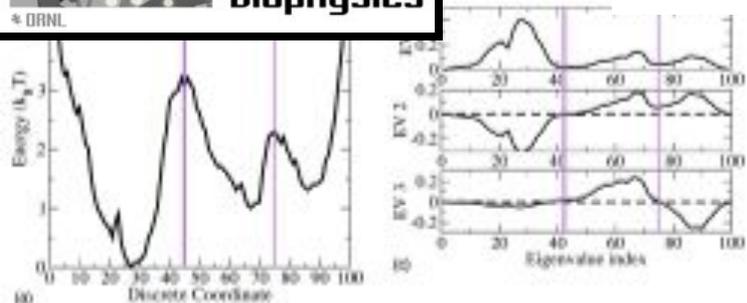
Localized diffusion

Methyl rotation

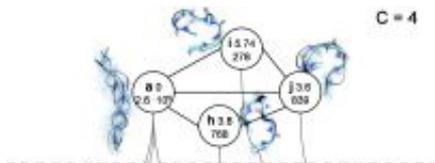
Non-methyl jumps



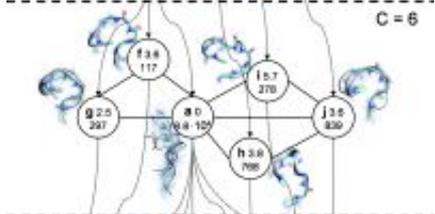
Exascale Concepts



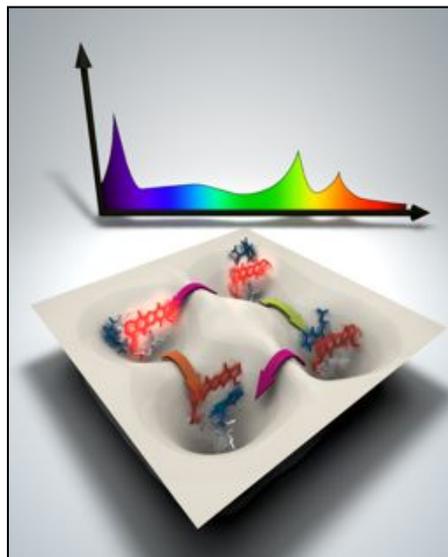
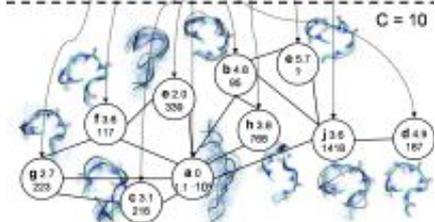
C = 4



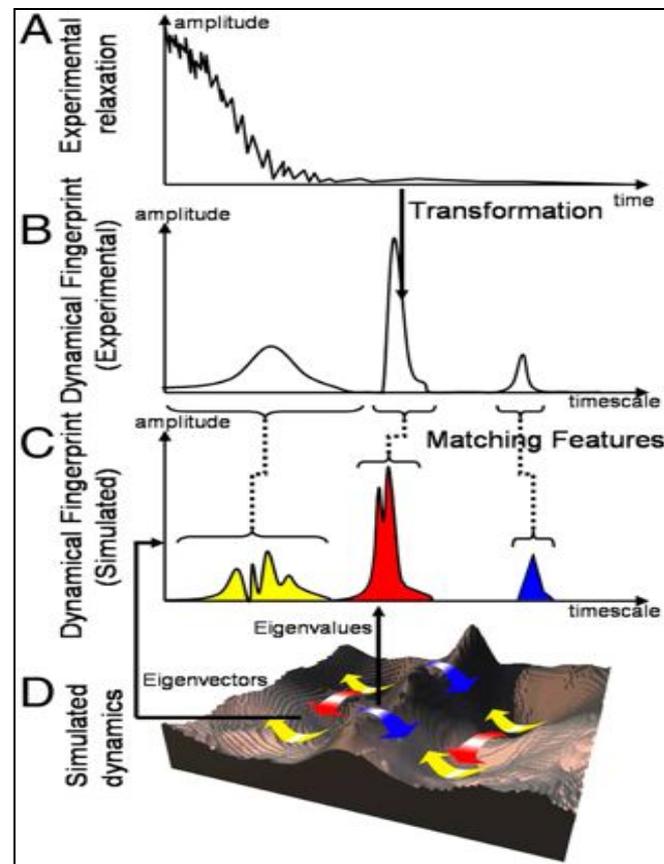
C = 6



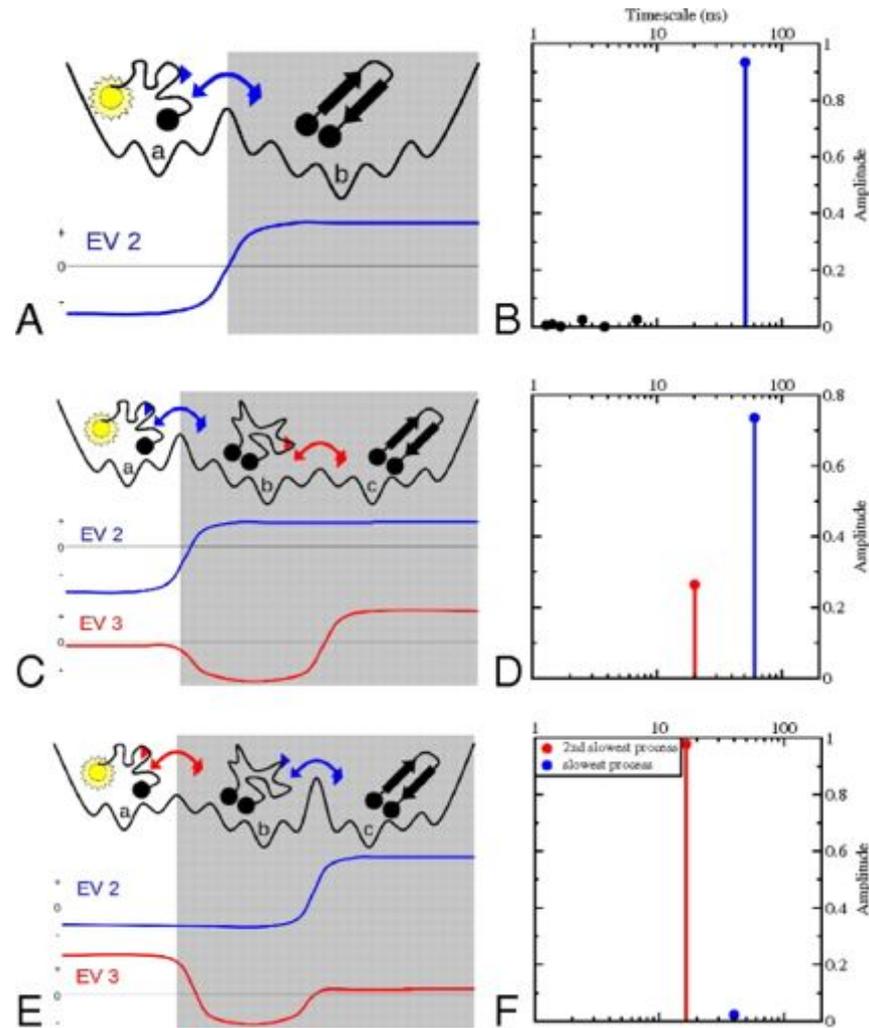
C = 10



Dynamical Fingerprints

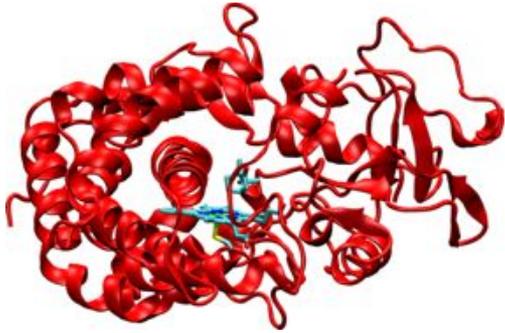


Illustrative models of systems probed by fluorescence correlation.



