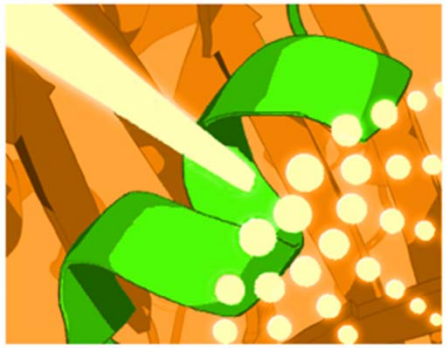
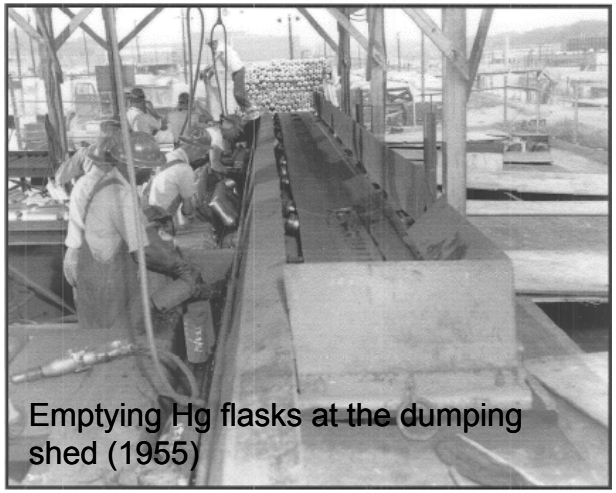
OAK RIDGE National Laboratory
Managed by UT-Battelle for the Department of Energy

University of Tennessee



UT ornl Center for Molecular Biophysics

Jeremy C. Smith

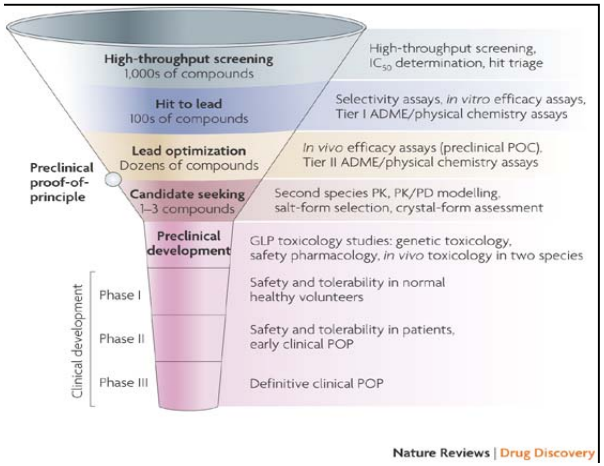


Emptying Hg flasks at the dumping shed (1955)

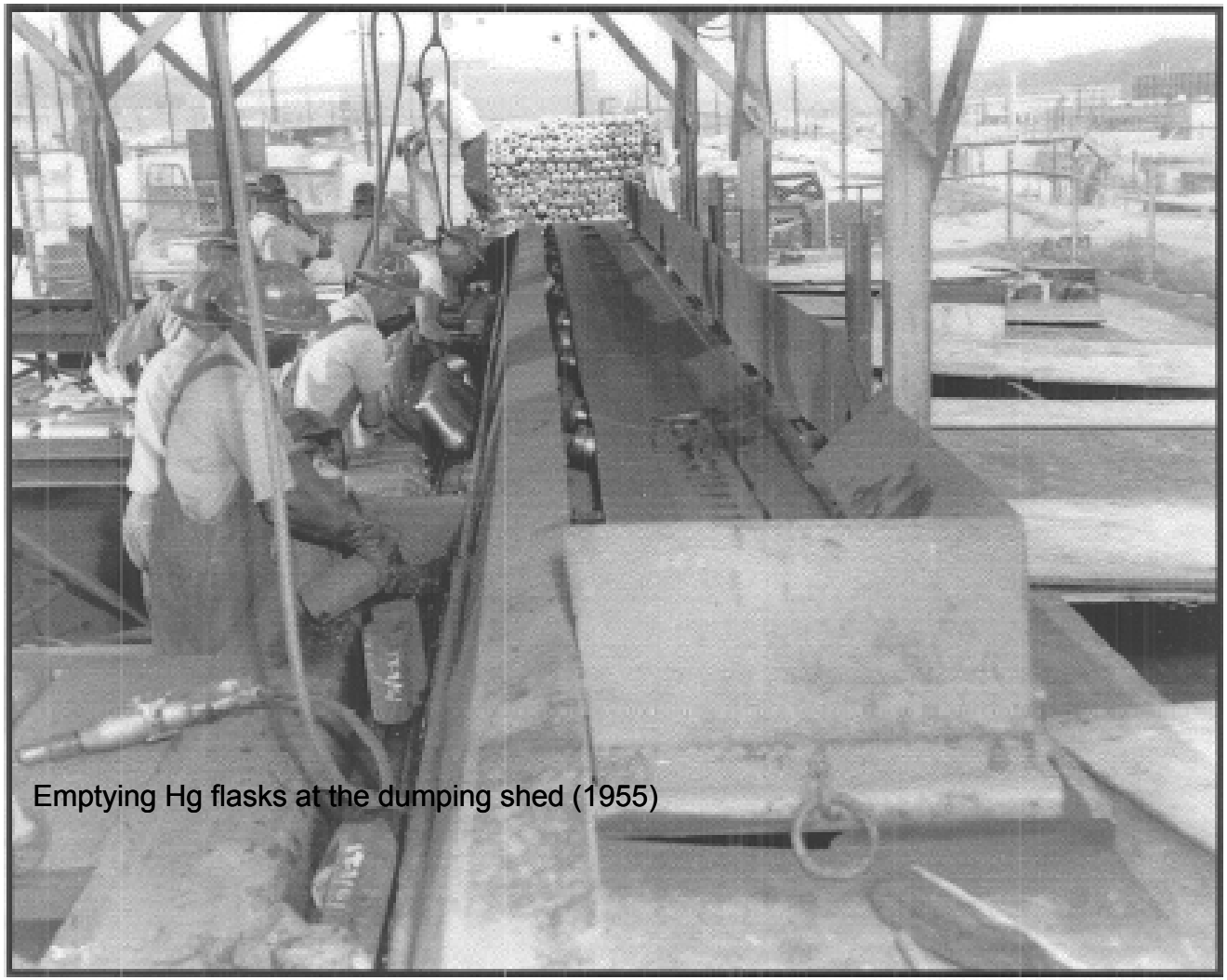
Environment

Energy

Disease

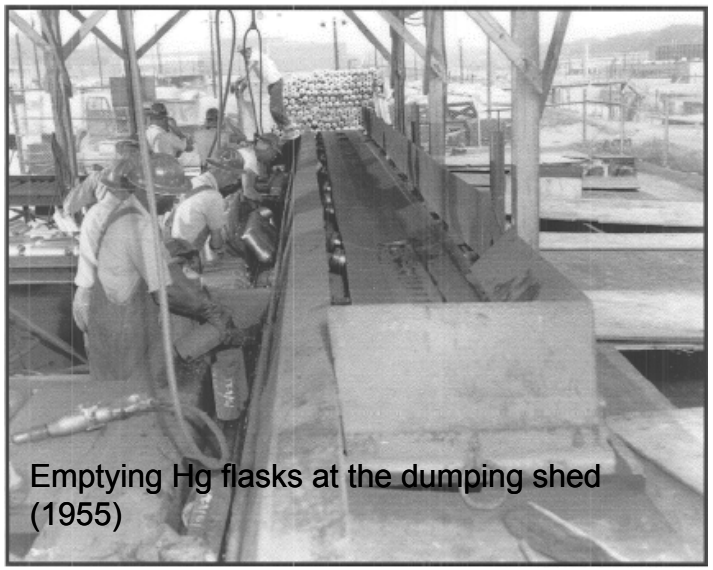


Cloud Gate, Anish Kapoor, Chicago



Emptying Hg flasks at the dumping shed (1955)

Oak Ridge



Emptying Hg flasks at the dumping shed (1955)

Hg(0)

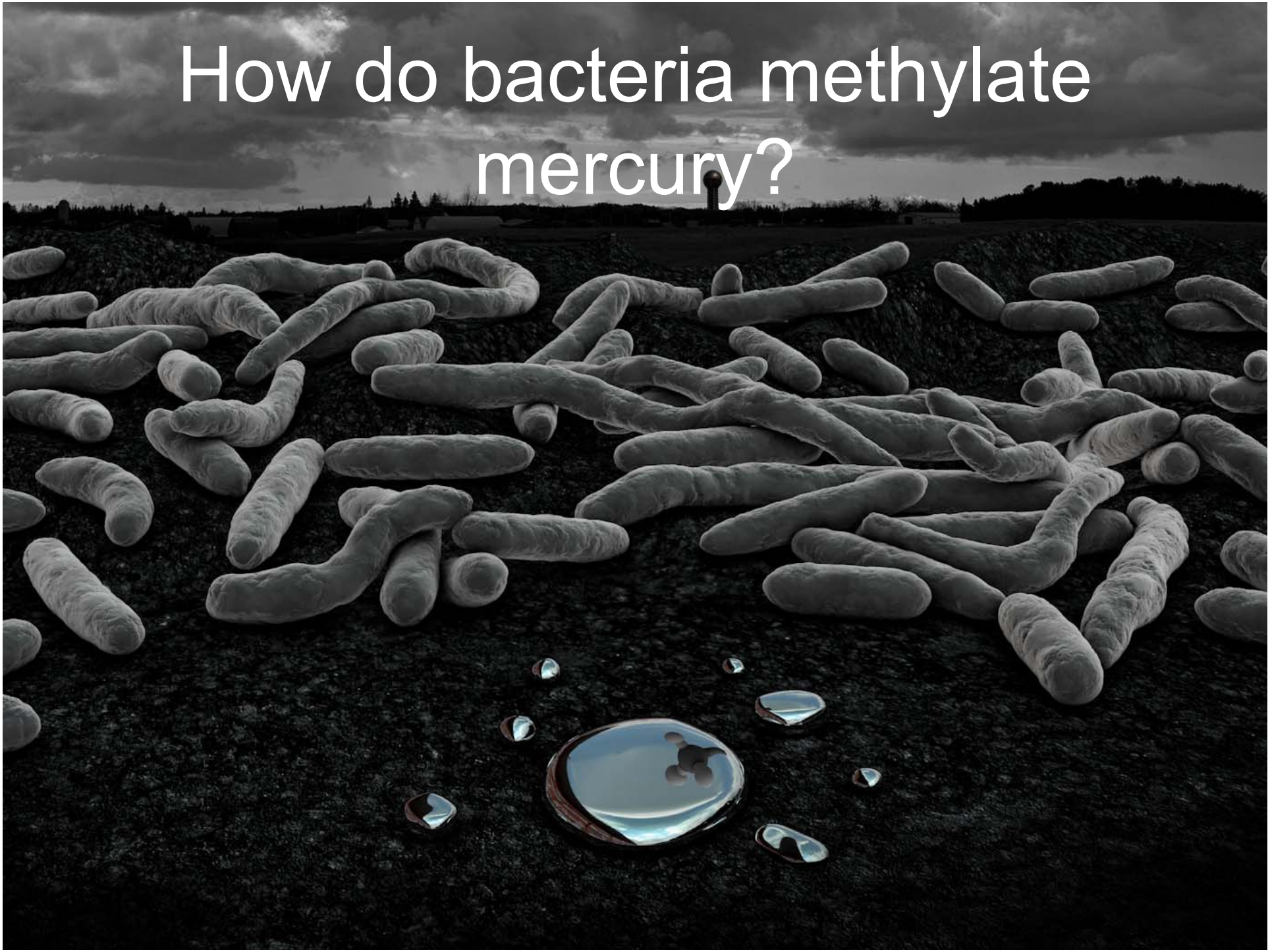
Oxidation

Hg(II)

Methylation by Bad Bacteria

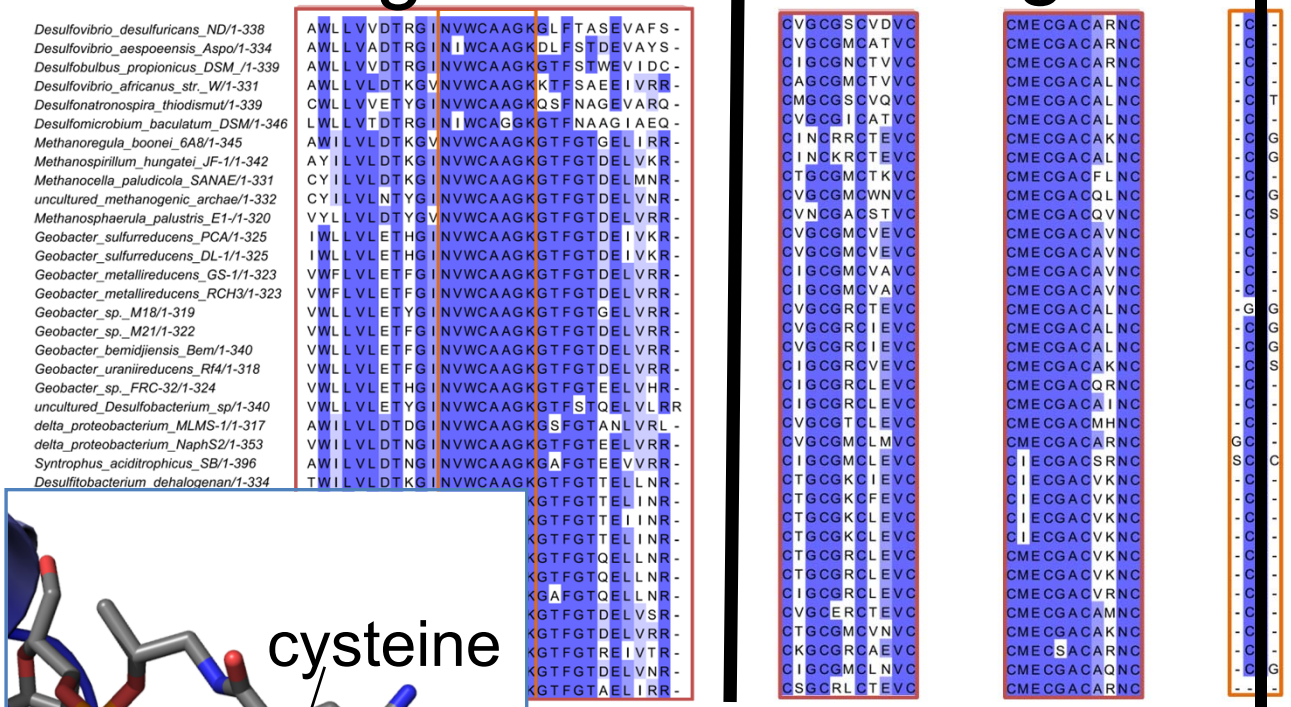
CH_3Hg^+

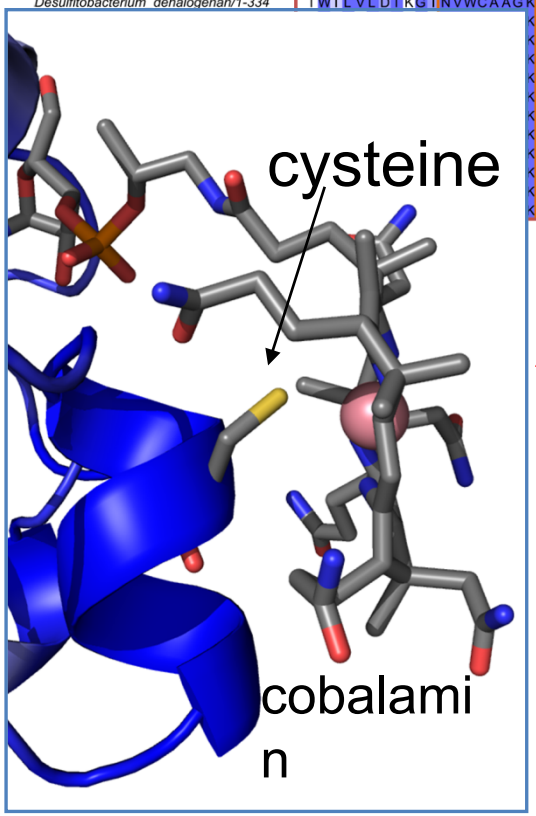
How do bacteria methylate mercury?



HgcA

HgcB

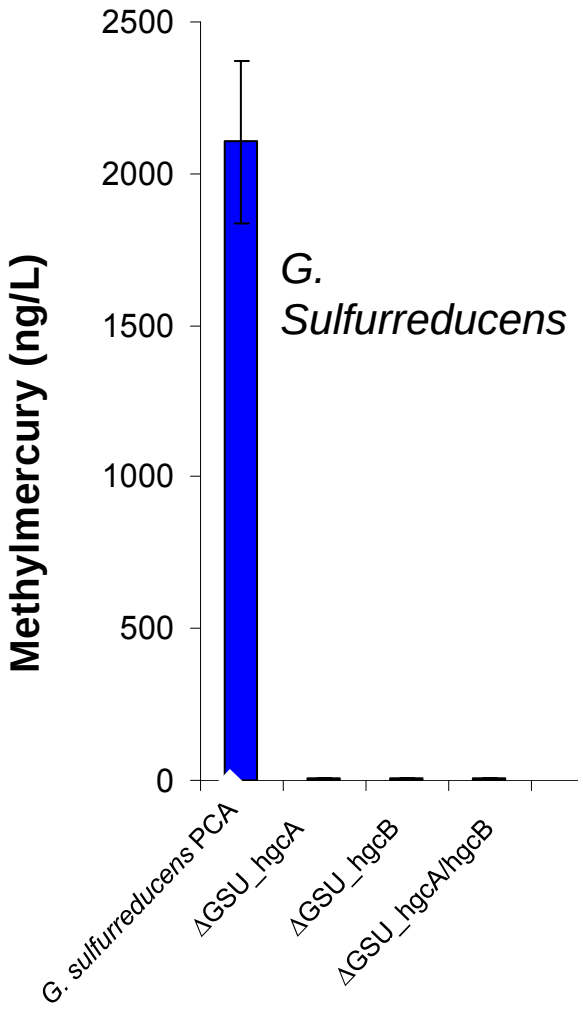




2 e$^-$

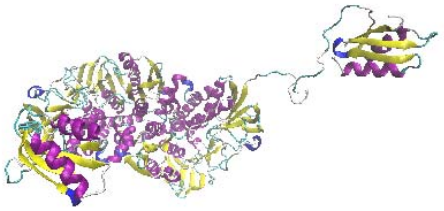
Science, 339 1332 (2013)

Experiment



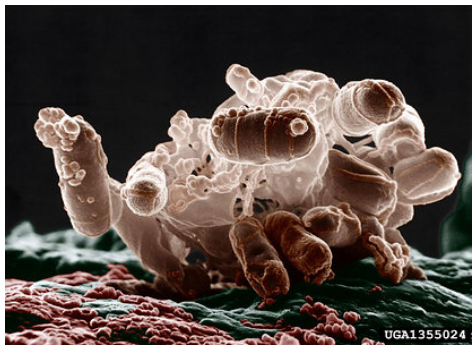
Good Bacteria!
Mer Operon

Hg(0)

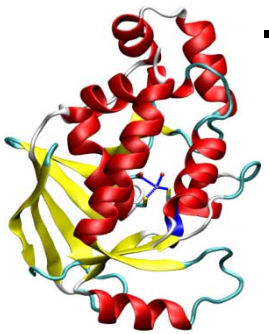


Reduction
- Mer A

Hg(II)



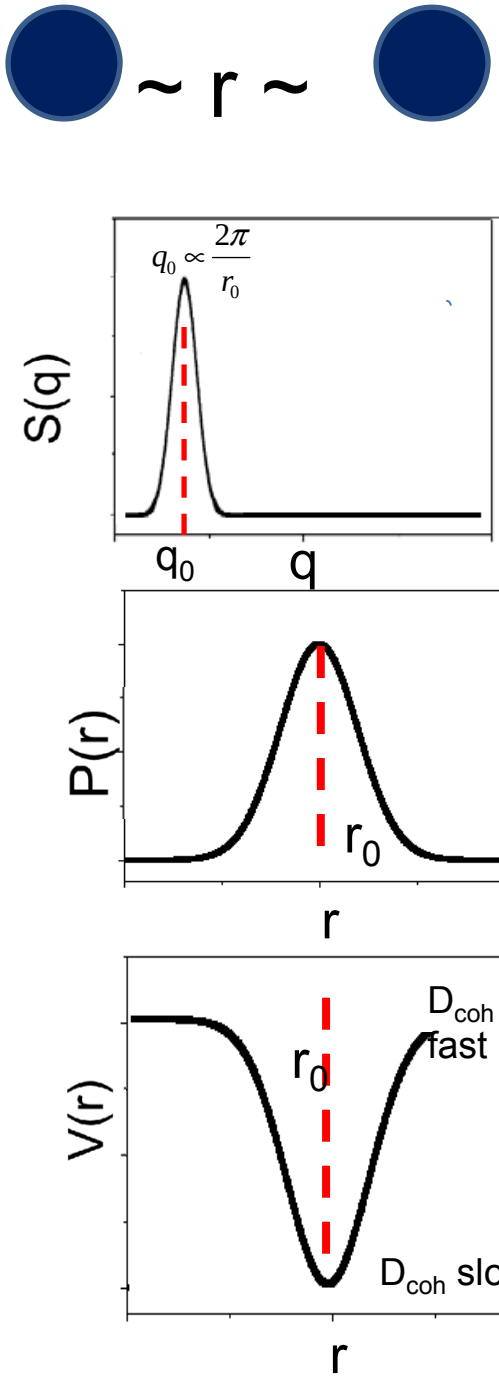
Demethylation
-Mer B

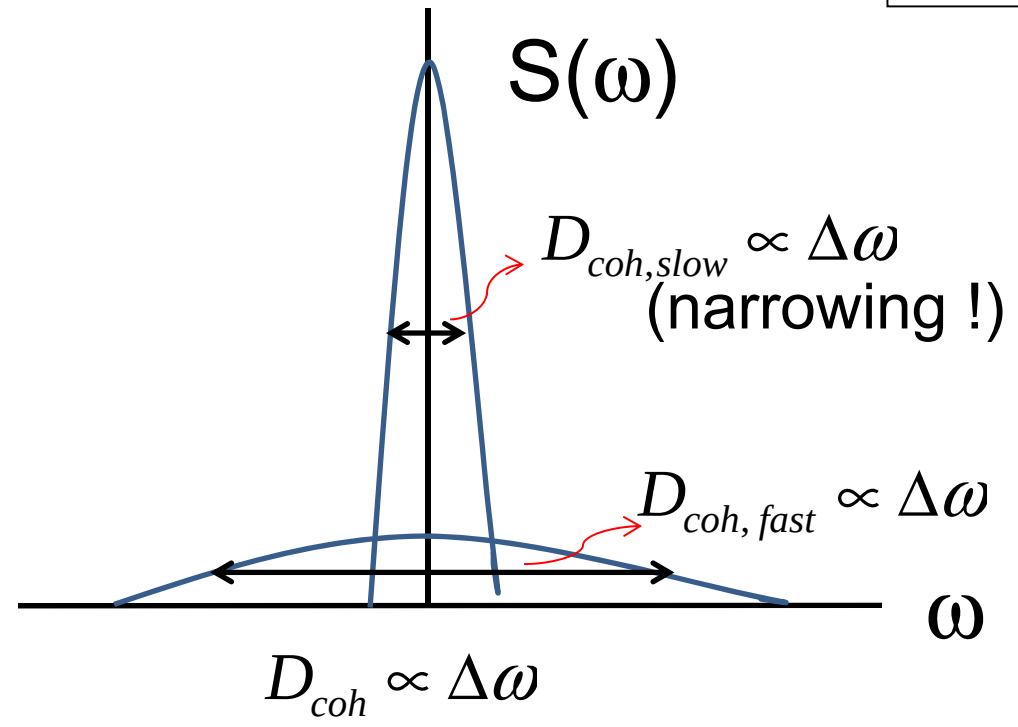


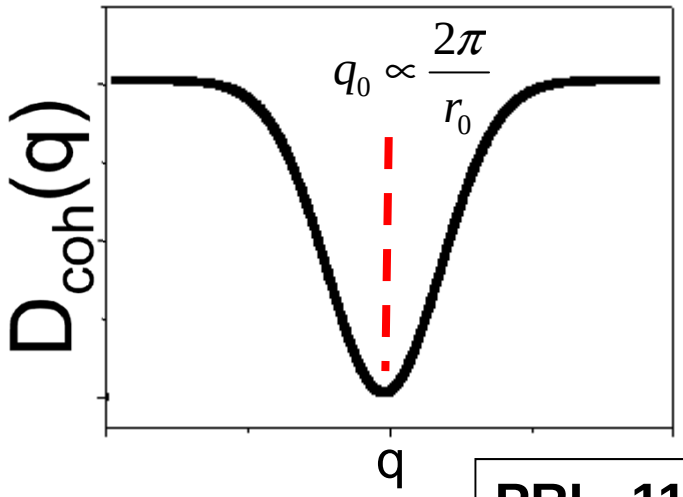
CH_3Hg^+

De Gennes Narrowing

LIANG HONG







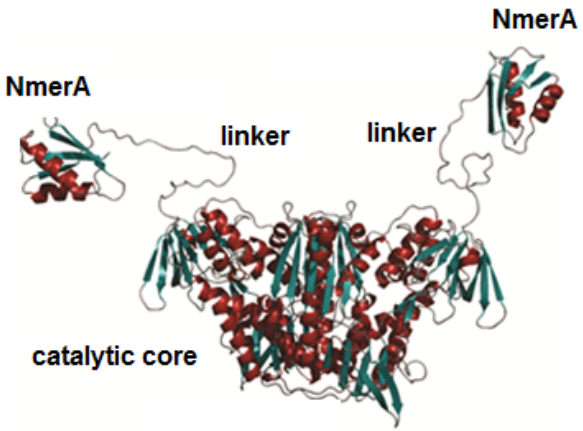
$$D_{coh}(q) = \frac{const}{S(q)}$$

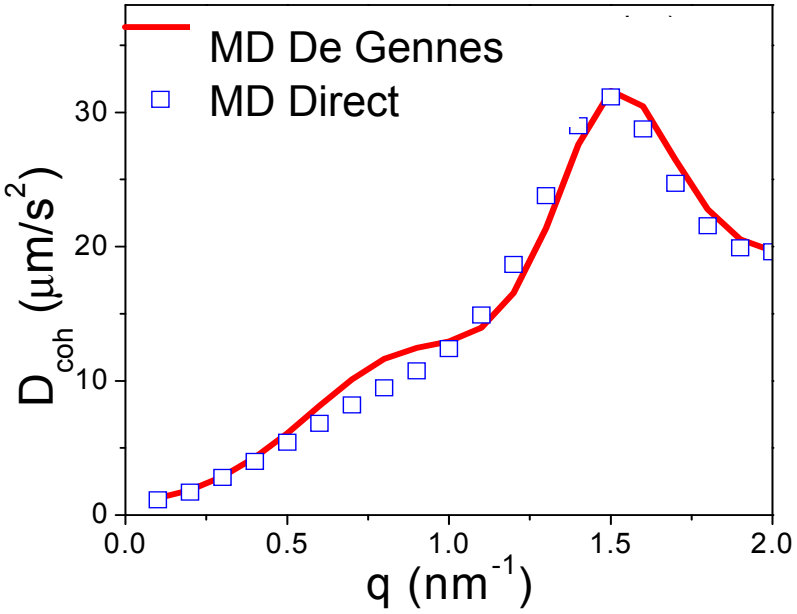
PRL, 112 158102 (2014)

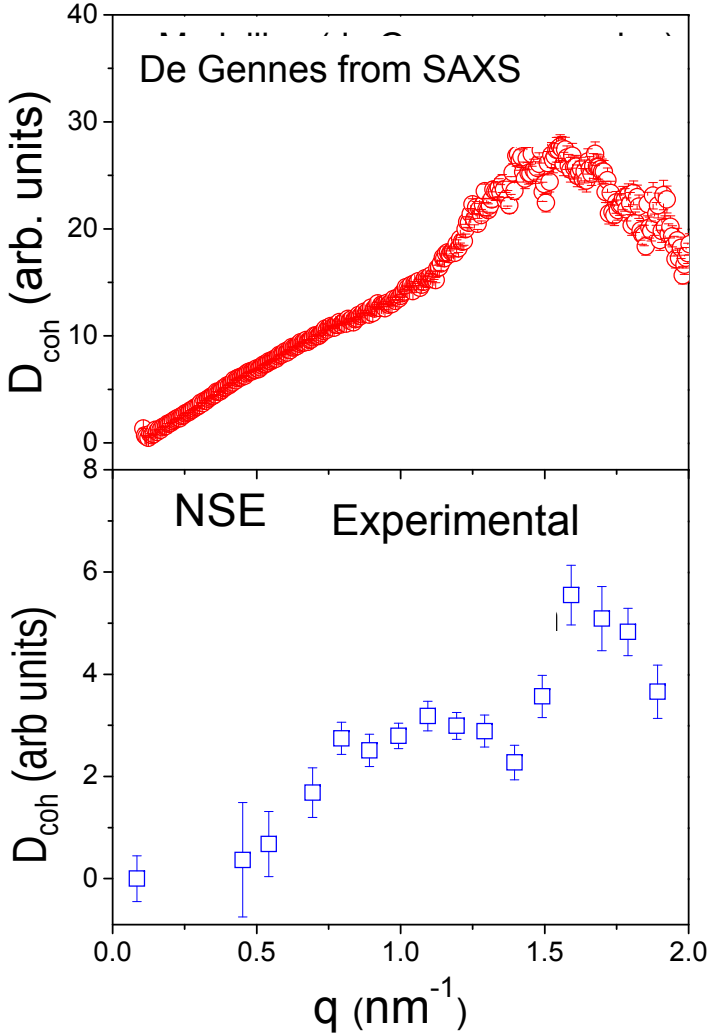
De Gennes Narrowing Describes Protein Interdomain Motion

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

LIANG HONG



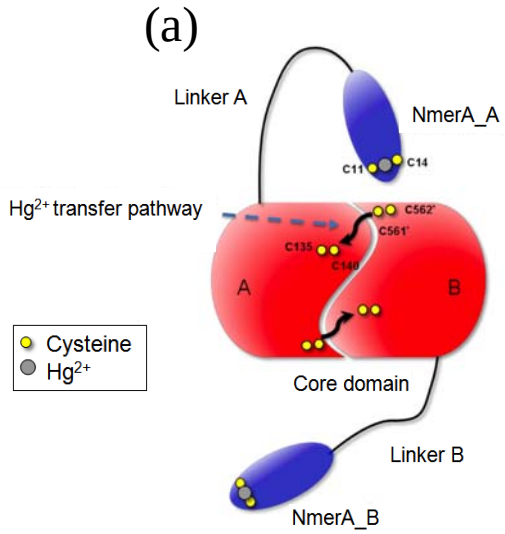


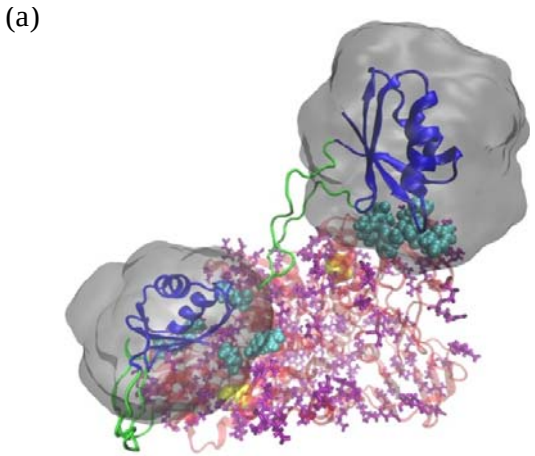


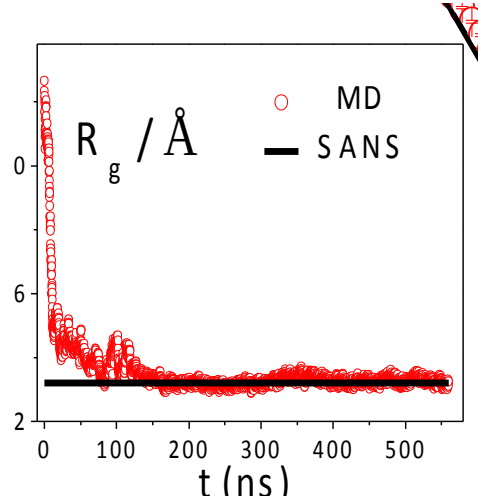
PRL, 112 158102 (2014)

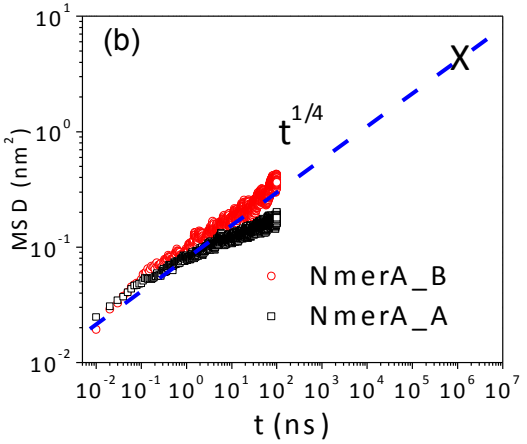
Functional Dynamics of a Mercury-Transforming Enzyme