Noé F et al. PNAS 2011;108:4822-4827

Elastic Incoherent Scattering and Mean-Square Displacements



Cytochrome
P450

$$S_{el}(\vec{q}, \omega = 0) = \frac{1}{N} \sum_{\alpha} \langle e^{i\vec{q} \cdot \Delta \vec{r}_{\alpha}^{\Gamma}(t_R)} \rangle \approx \langle e^{i\vec{q} \cdot \Delta \vec{r}^{\Gamma}(t_R)} \rangle$$

Gaussian Approximation:

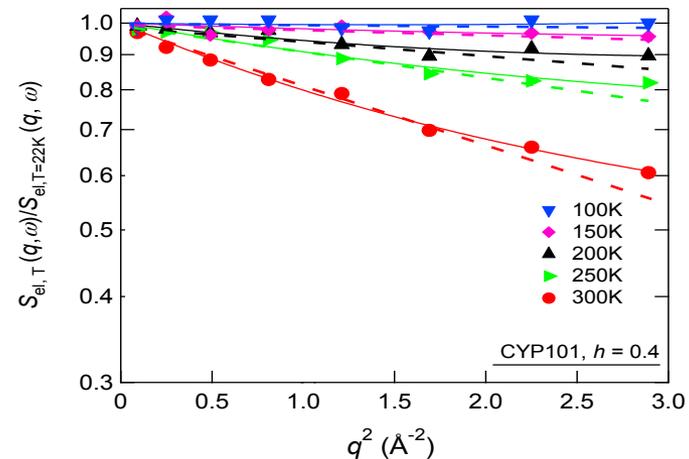
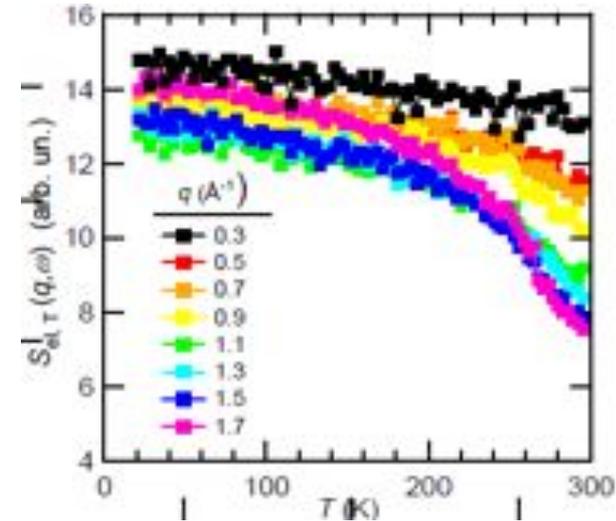
$$S_{el}(q, \omega = 0) = e^{-\frac{1}{6}q^2 \langle \Delta r^2 \rangle}$$

q^4 term:

$$\approx e^{-\frac{1}{6}q^2 \langle \Delta r^2 \rangle} \left(1 + \frac{q^4}{72} \sigma^2 \right)$$

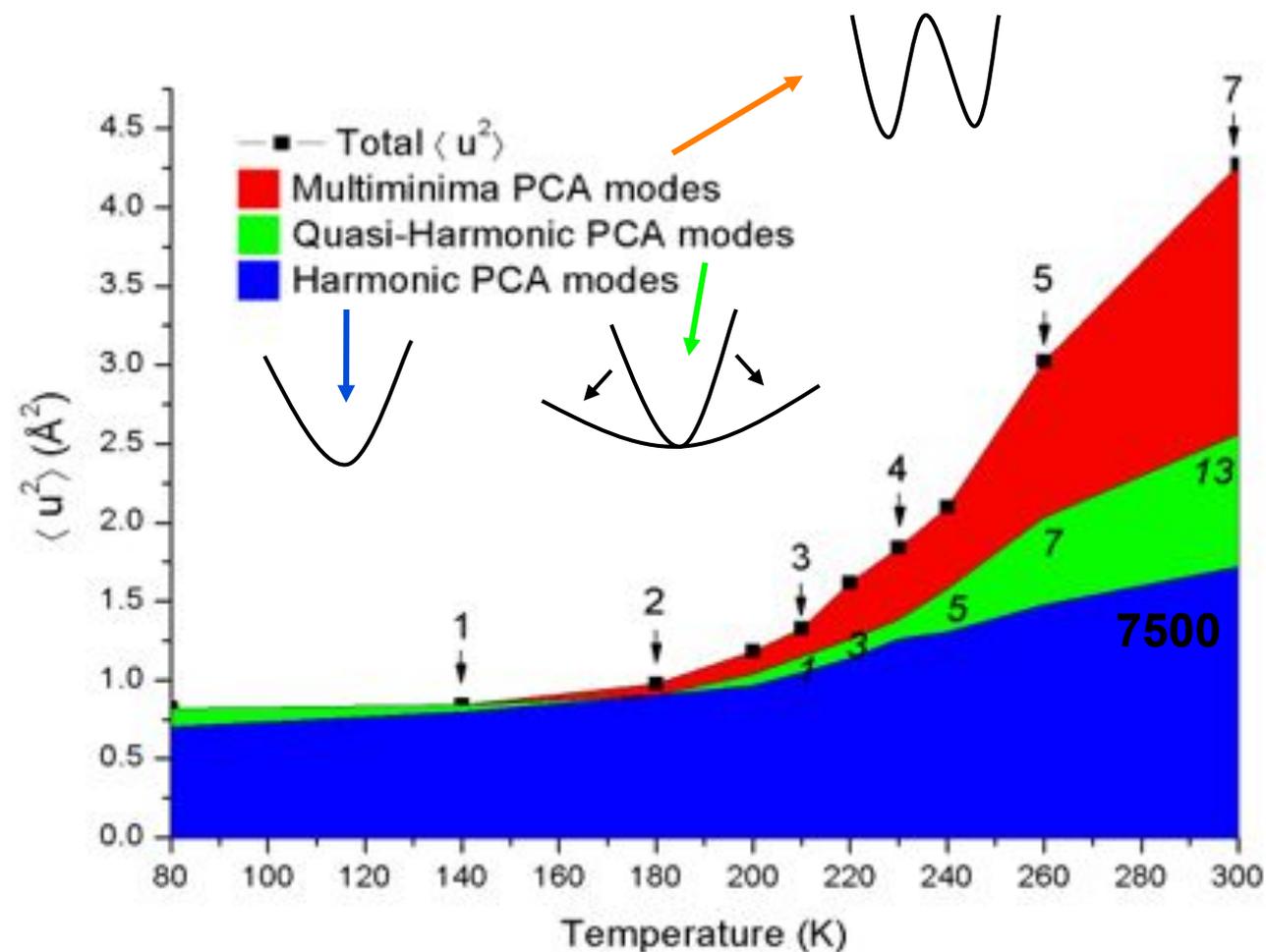
σ^2 = variance of MSD

BASIS spectrometer at SNS



Principal Component Analysis of the Myoglobin Glass Transition

$$A_{ij} = \langle (r_i(t) - \bar{r}_i)(r_j(t) - \bar{r}_j) \rangle$$



PRL 91 208106 (2003)