LIANG HONG

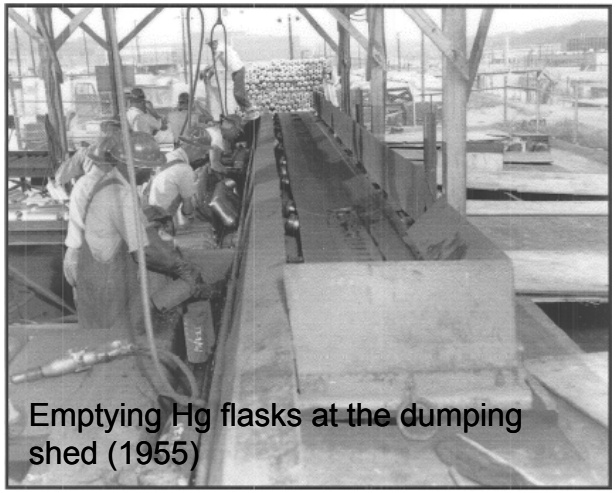








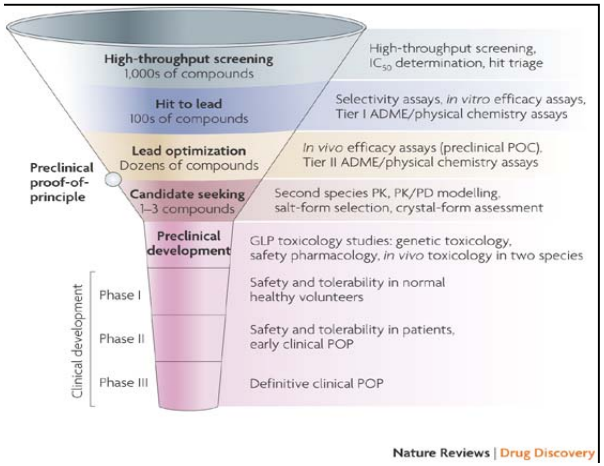
Biophys. J. In Press (2014)



Emptying Hg flasks at the dumping shed (1955)

Environment

Energy



Disease

Cellulosic Ethanol

Fermentation

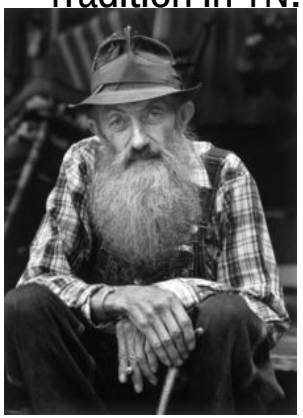
Fuel

Hydrolysis

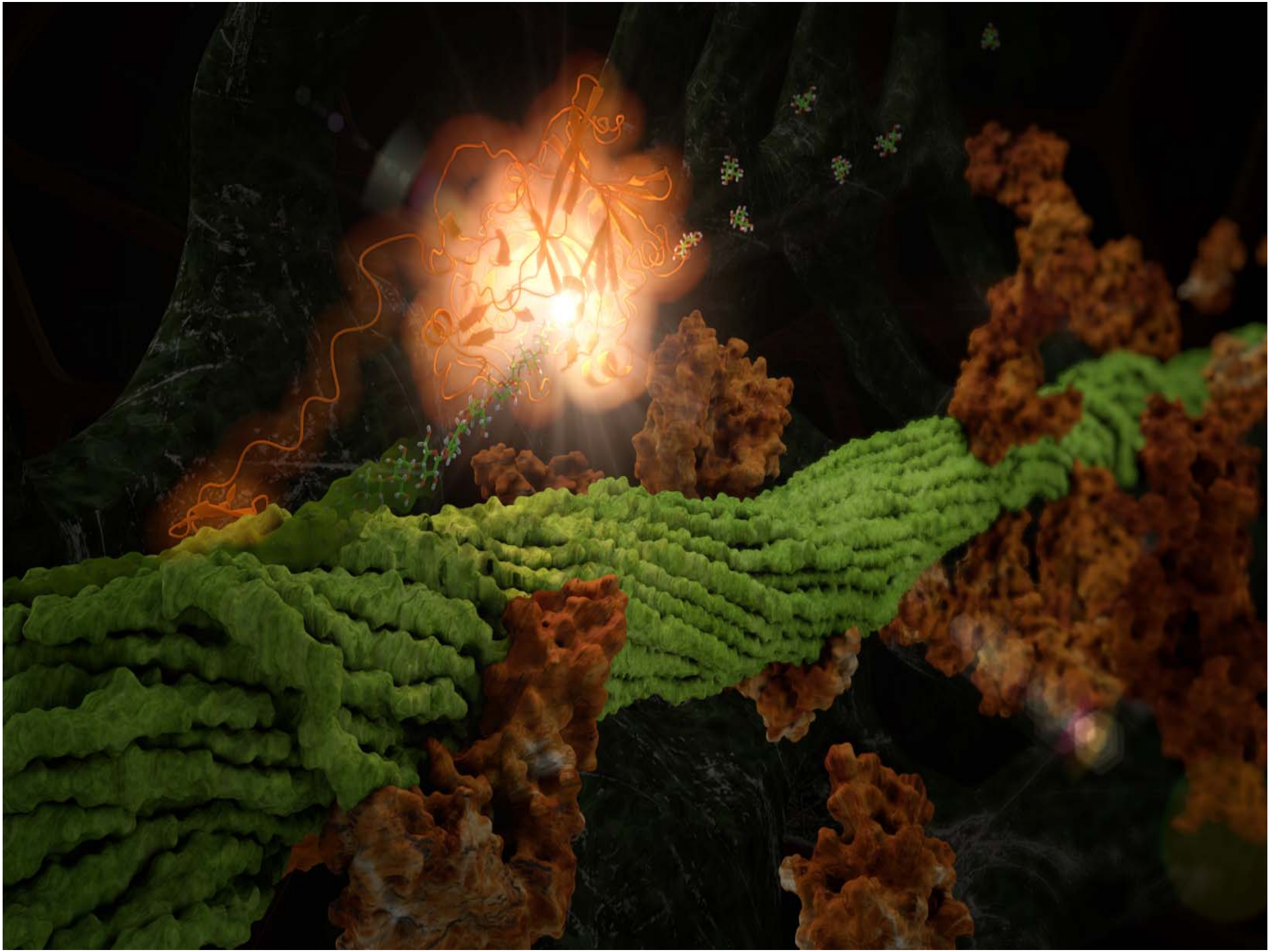
Breakdown into sugars

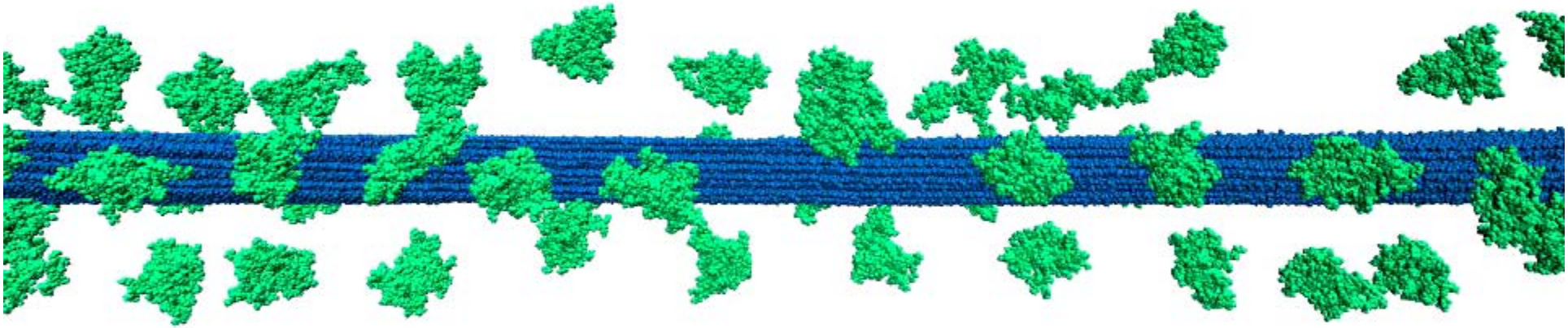
Strong Fermentation Tradition in TN!

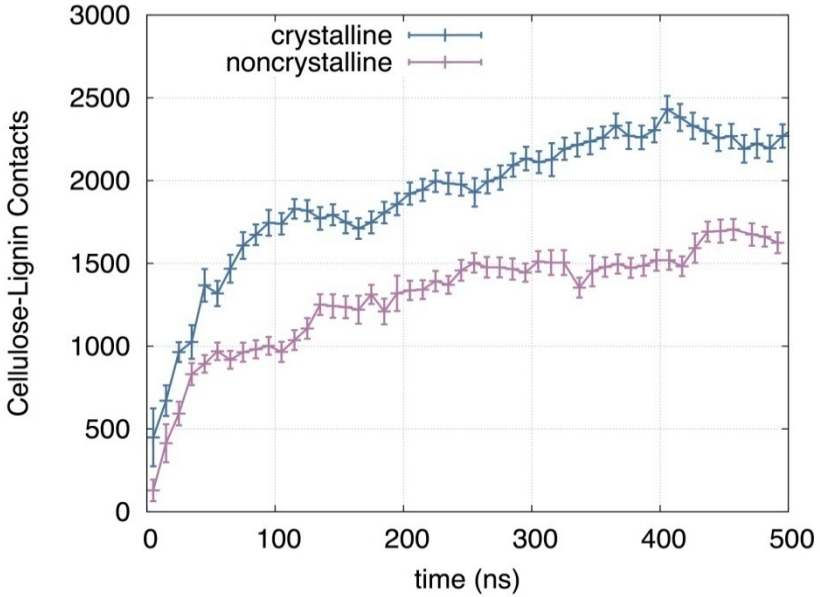
RECALCITRANCE!



Cellulosic Biomass



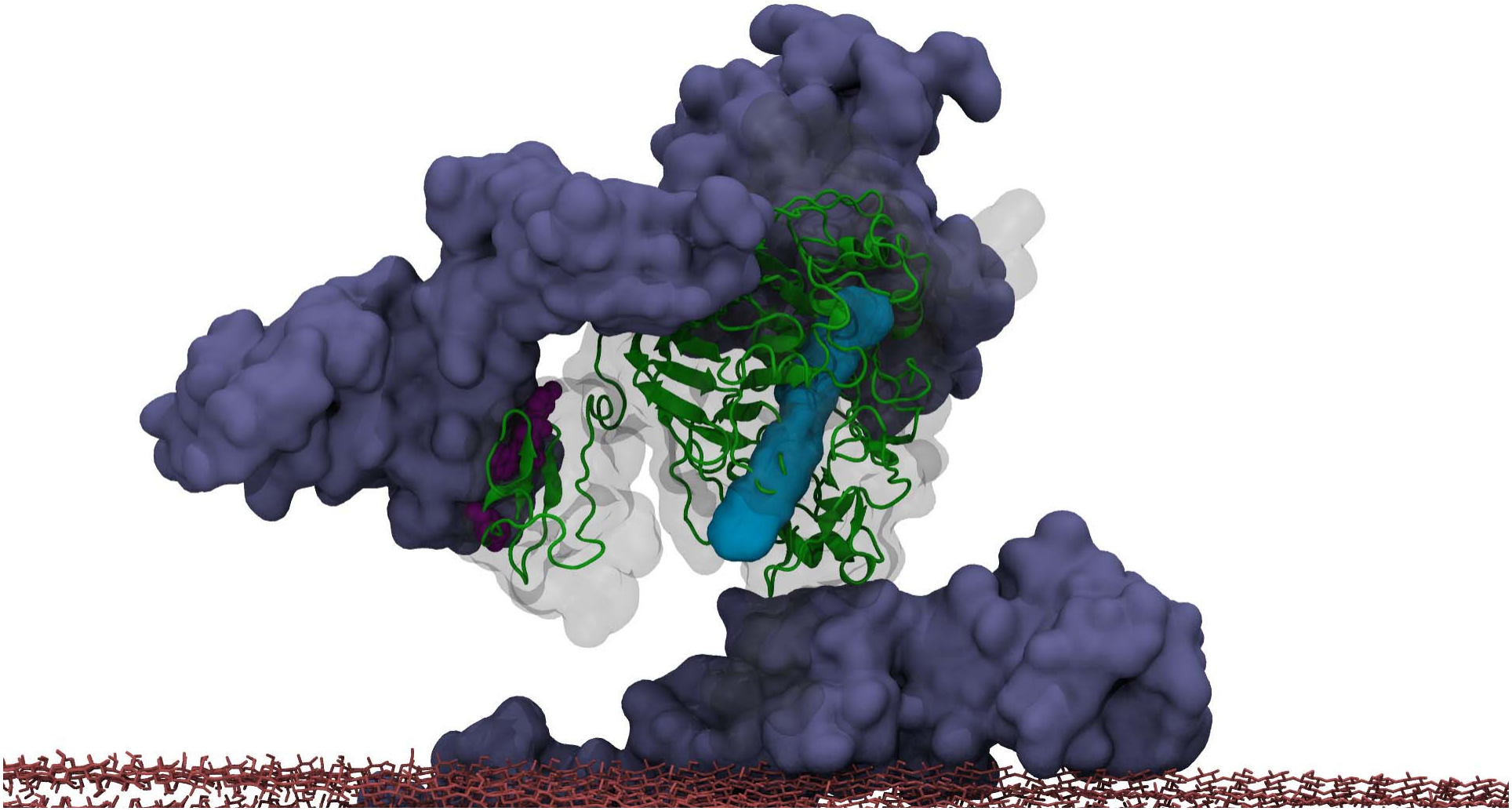




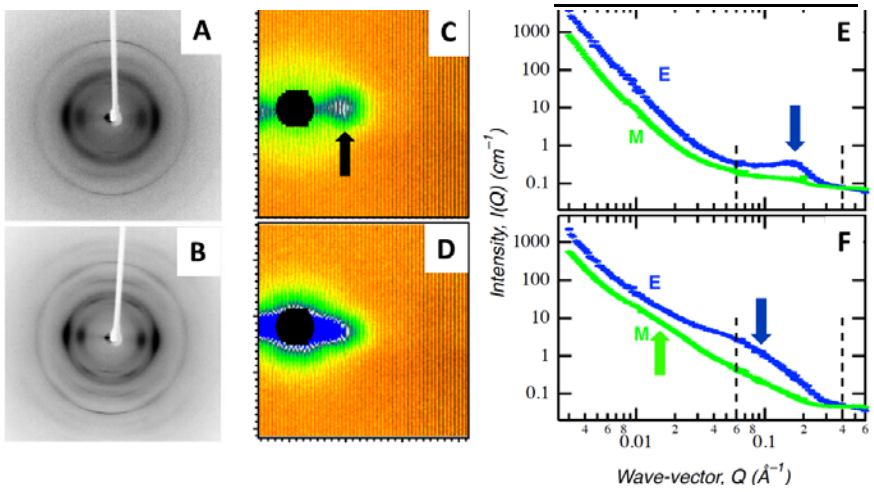
Interface	Interaction Energy Density ($kJ/mol/nm^2$)
lignin: crystalline cellulose	-49±2
lignin: non-crystalline cellulose	-50±2
water : crystalline cellulose	-94±2
water : non-crystalline cellulose	-107±2

Solvent-Driven Preferential Association of Lignin with Crystalline Cellulose

Biomacromolecules, 14 3390 (2013)

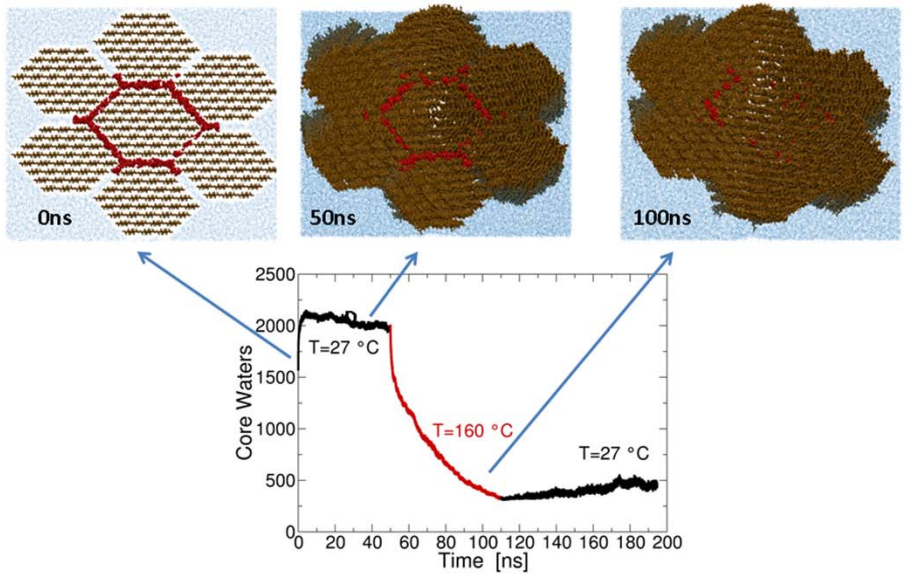


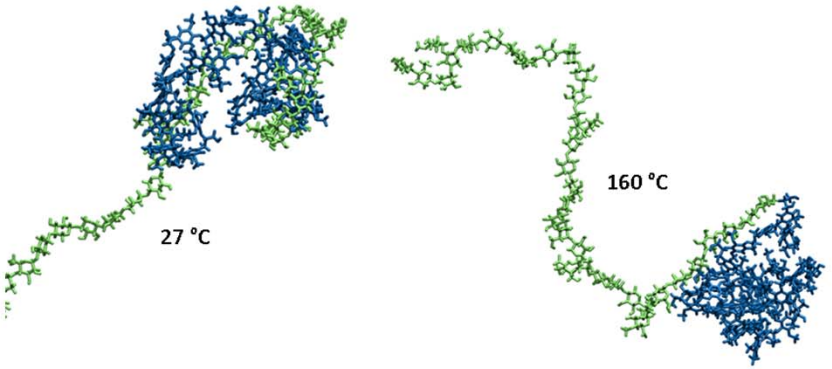
Effect of Pretreatment on Biomass Structure



Untreated

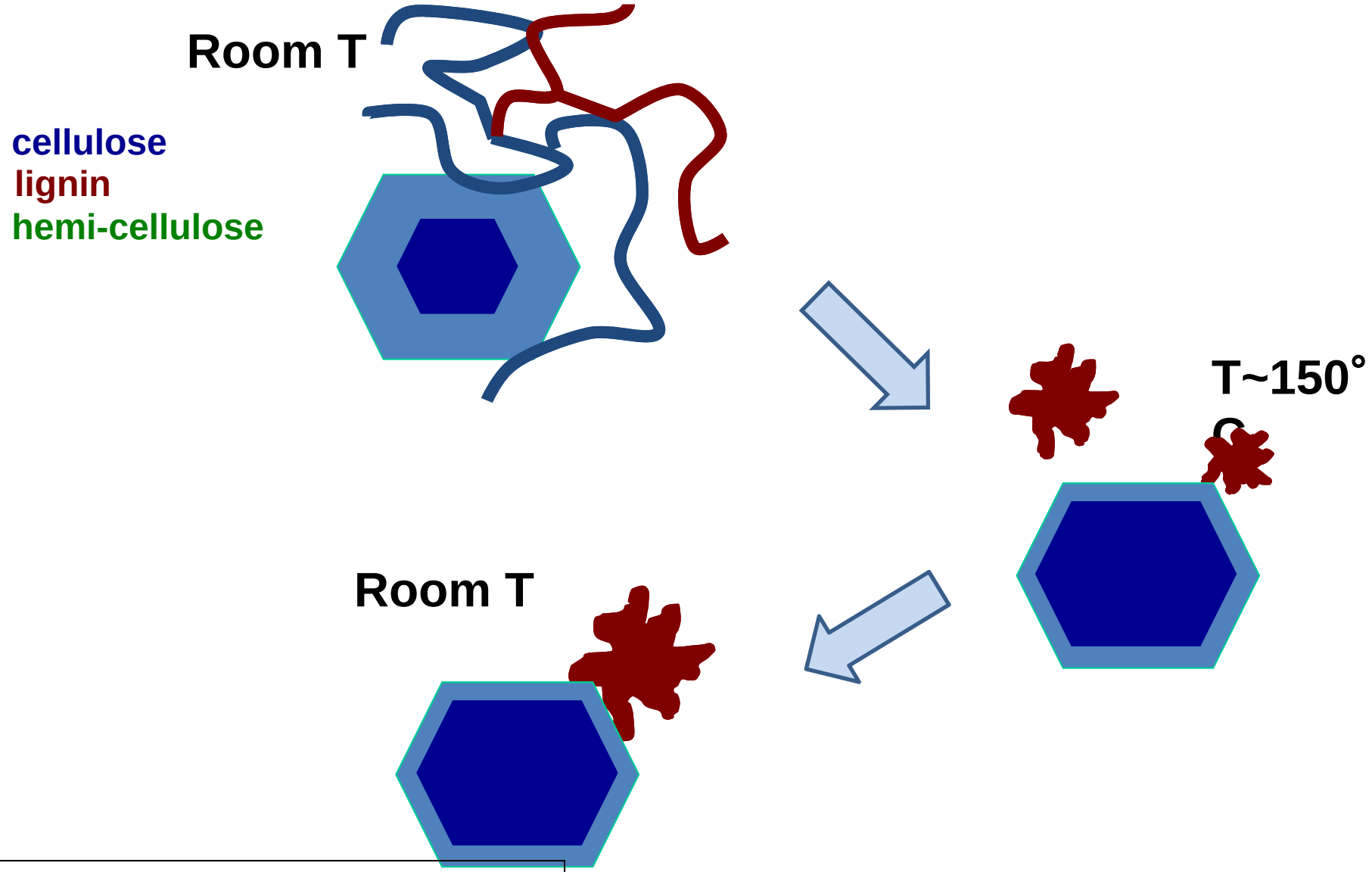
Pretreated



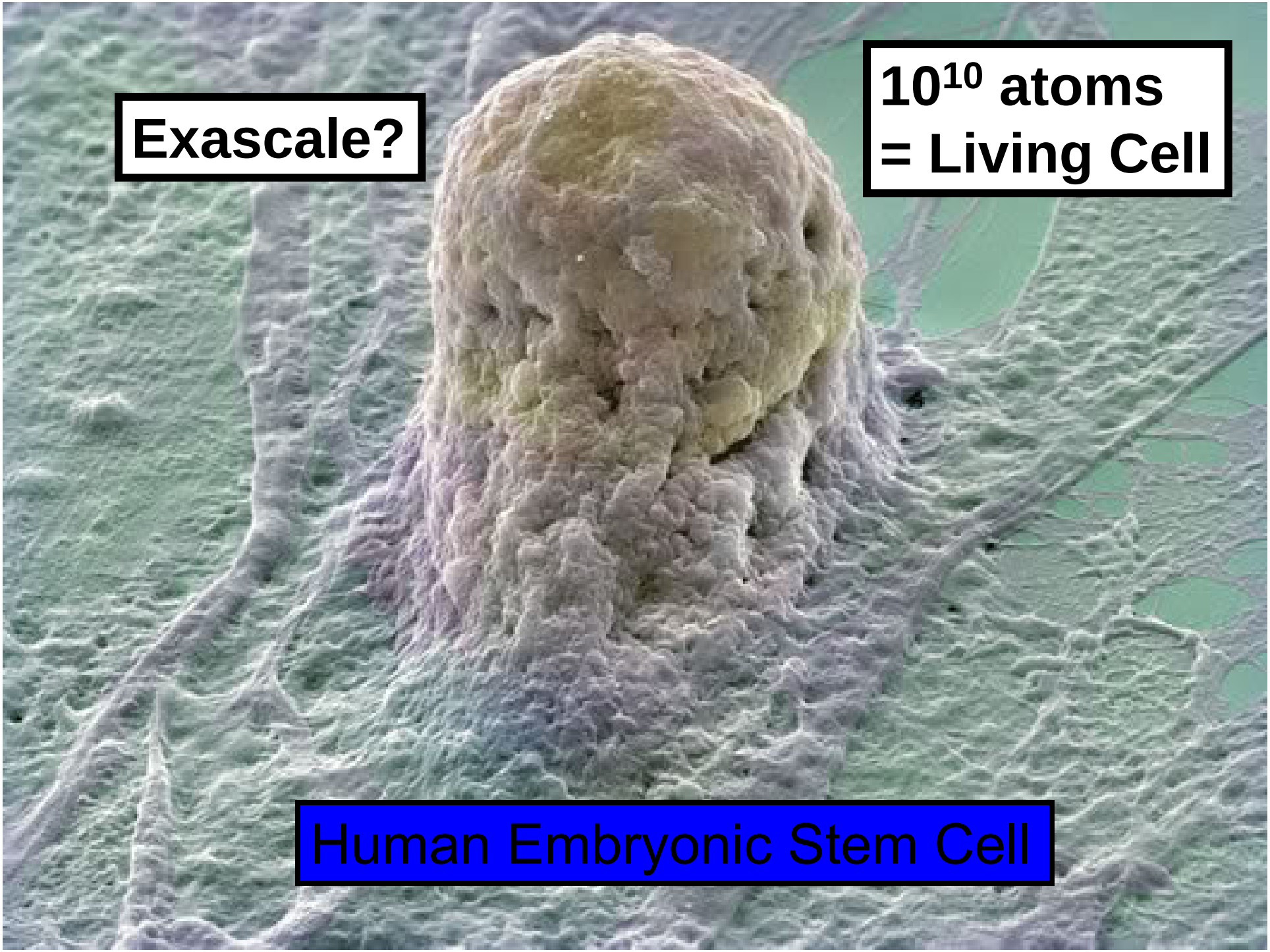


Green Chemistry 16 1 (2014)

New View of Pretreatment



Green Chemistry 16 1 (2014)

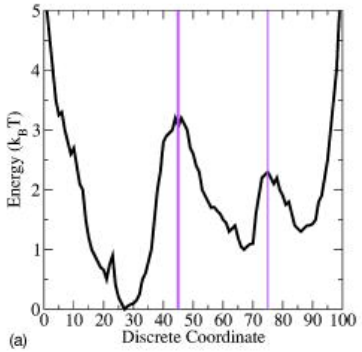

Exascale?
10^{10} atoms
= Living Cell
Human Embryonic Stem Cell

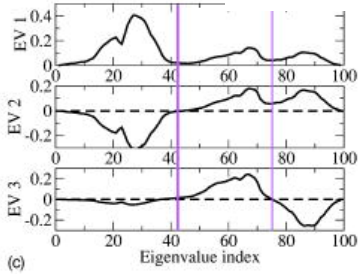
But…

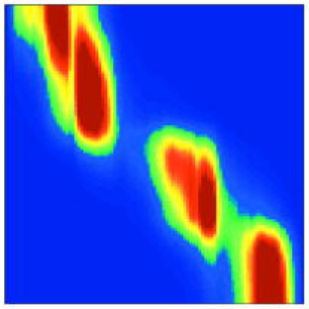
Microsecond Timescale Limitation!

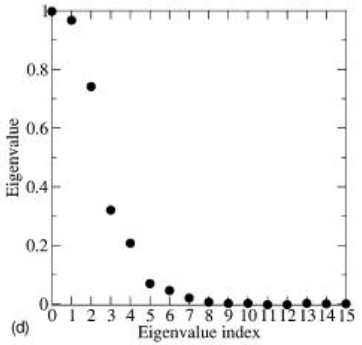
New Concepts Needed….

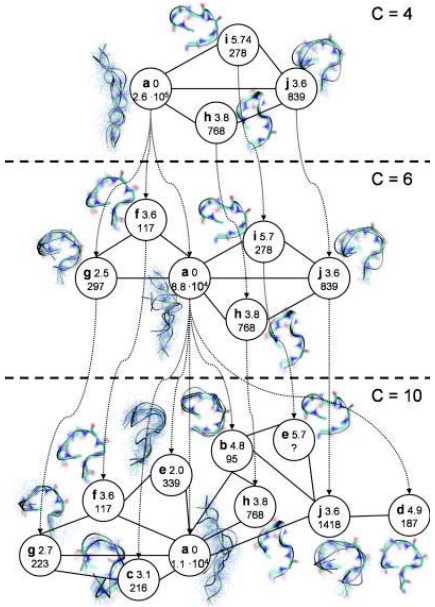
Exascale Concepts

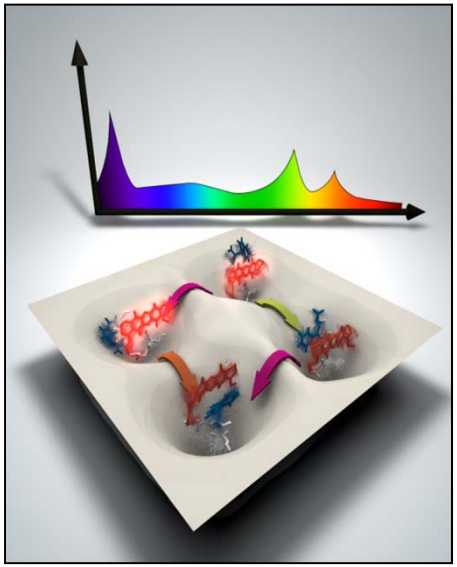




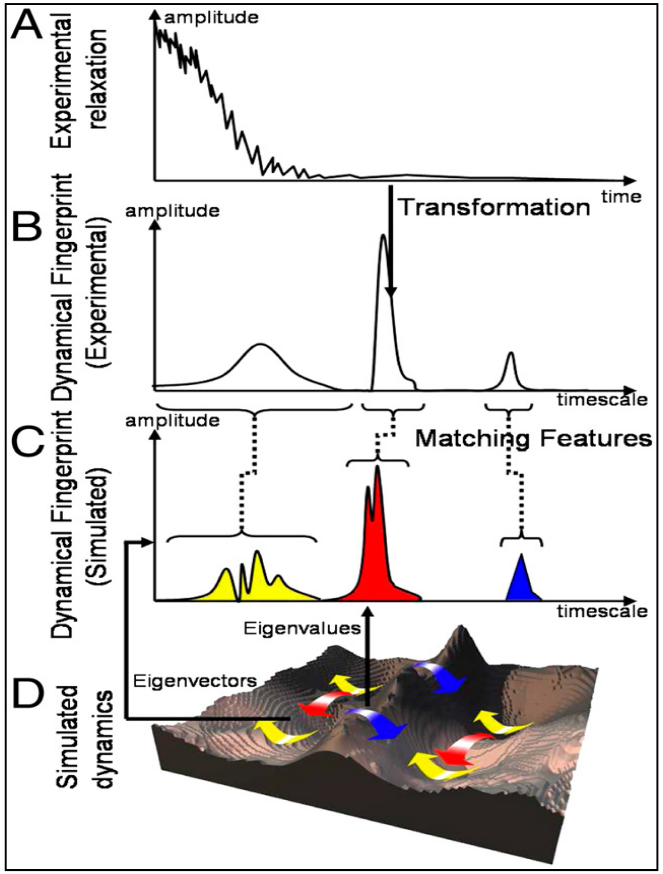




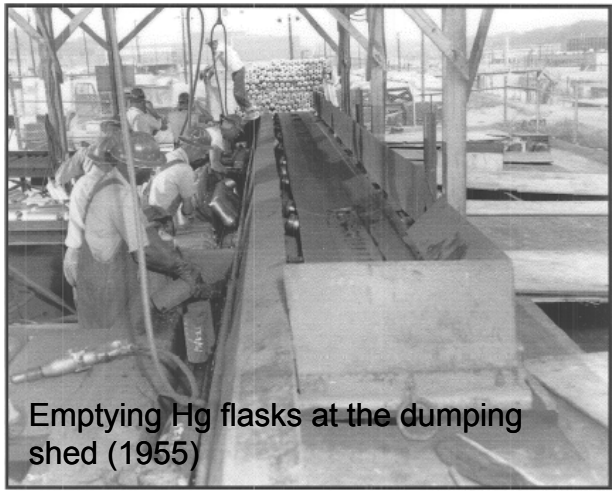




Dynamical Fingerprints



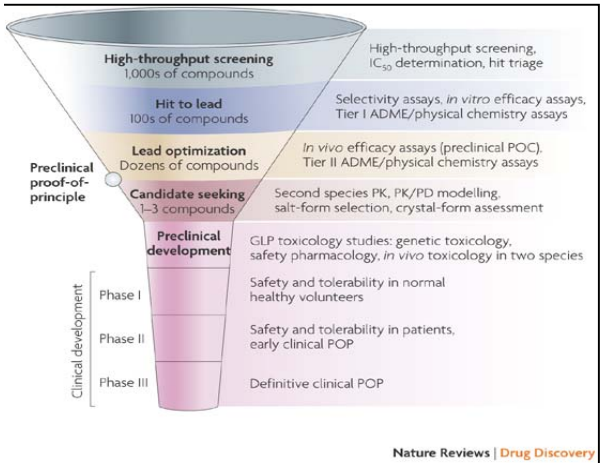
JCP 126 840 (2007); 134 244108 (2011); PNAS 108 4822 (2011)



Emptying Hg flasks at the dumping shed (1955)