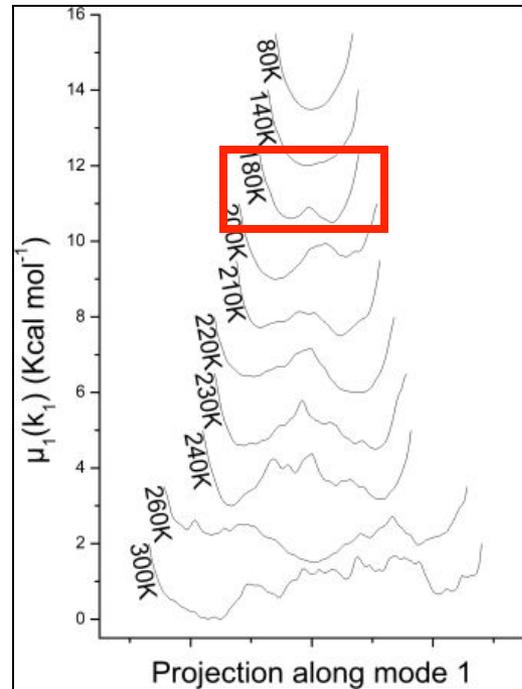
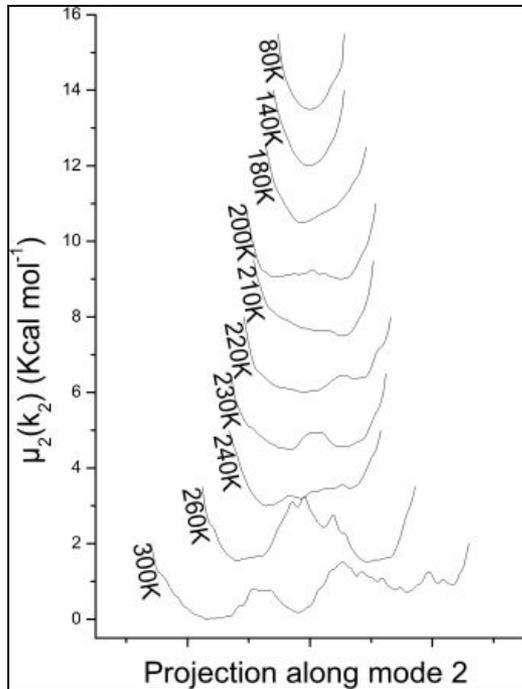
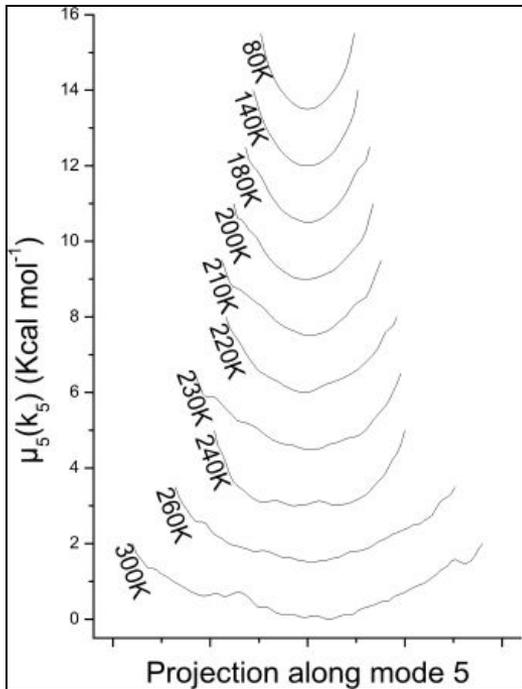
PRL 99 138101 (2007)

PRL 100 18 188103 (2008)

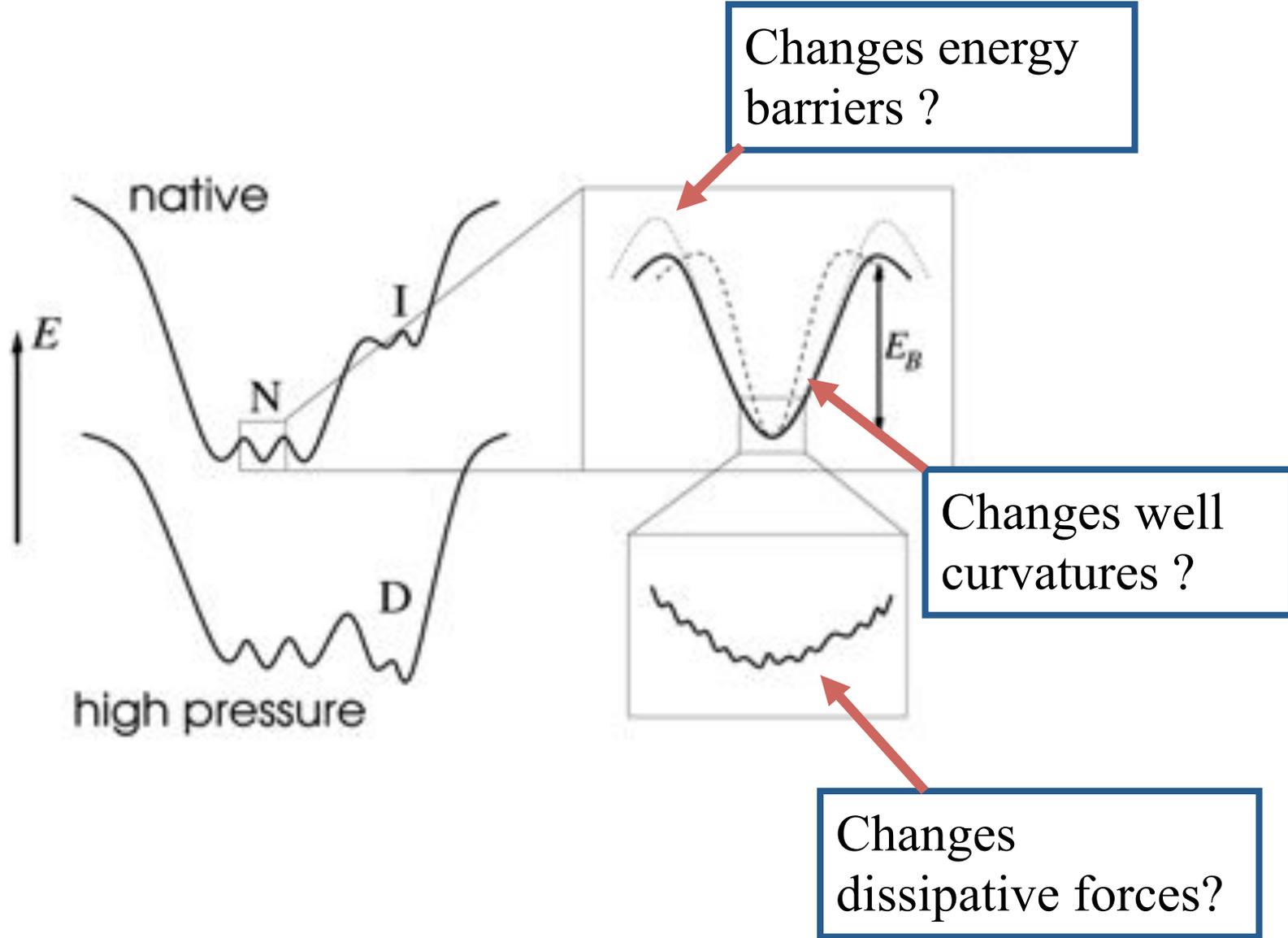
Mode Incipient at Myoglobin Glass Transition

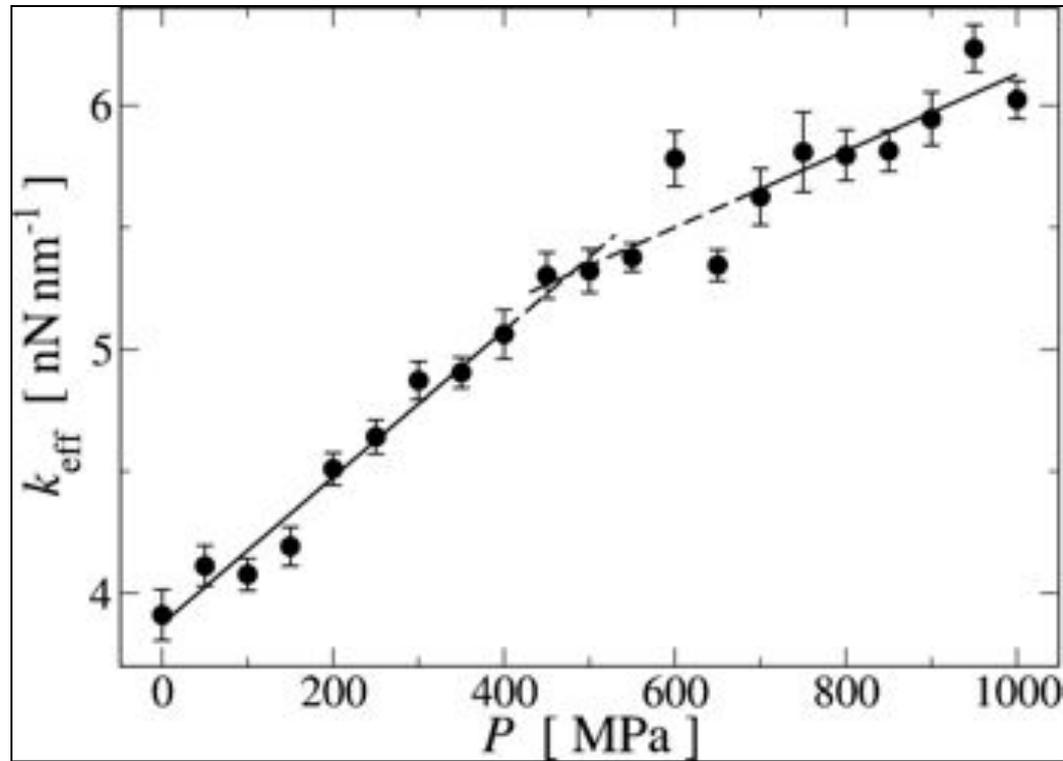
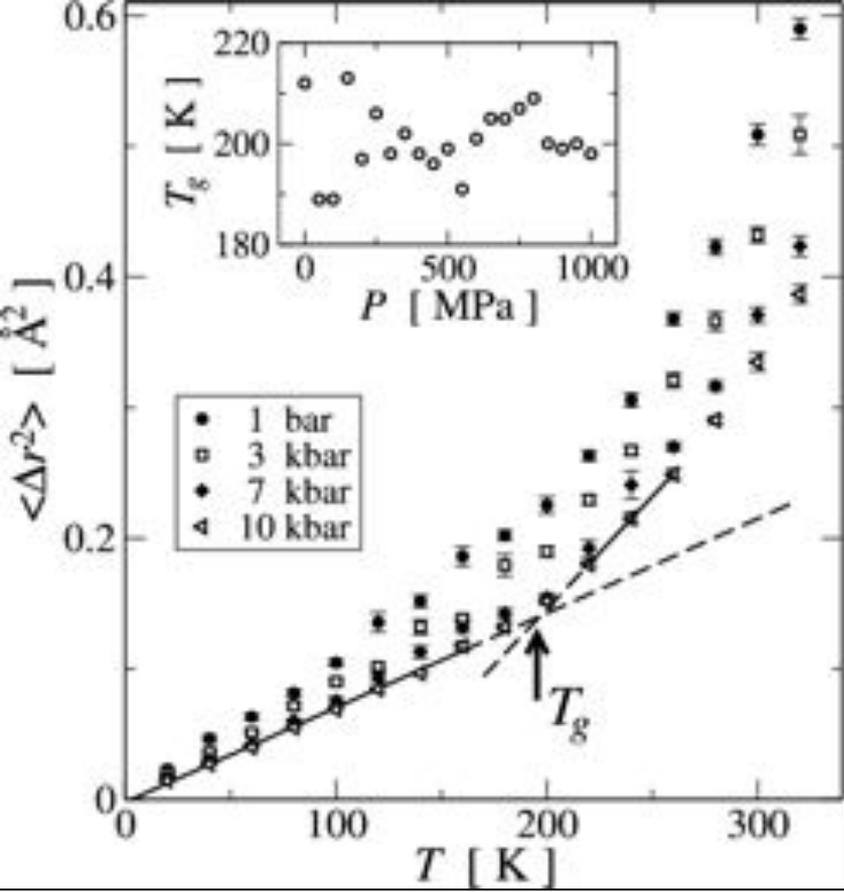