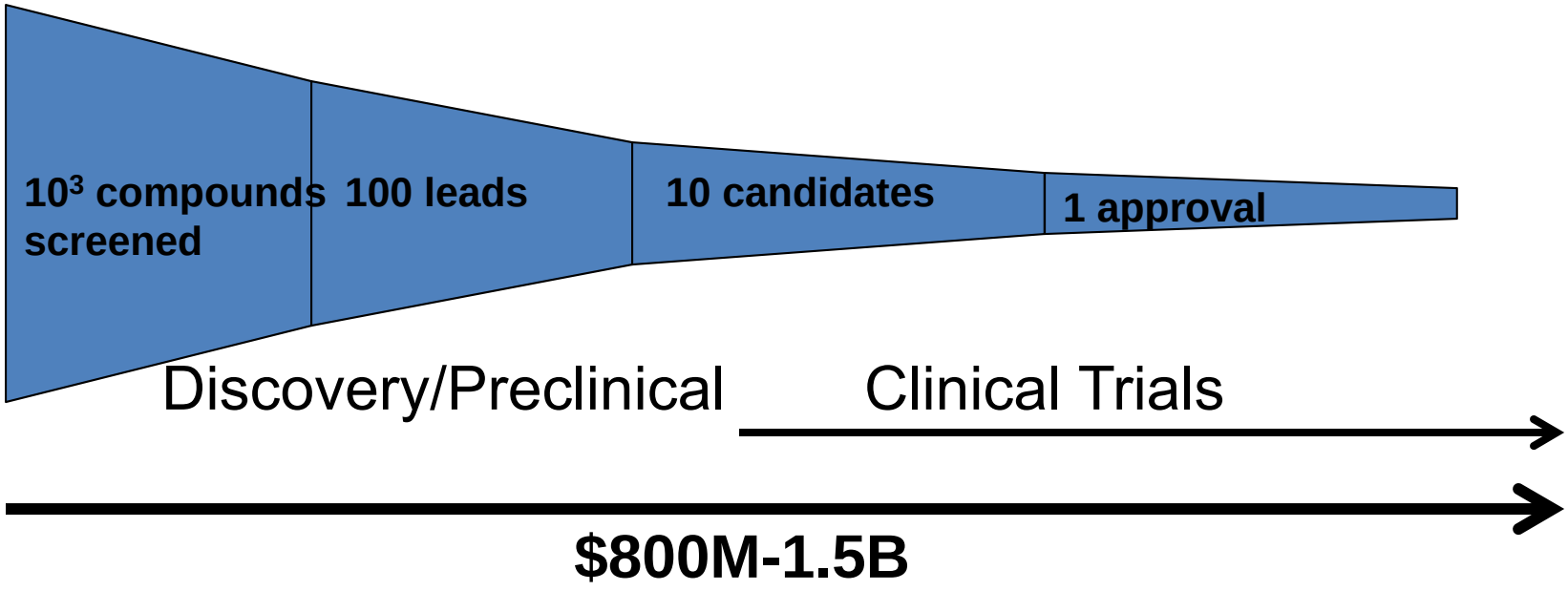
Environment

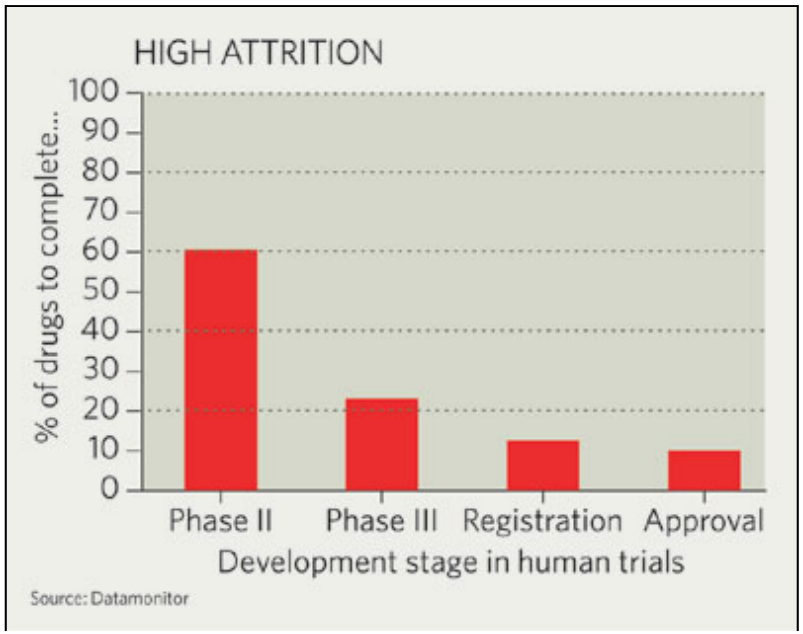
Energy



Disease

Drug Development: Too costly, Too random.





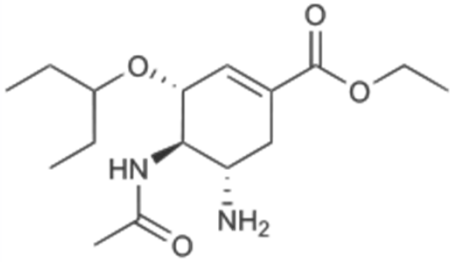
Reasons:

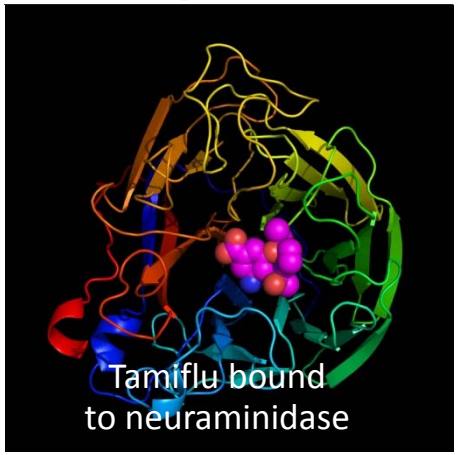
Safety

Efficacy

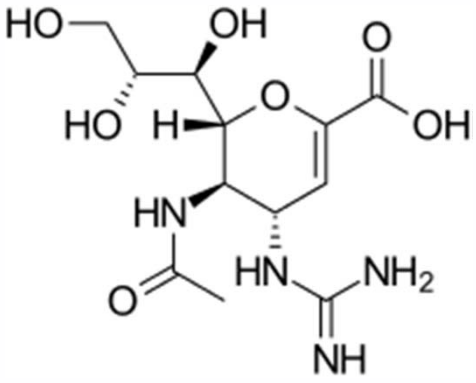
Static Structure-Based Design of Viral Inhibitors

Oseltamivir (Tamiflu))

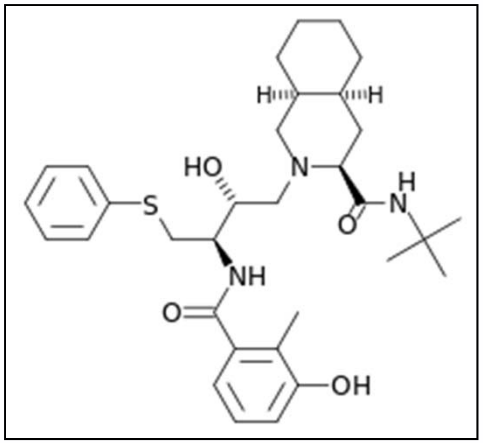




Zanamivir (Relenza))



HIV-protease inhibitor: Nelfinavir (Viracept)



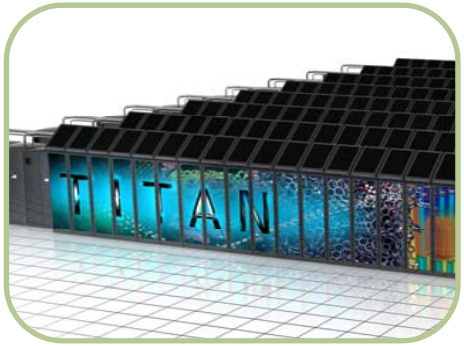
What has changed in the last 20 years?

Genomics

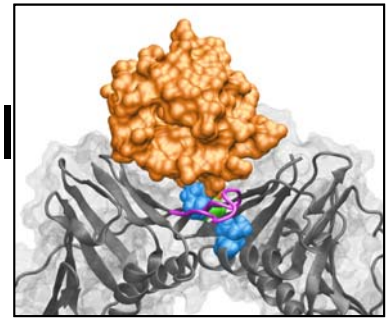
Systems

Structures

Computers

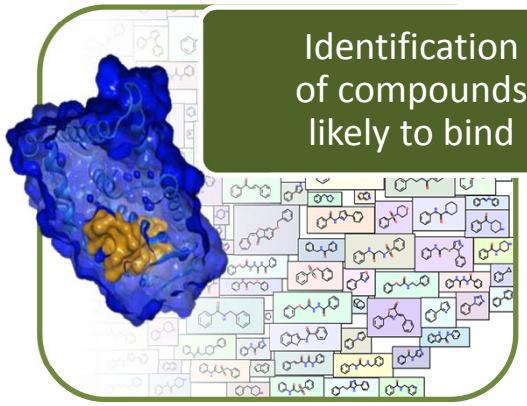


Computational Methods



Supercomputing and Drug Discovery

Modeling and simulation

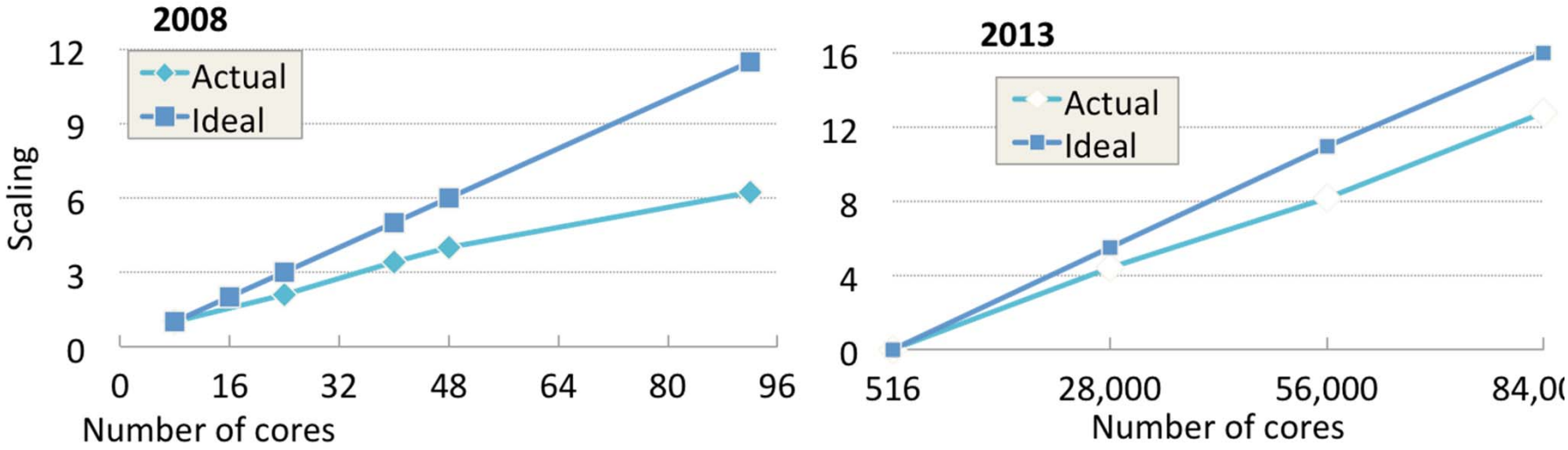


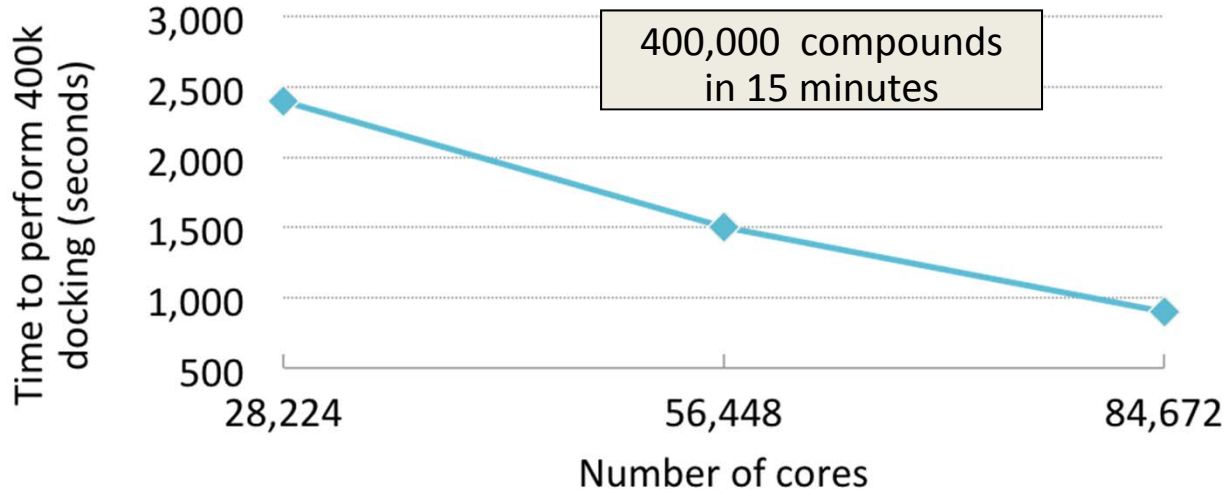
Identification of compounds likely to bind

Drug development, drug repurposing, personalized medicine

Supercomputer Scaling Reduces Time to Solution

SALLY ELLINGSON

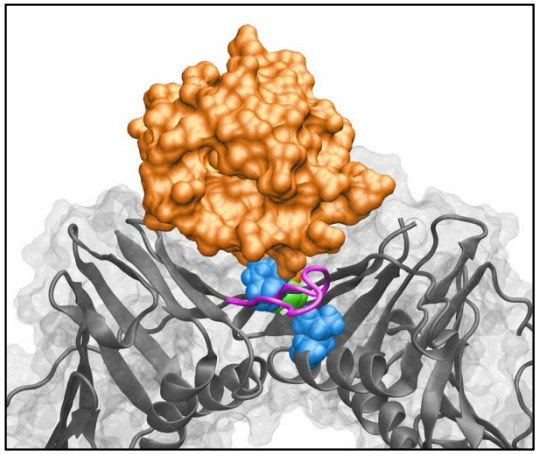




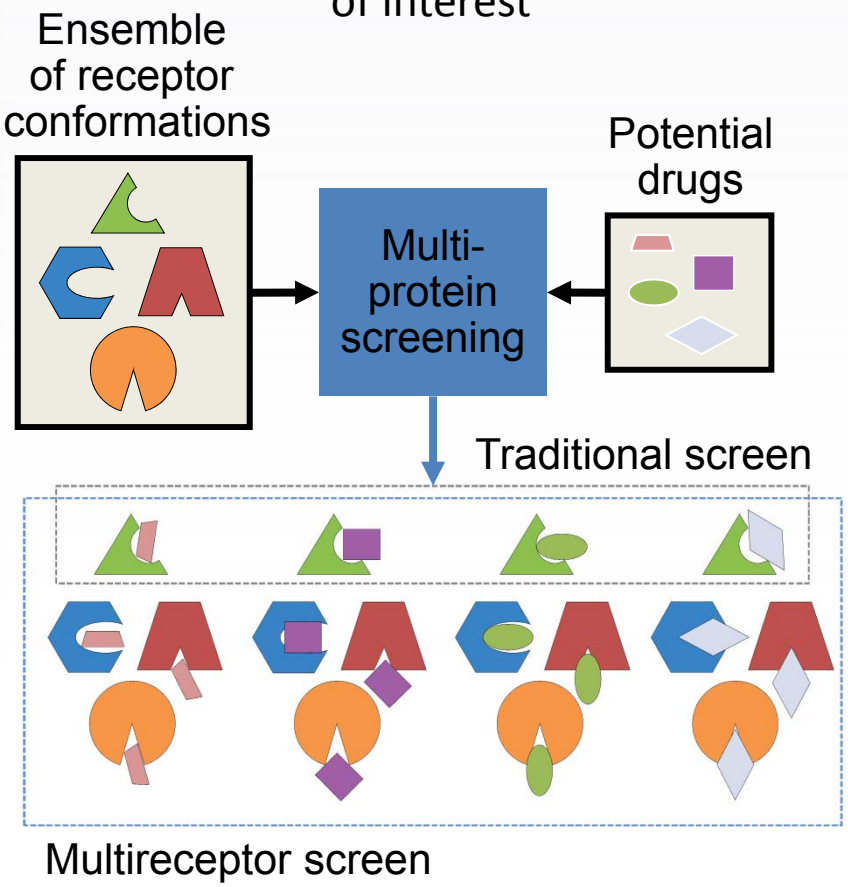
J Comp Chem 34 2212 (2013)