Free Energy Profiles of Dominant Principal Components



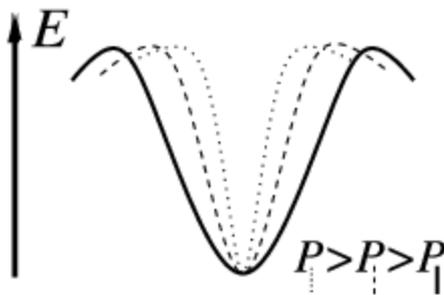
Proteins Under Pressure

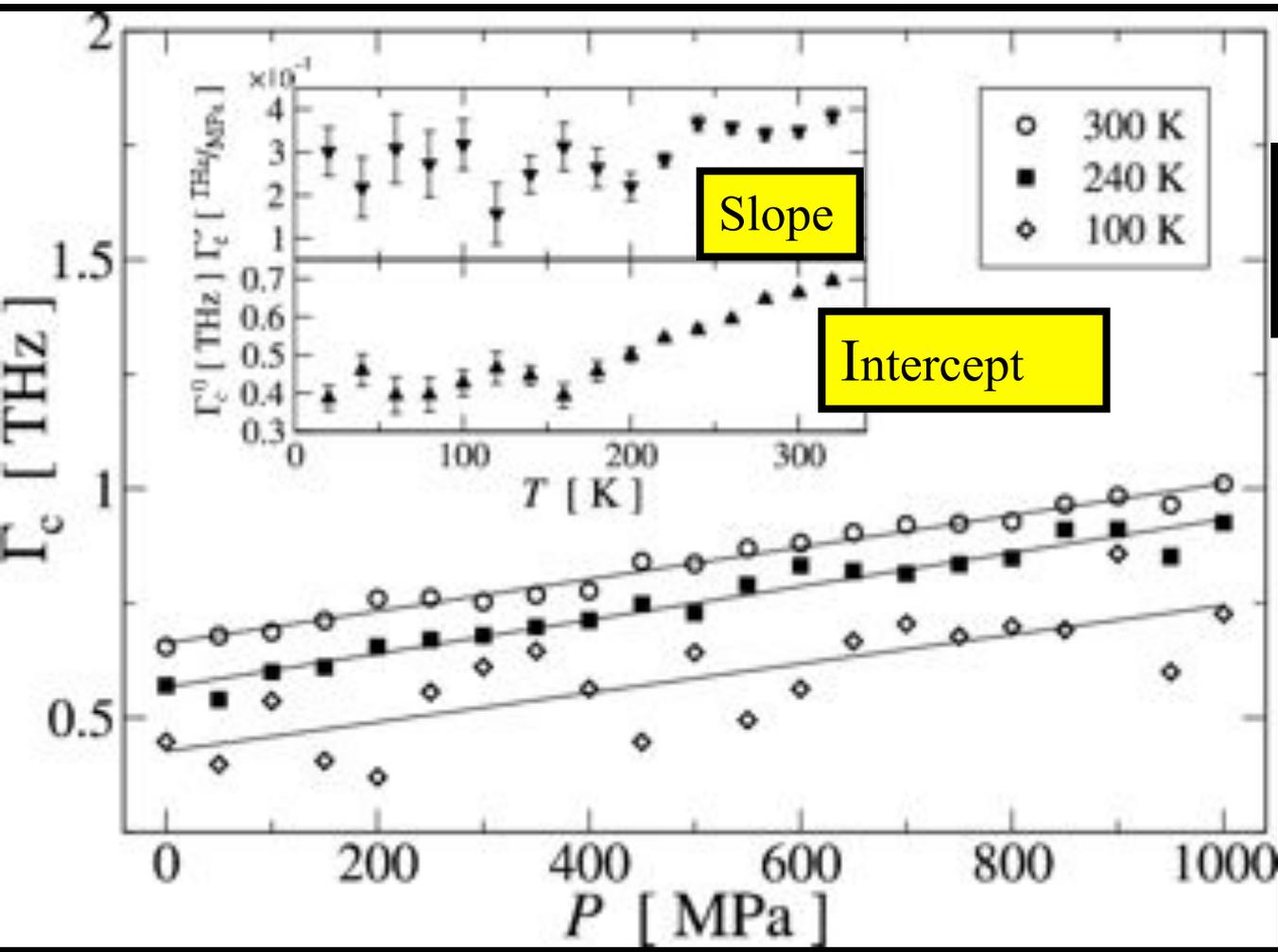




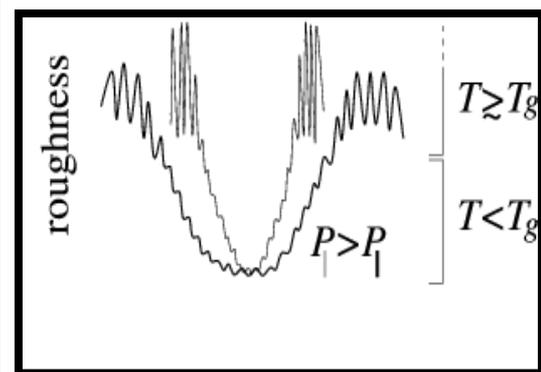
T_g independent of P :
No change in barrier heights

$T < 160\text{K}$ force constant P dependent:
Local curvature changes



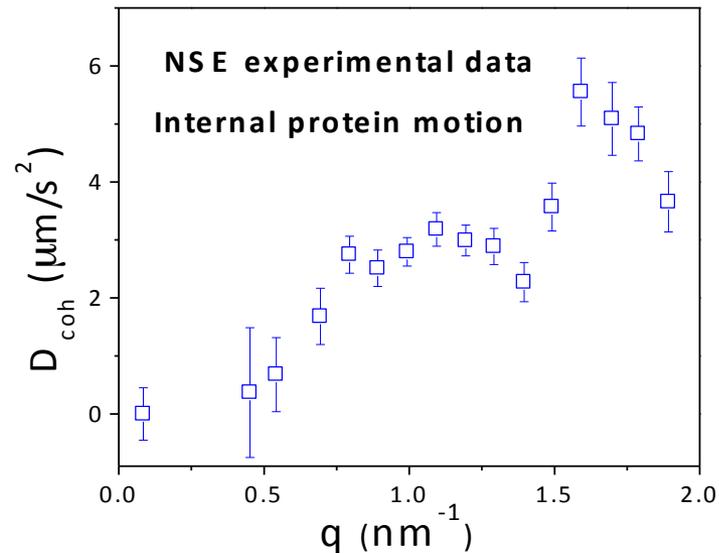
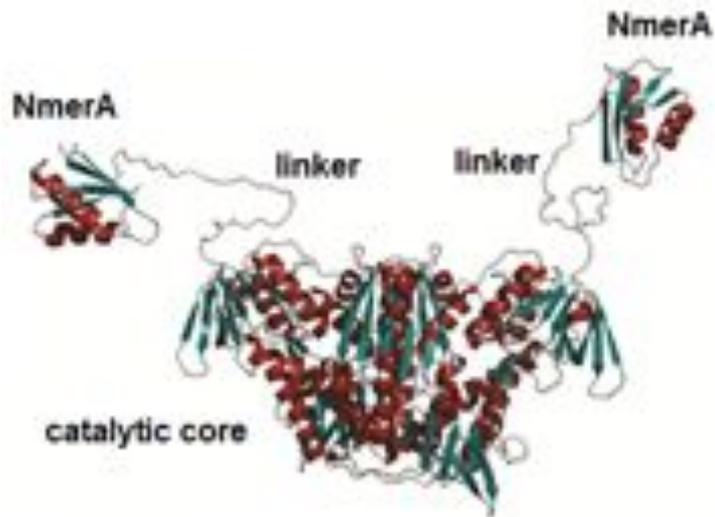


Langevin equation for principal component modes
 $dv/dt = -2\Gamma v(t) - \omega^2 \sigma(t) + \xi(t)$

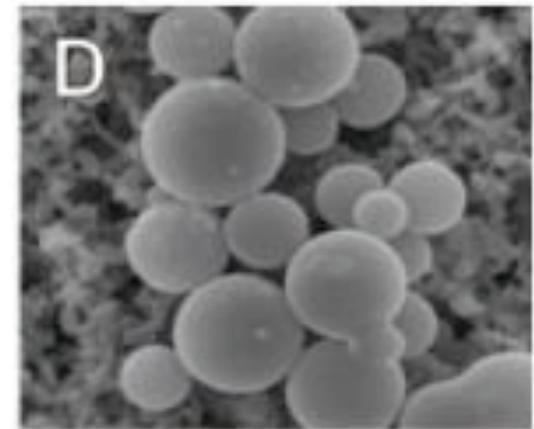
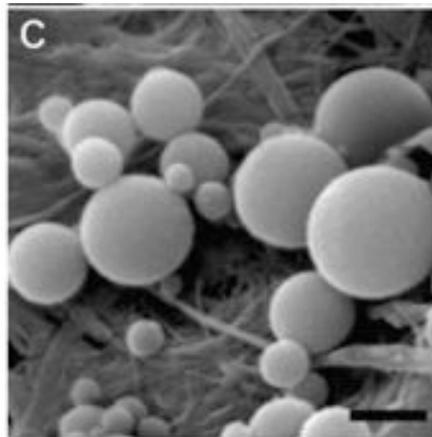
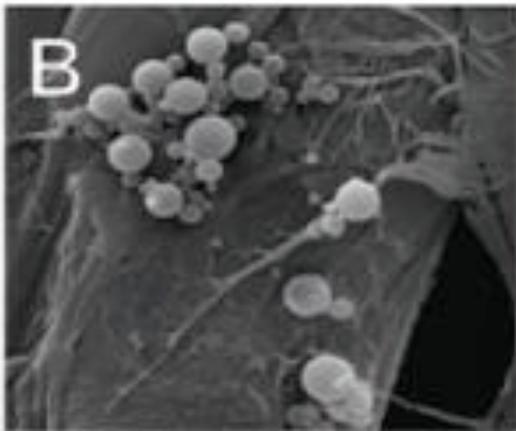
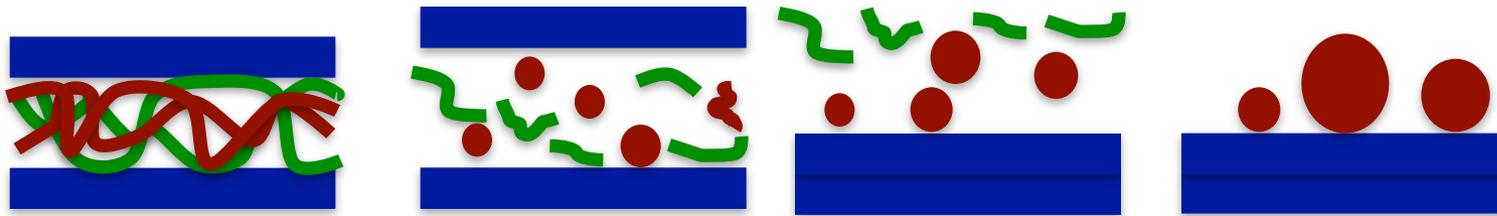


Critical Damping

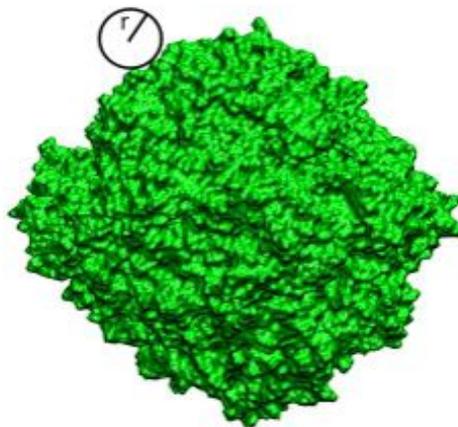
Domain Motions in Mer A



Length dependent
diffusion coefficient



Are Lignin Aggregates Spheres?

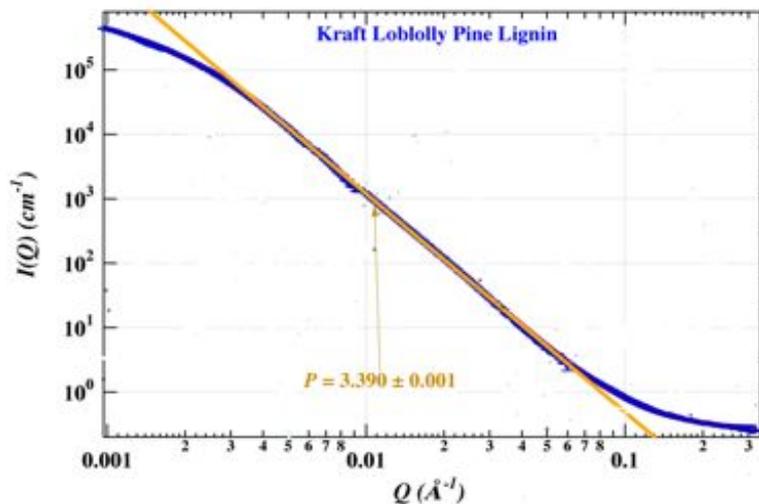


Molecular
Dynamics

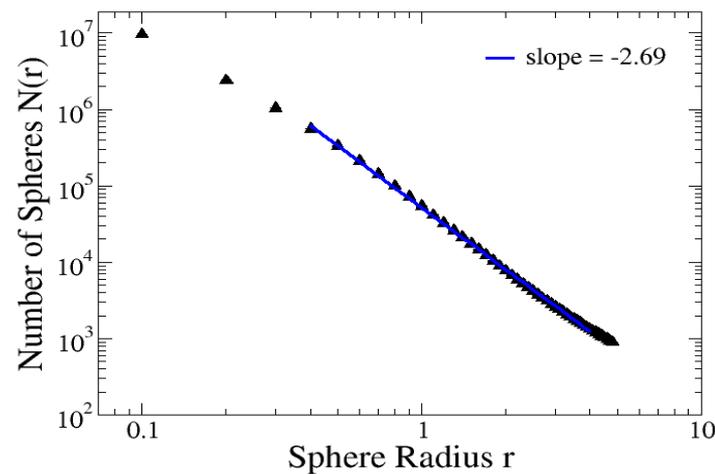
$$N(r) = r^{-d_s}$$

Small-Angle
Neutron Scattering

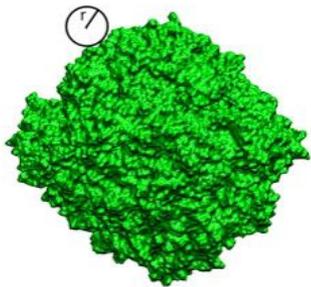
$$S(q) \propto Q^{d_s - 6}$$



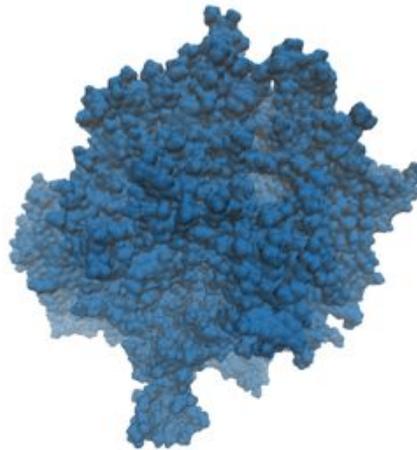
$$d_s = 2.62 \pm 0.02$$



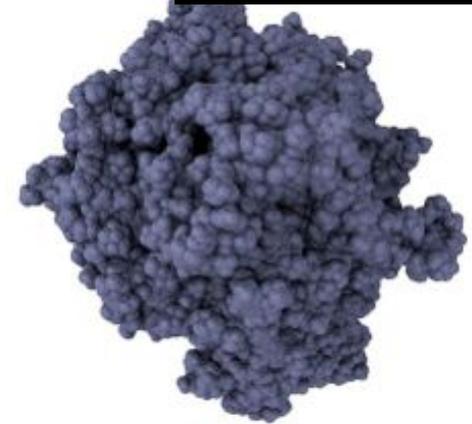
$$d_s = 2.65 \pm 0.01$$



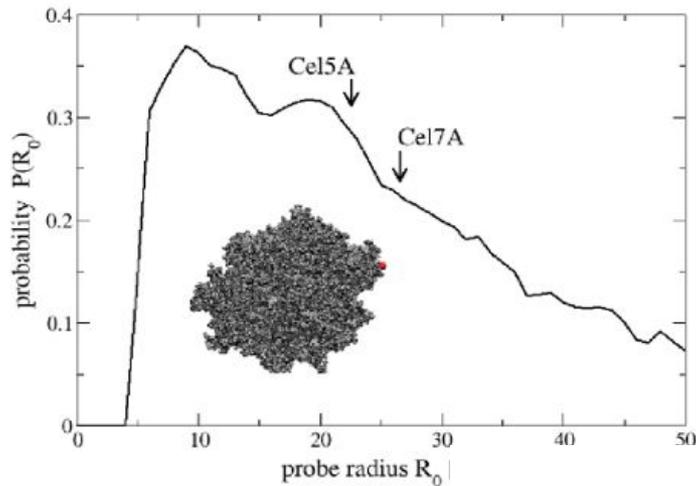
$$R_g = 4.2 \text{ \AA}$$