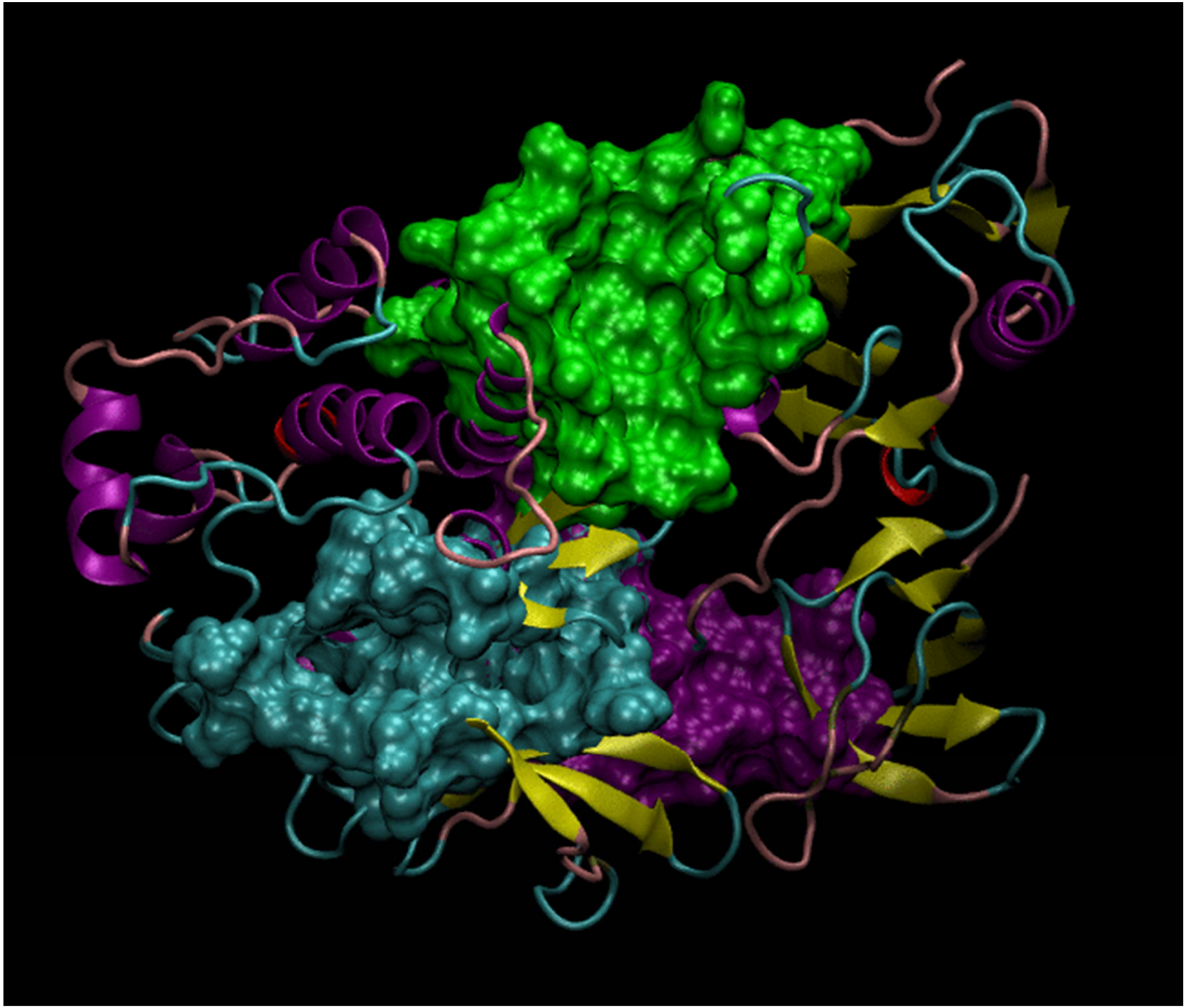
Ensemble-based docking

Molecular dynamics (MD) of each protein: Identify permanent and transient binding pockets

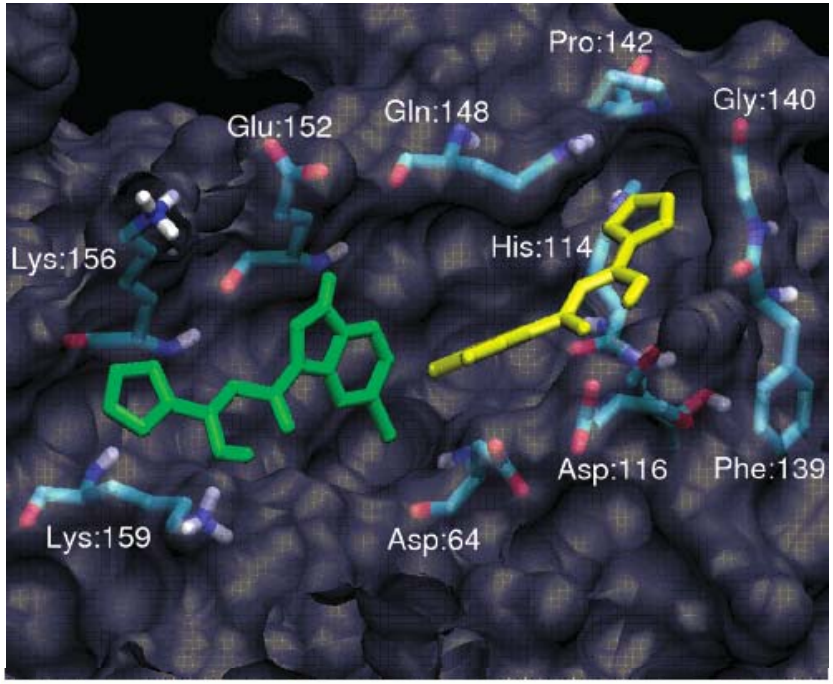


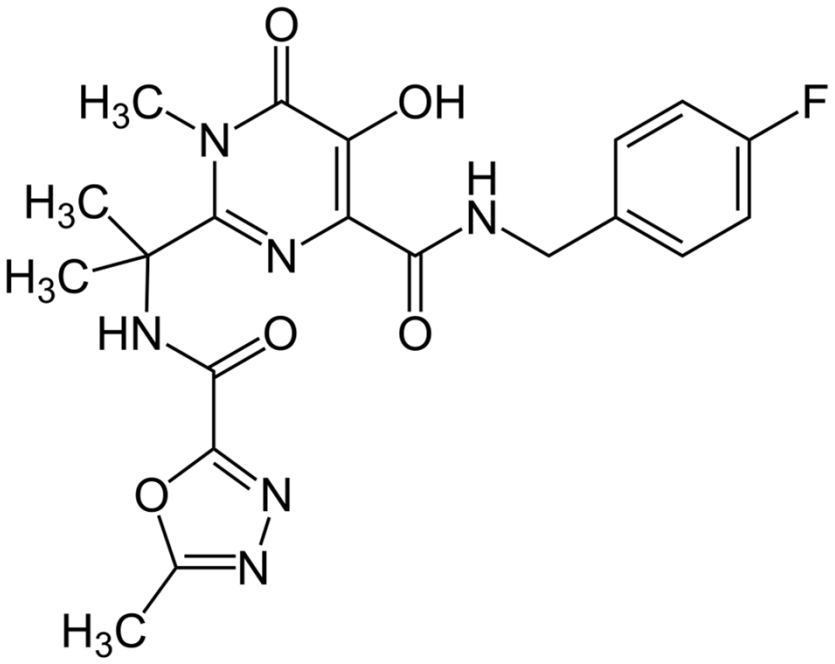
High-throughput screening (HTS) *in silico* on each structure of interest





Binding to MD snapshots



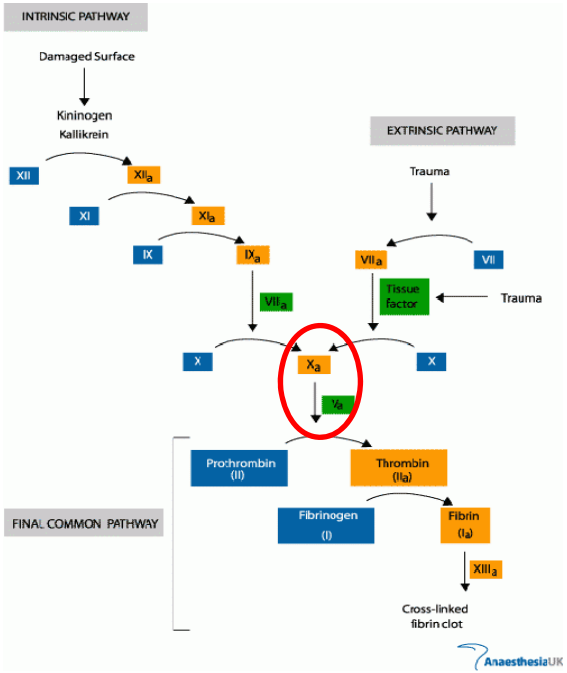


Schames et al., "Discovery of a Novel Binding Trench in HIV Integrase," J. Med. Chem. 47, 1879–1881 (2004)

Raltegravir (HIV integrase inhibitor): FDA approval, 2007

Discovery of molecular effectors of the coagulation cascade

JASON HARRIS
JEROME BAUDRY



FXa/FVa complex formation:

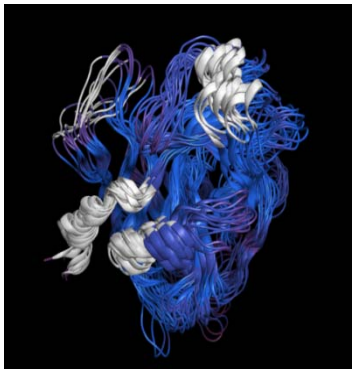
535 docked compounds suggested

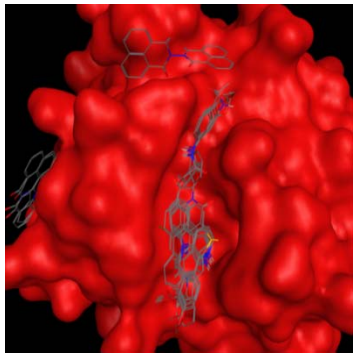
97 tested experimentally

24 bind

10 work (modulate coagulation)

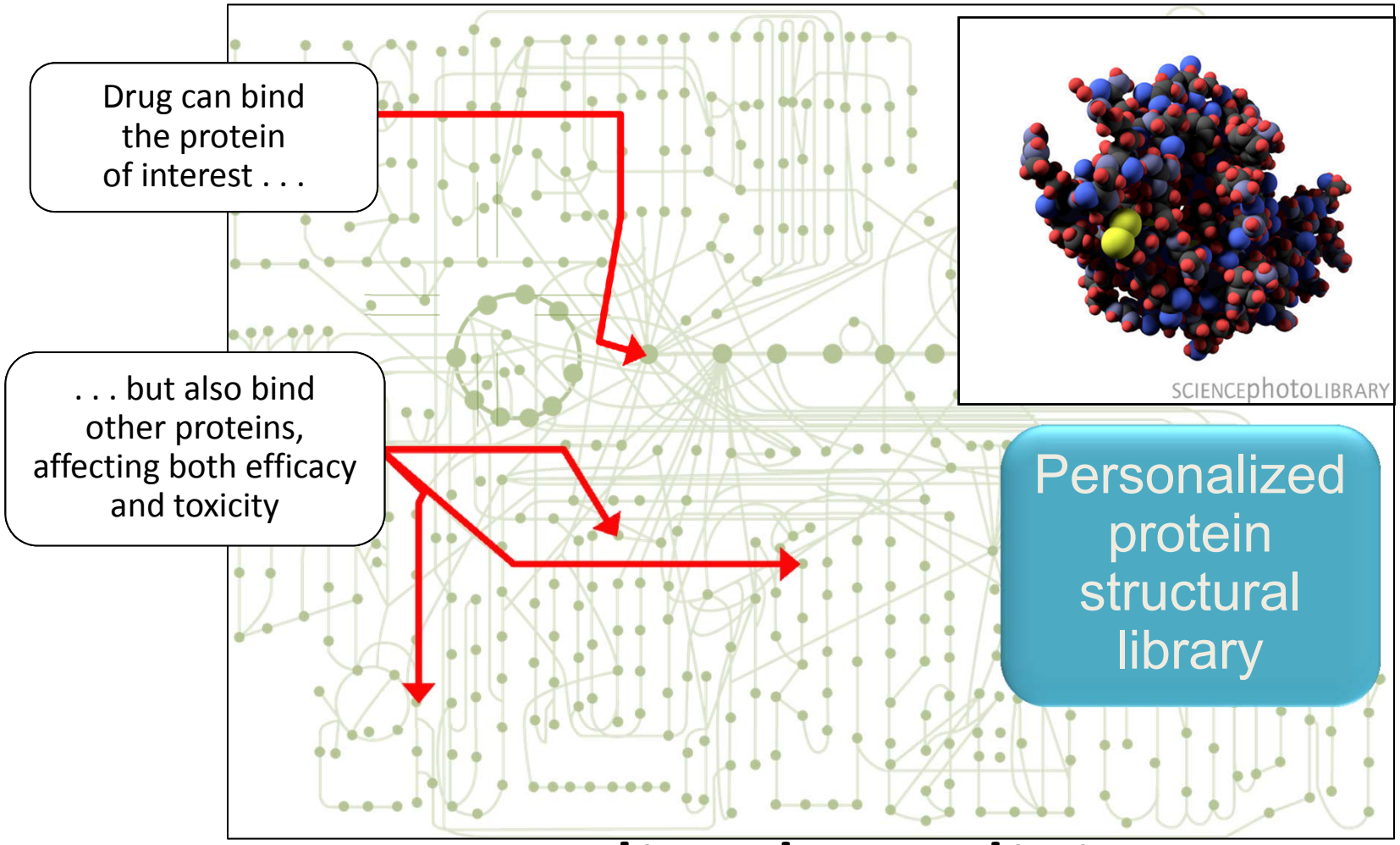
8 would not bind in crystal structure





Ensemble of structures
(11 MD snapshots + 1 crystal structure)

Systems-Level Toxicity Prediction



Personalized Medicine

Supercomputing: The Future

	Protein	Ligands	Time
Today: 10 PF	1	10^8	1 day
	100	10^6	1 day
Exascale	1,000	10^7	1 day

Center for Molecular Biophysics

OAK RIDGE National Laboratory

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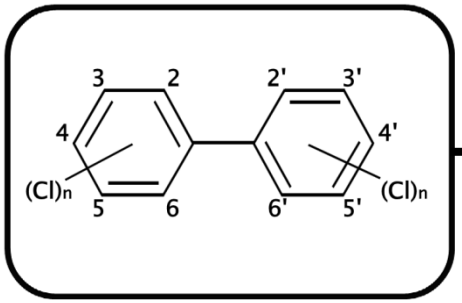
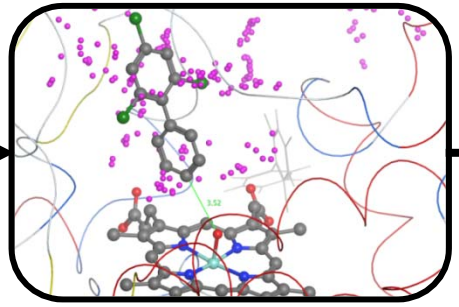
Salim Shah (Georgetown U Med Center)

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

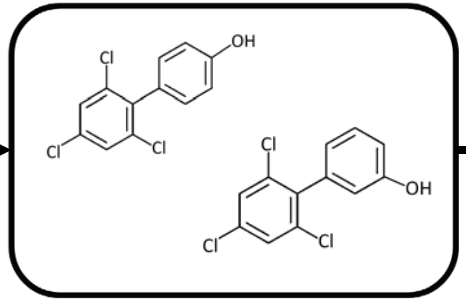
Toxicity Prediction: PCB Estrogenicity



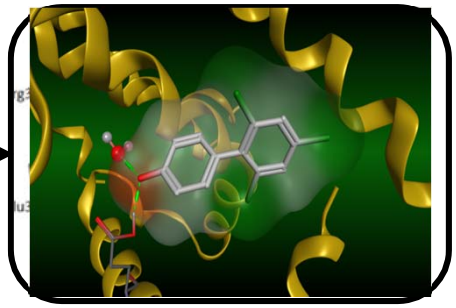
Binds to specific P450



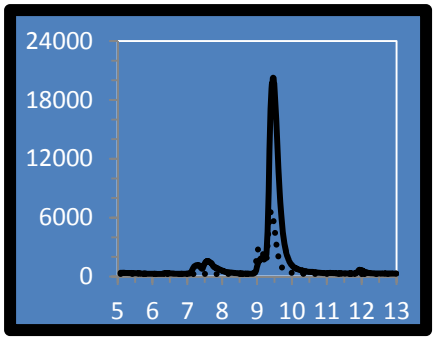
Geometry predicts metabolites



Metabolites bind to human ERα



Experimental confirmation



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Biomass Pretreatment

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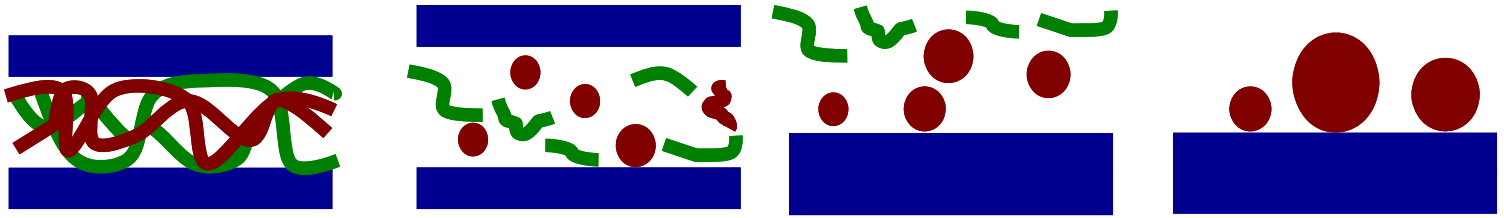

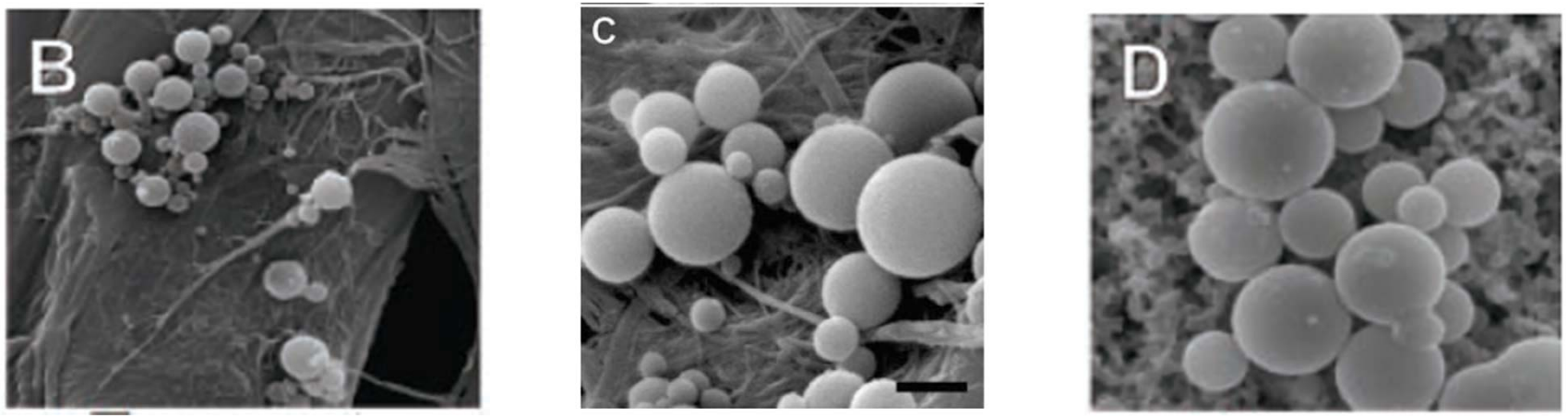

Are Lignin Aggregates Spheres?

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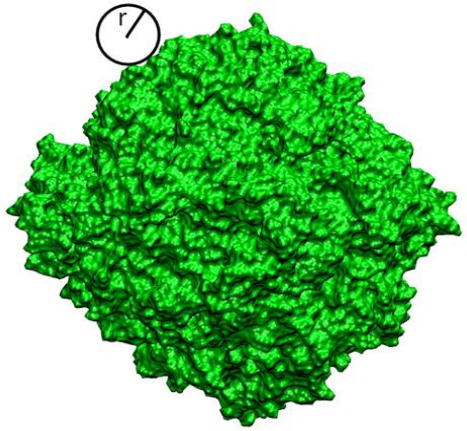
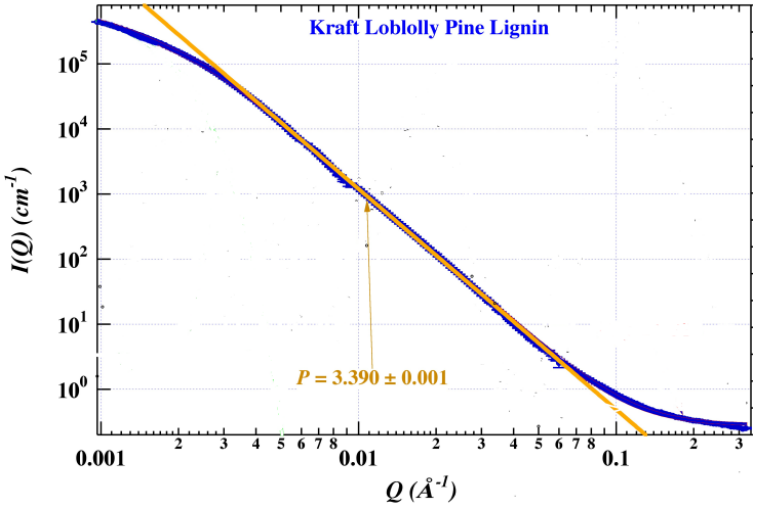


Small-Angle Neutron Scattering

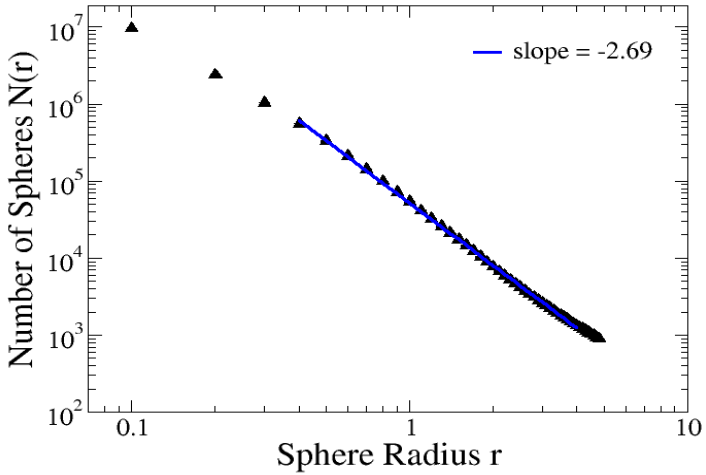
$$S(q) \propto Q^{d_s - 6}$$



$d_s = 2.62 \pm 0.02$

Molecular Dynamics

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



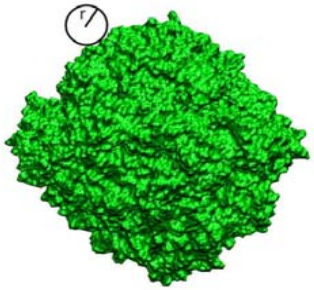
$d_s = 2.65 \pm 0.01$

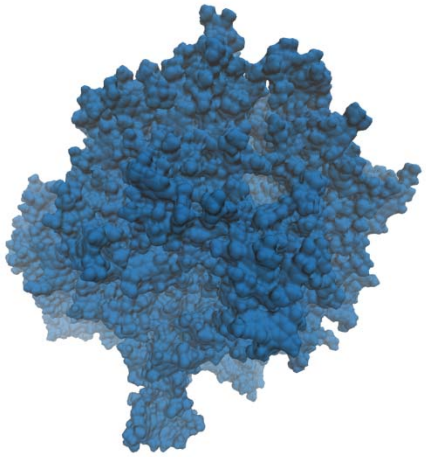
Petridis et al Physical Review E 83(61):061911 (2011)

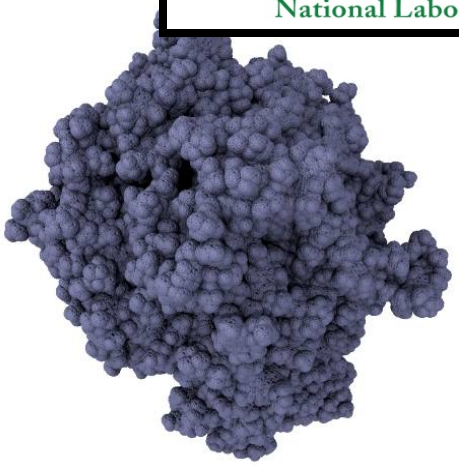
Center for Molecular Biophysics

Surface Fractals Three Orders of Ma

OAK RIDGE National Laboratory



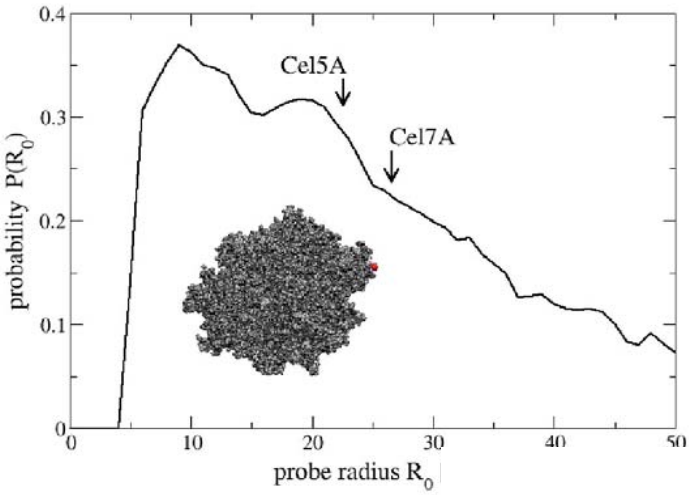




R_g=4.2Å

R_g=42Å

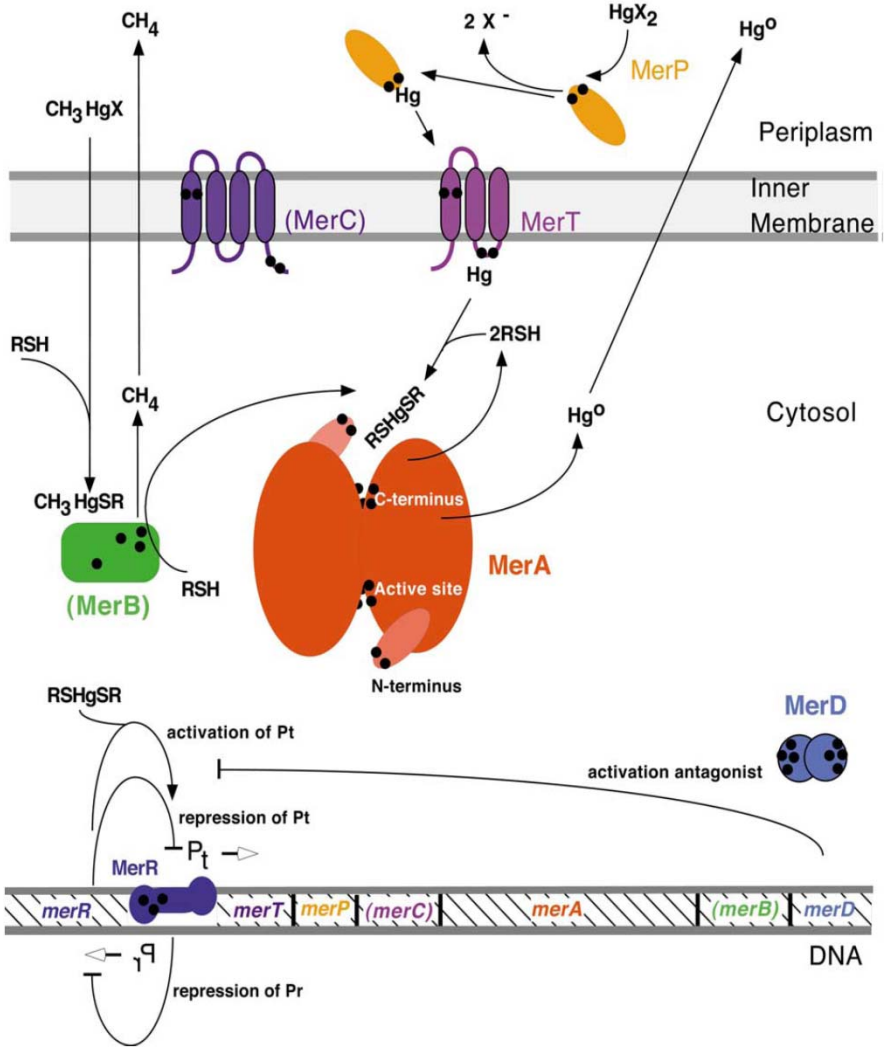
R_g=420Å



Enzyme:lignin interaction distribution

Petridis et al Physical Review E 83(61):061911 (2011)

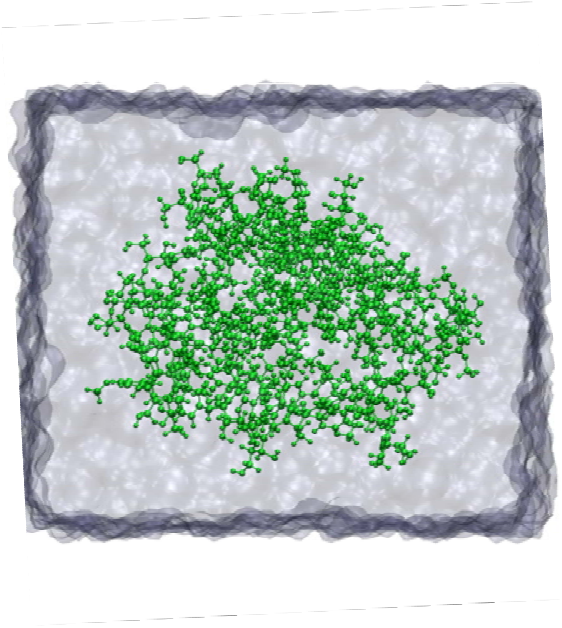
Bacterial Mercury Resistance – The ***Mer*** Operon

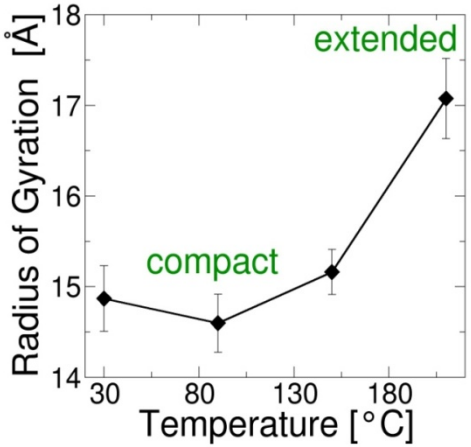


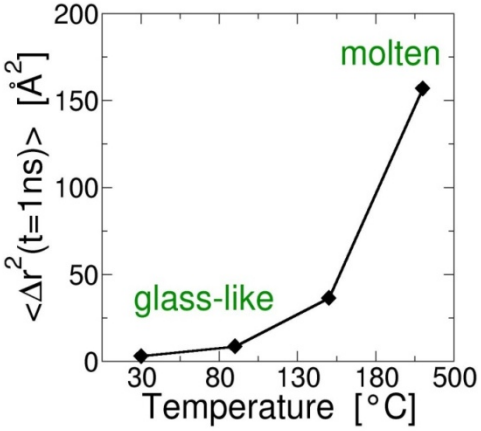
- MerR – regulation (transcriptional activator)
- MerB – organomercurial lyase
- MerA – mercuric reductase

Loukas Petridis

MD Simulation of Softwood Lignin

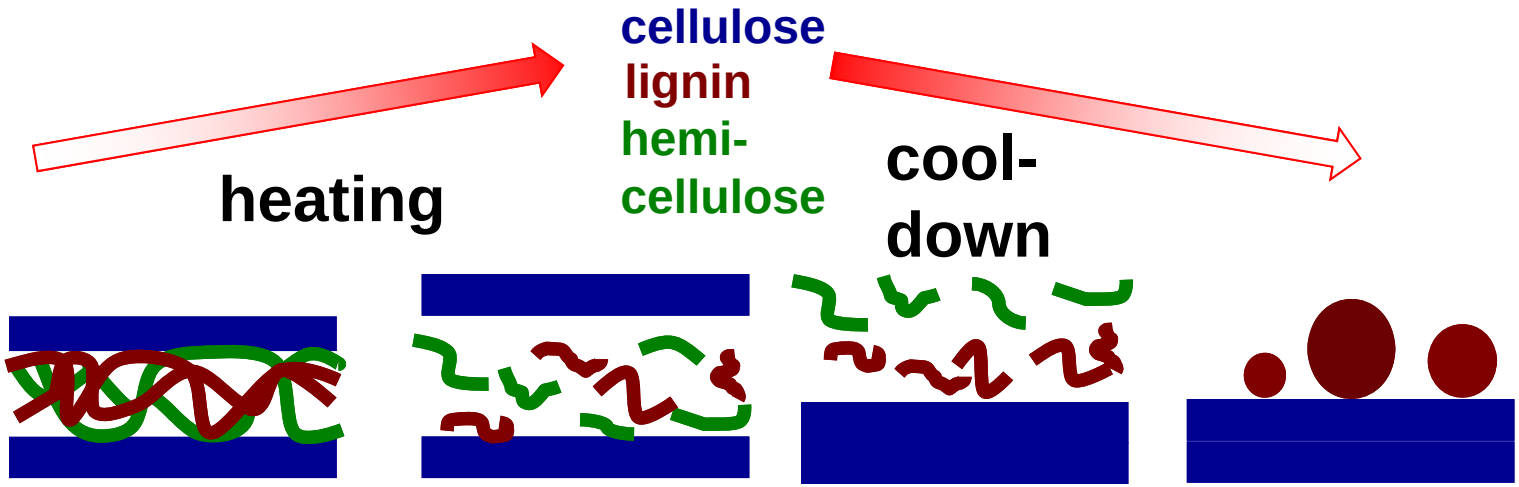




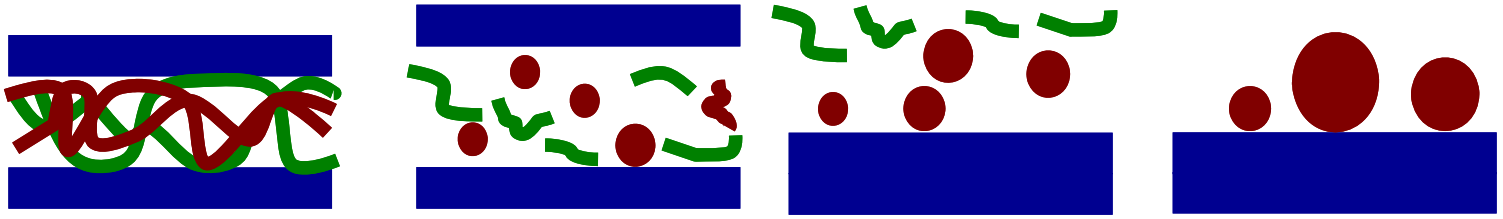


JACS 133 20277 (2011)