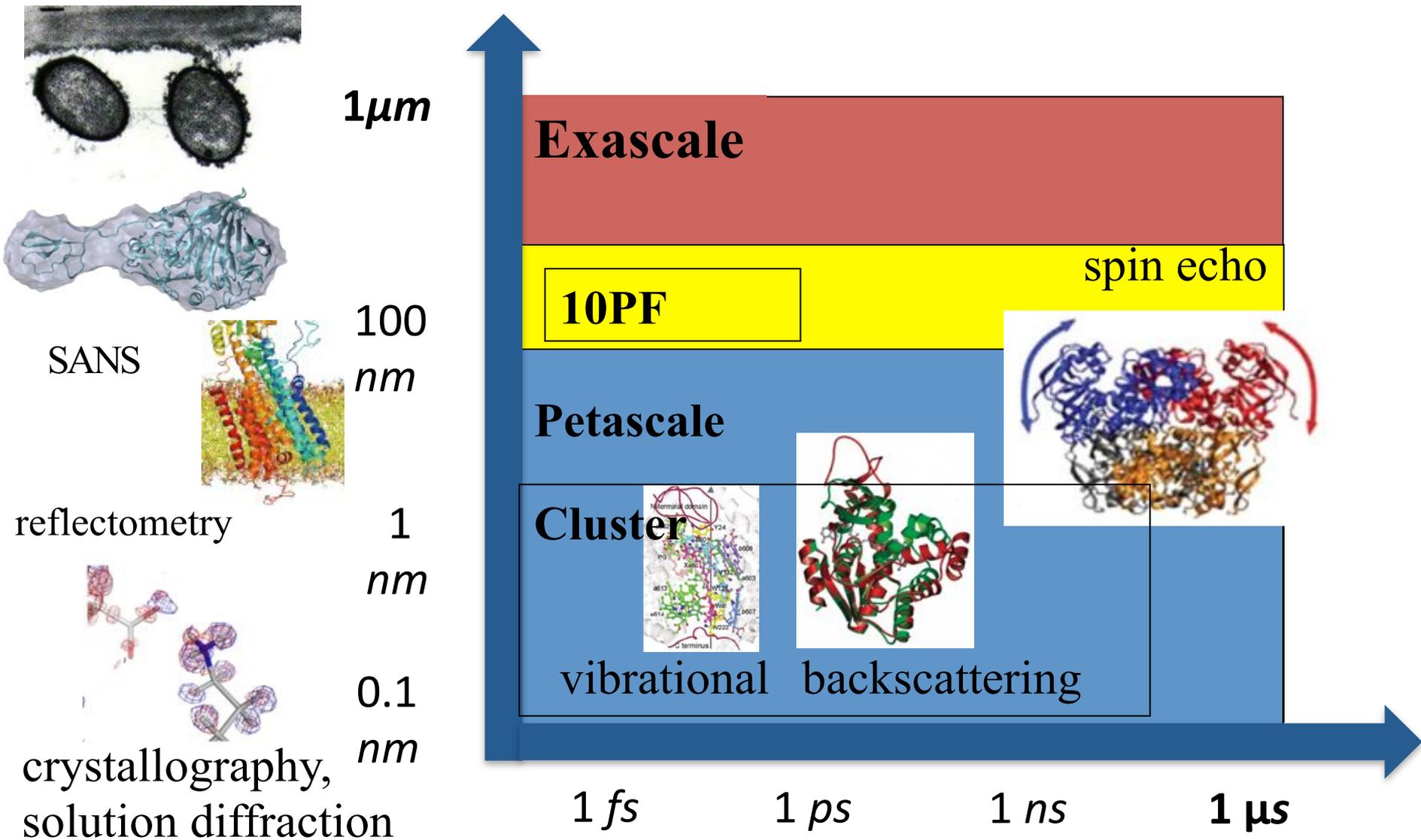
$$R_g = 42 \text{ \AA}$$



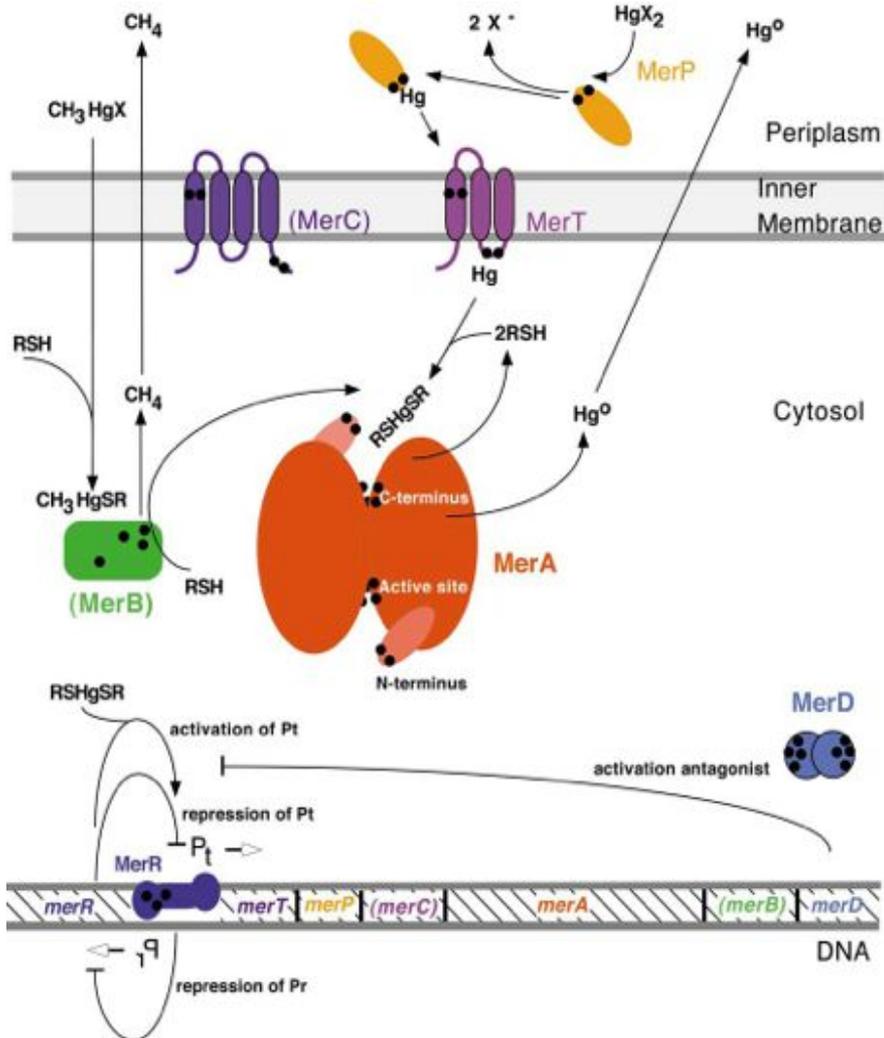
$$R_g = 420 \text{ \AA}$$



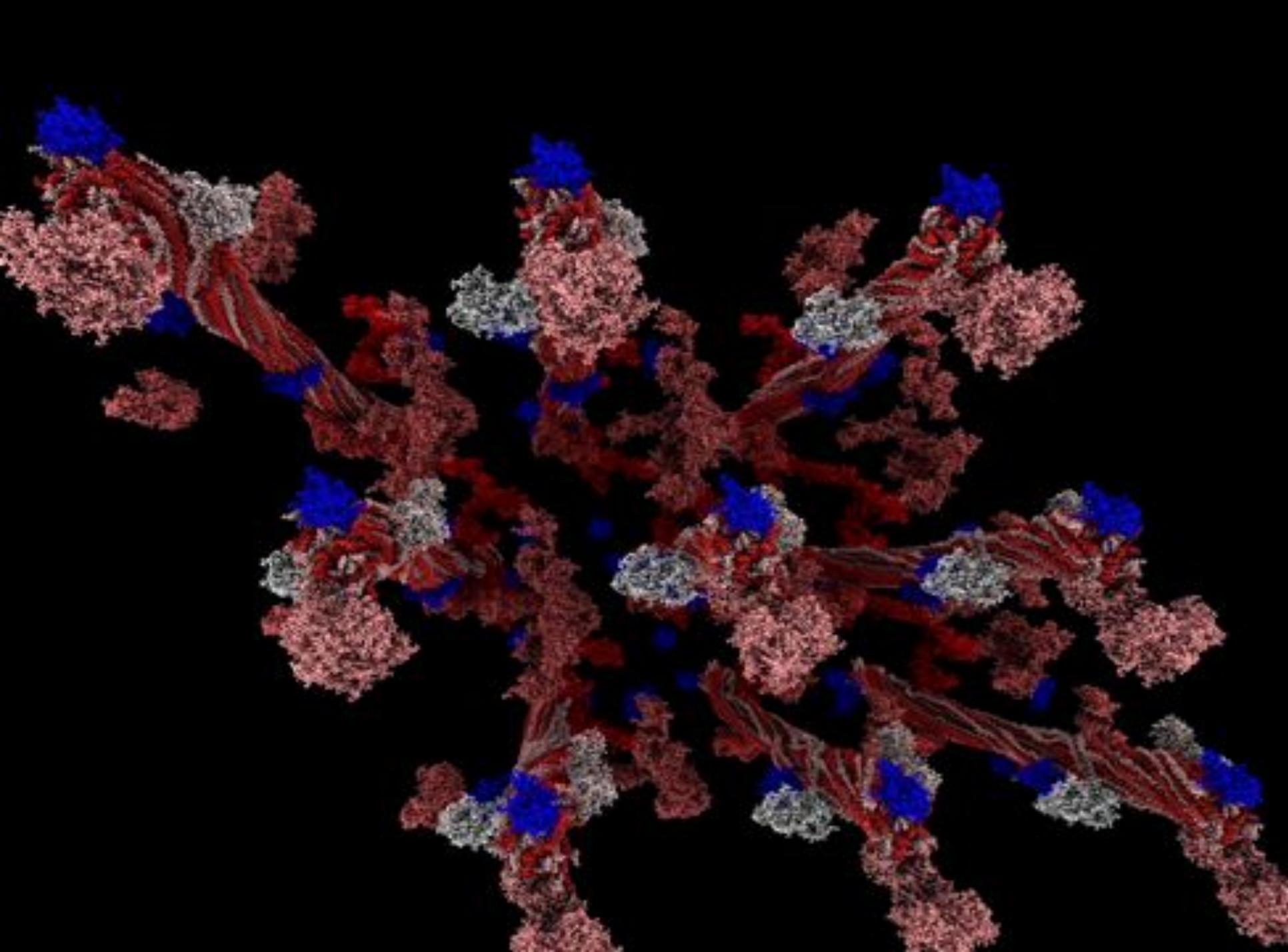
Enzyme:lignin
interaction
distribution



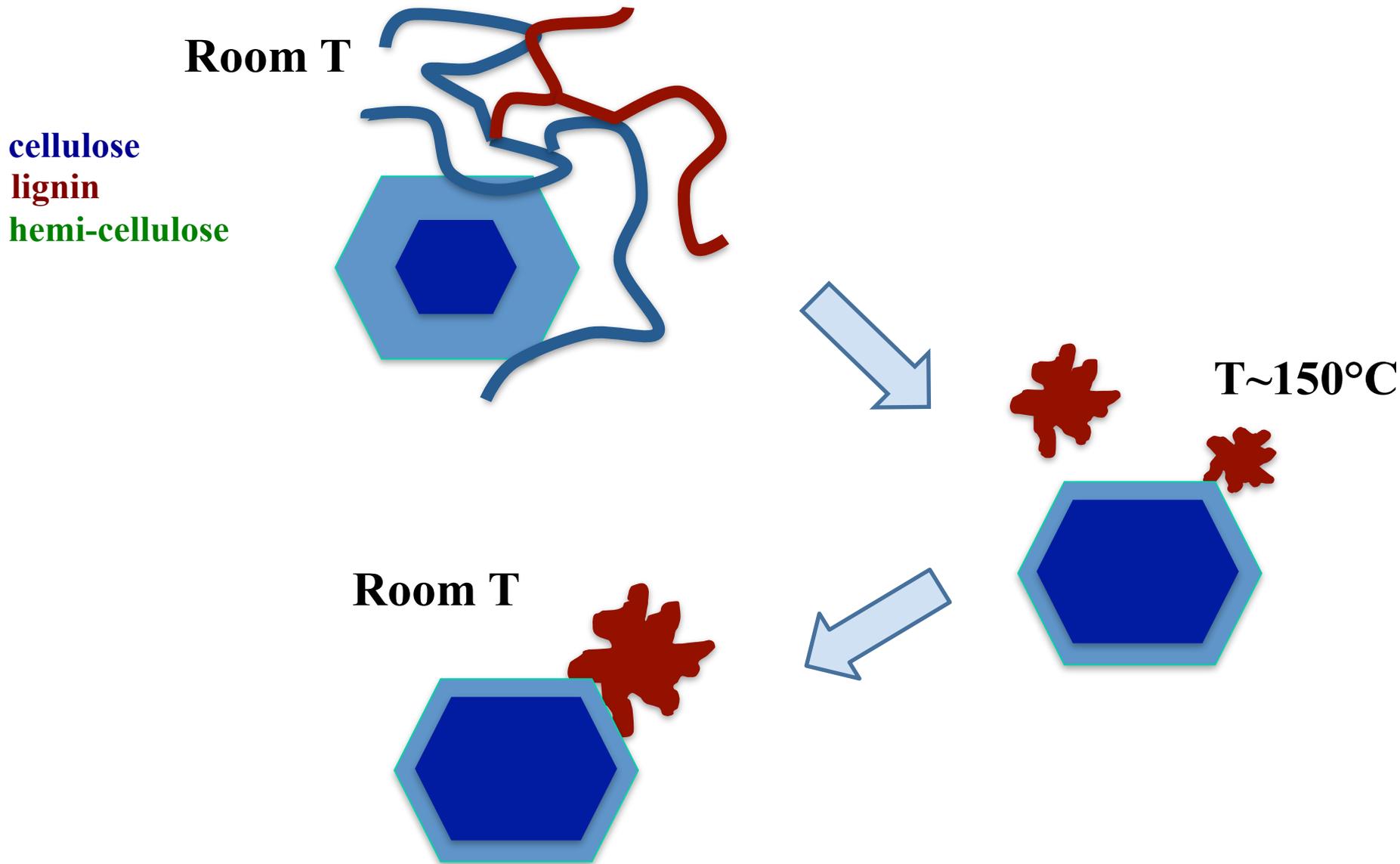
Bacterial Mercury Resistance – The *Mer* Operon



- **MerR** – regulation (transcriptional activator)
- **MerB** – organomercurial lyase
- **MerA** – mercuric reductase



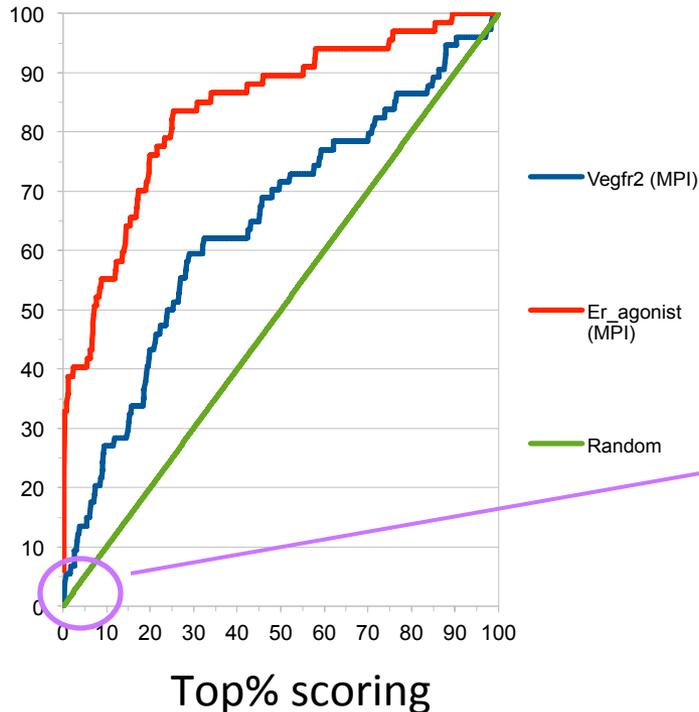
New View of Pretreatment



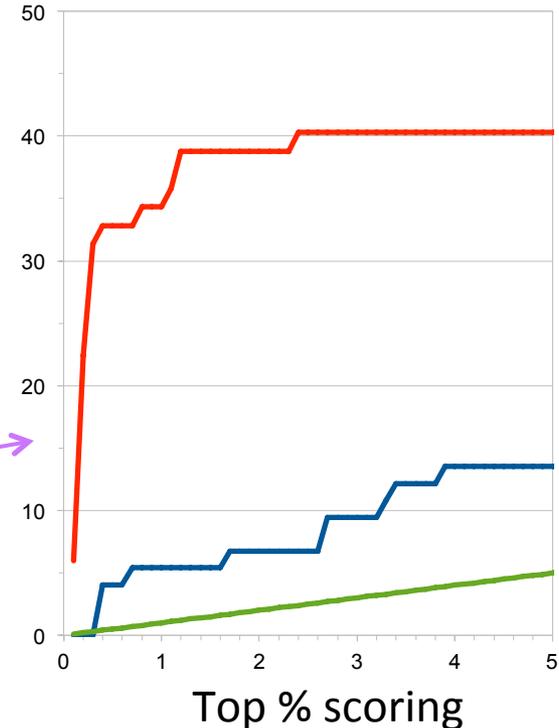
Hit Enrichment

TEST: 98,163 compound database, 2 drug targets:
ER: 67 known ligands ; VEGFr2: 74 known ligands

% of known ligands



% of known ligands



ER: Top 0.3 % of total database (295 candidates, 31 hits): Enrichment = ~104
VEGFr2: Top 0.4 % of total database (393 candidates, 4 hits): Enrichment = 10

Oak Ridge



Oxidation



Methylation by
Bad Bacteria