Lignin Aggregation During Heating Phase of Dilute-acid Pretreatment



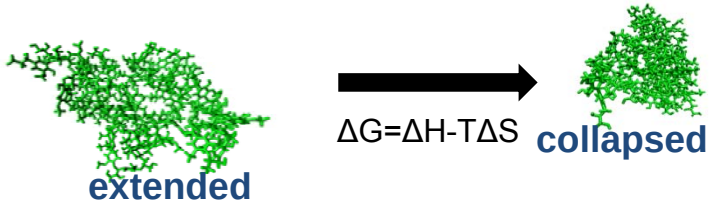
aggregation occurs during cool-down



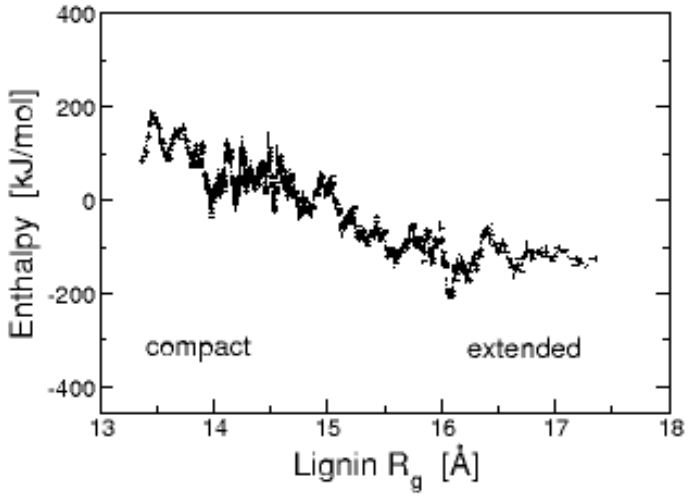
aggregation occurs during heating

Why does Lignin Collapse at Room Temperature?

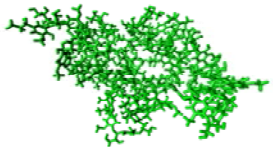
Loukas Petridis



- **Enthalpy**
- ΔH ≈ +200 kJ/mol **Unfavorable**

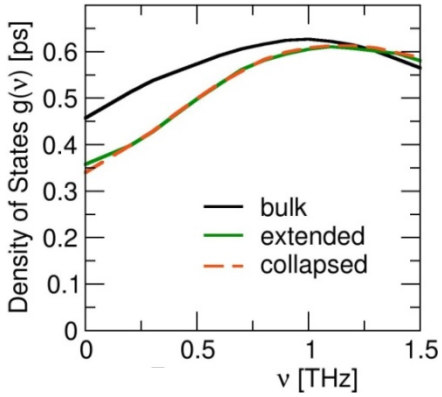


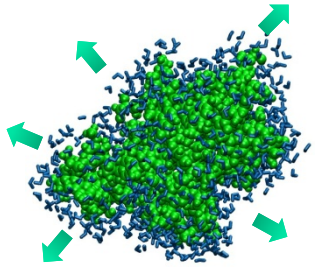
- **Lignin configurational entropy**
- $-T\Delta S_{conf} \approx$ +10 kJ/mol **Unfavorable**



JACS 133 20277 (2011)

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

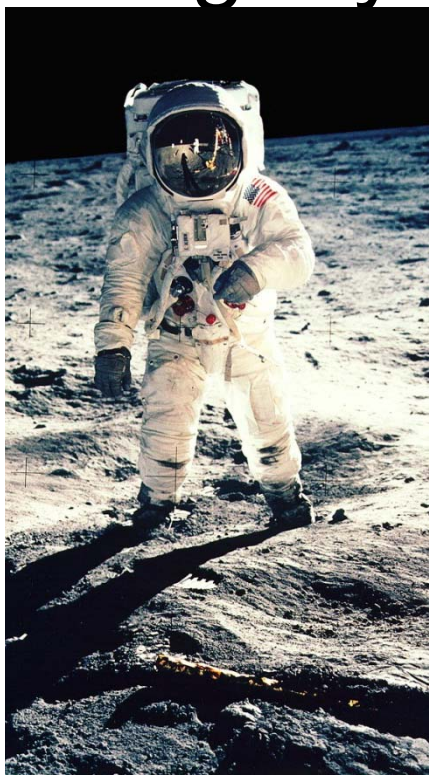




- Hydration **water compressibility**
- $-T\Delta S_{fluc} \approx$ -300 kJ/mol **Favorable**

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

45 years of agony



Geobacter chapelleii, 172
Geobacter pelophilus, Dfr2
Geobacter bremensis, Dfr1
Geobacter lovleyi, SZ
Geobacter metallireducens, GS-15
Geobacter grbiciae, TACP-2
Geobacter hydrogenophilus, strain H4
Geobacter sulfurreducens, PCA
Desulfuromonas palmitatis, SDBY1
Desulfuromonas chloroethenica, TT4B
Desulfuromonas thiophila, NZ27 (DSMZ 8987)
Desulfuromonas acetoxidans, DSM 624

Desulfuromonales

Desulfocapsa sulfexigens, SB164P1
Desulfotalea psychrophila, LSv54
Desulforhopalus vacuolatus, ltk10
Desulfobulbus propionicus, DSM 2032
Desulfosarcina variabilis
Desulfococcus multivorans, DSM 2059
Desulfofrigus oceanense, ASv26
Desulfobacterium sp., BG33
Desulfobacterium autotrophicum, DSM 3382
Desulfobacter vibrioformis, B54
Desulfobacter species, 4ac11 DSM 2057
Desulfobacter species, 3ac10 DSM 2035
Desulfobacter hydrogenophilus DSM 3380
Desulfobacter curvatus, DSM 3379
Desulfobacter sp., BG8

Desulfobacterales

Corallococcus coralloides, DSM 2259
Myxococcus xanthus, DSM 435 (Mx x1)

Myxococcales

Desulfovibrio dechloracetivorans, ATCC 700912
Desulfovibrio desulfuricans, ND132
Desulfovibrio profundus, DSM 11384
Desulfovibrio sp., T2
Desulfovibrio sp., W3A
Desulfovibrio gigas
Desulfovibrio sp., X2
Desulfovibrio desulfuricans, DSM1926 El Agheila Z
Desulfovibrio africanus
Desulfovibrio desulfuricans , MB; ATCC27774
Desulfovibrio desulfuricans, Essex 6; ATCC29577
Desulfovibrio vulgaris, Hildenborough
Desulfovibrio alaskensis, G20
Desulfovibrio alaskensis, NCIMB 13491
Desulfomicrobium baculatum, DSM 4028T
Desulfomicrobium orale, DSM12838

Desulfovibrionales

Shewanella algae, Bry
Shewanella oneidensis, MR-1
Shewanella putrefaciens, CN-32

0.10

Non Hg methylator
Weak Hg methylator
Strong Hg methylator

Chemistry of mercury methylation

JERRY PARKS

$$CH_3^- + Hg^{2+} \rightarrow CH_3Hg^+$$

Generate carbanion, CH_3^-:

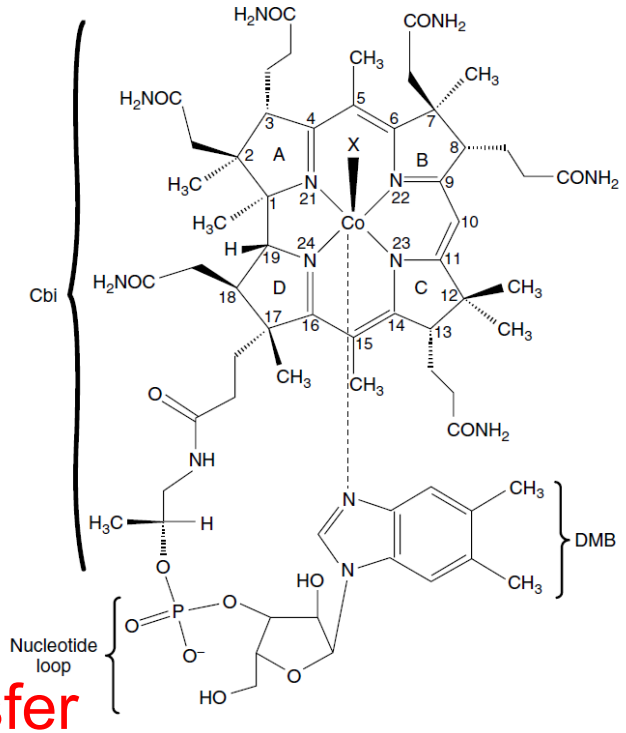
CH_3^+ + Co(I)-protein $\rightarrow CH_3$-Co(III)-protein

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

CH_3-Co(III)-protein + $Hg^{2+} \rightarrow$ Co(III)-protein + CH_3Hg^+

Regenerate Co(I):

Co(III)-protein + 2 e- $\rightarrow$ Co(I)-protein



cobalamin

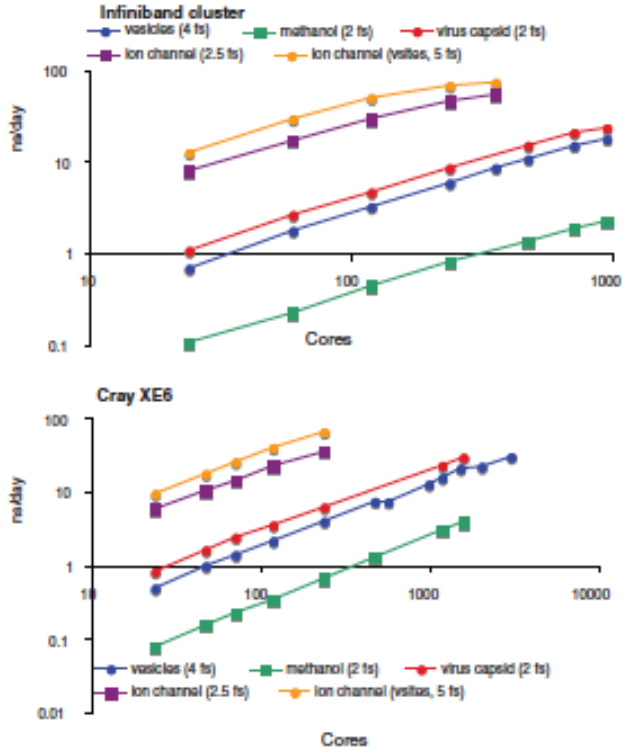
Need to find protein(s) that can:

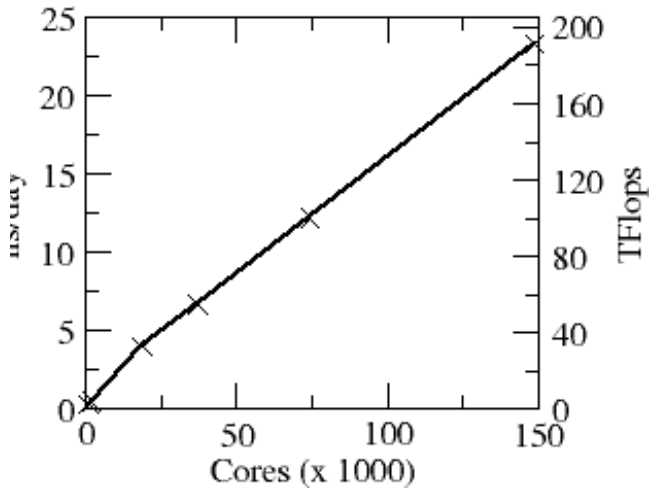
1. Stabilize Co(III) for carbanion transfer
2. Provide 2 electrons to generate Co(I)

Science, 339 1332 (2013)

ROLAND SCHULZ

Molecular Dynamics Supercomputer Scaling





~ 100 million atoms.

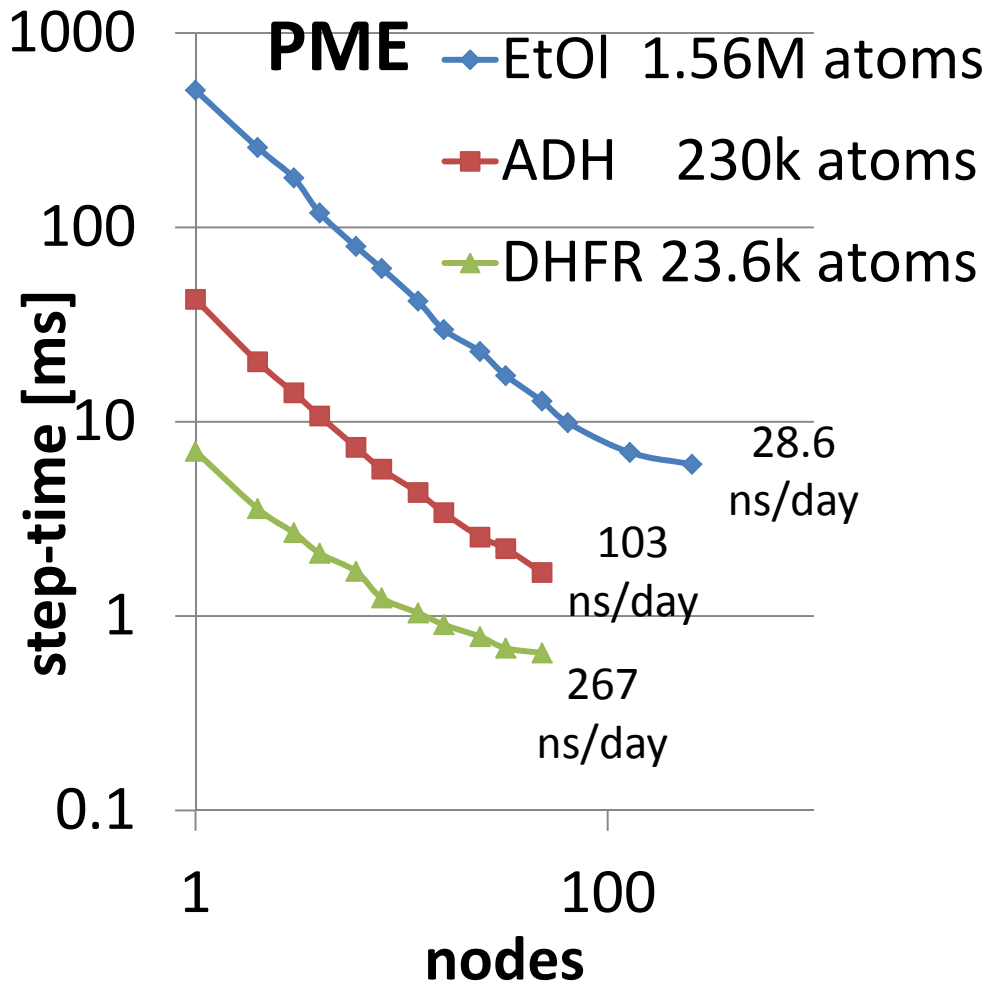
- Scales to 150,000 cores

Bioinformatics, 29 845 (2013)

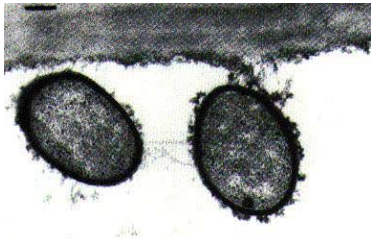
ROLAND SCHULZ

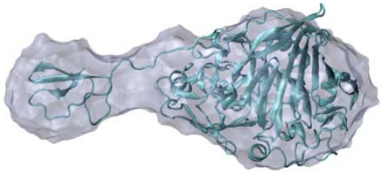
TITAN

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



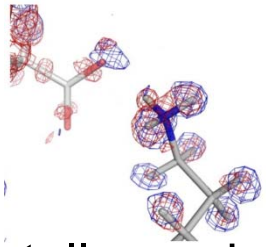
Multiscale Structure and Dynamics





SANS

reflectometry



crystallography,
solution diffraction

1*μm*

100
nm

1
nm

0.1
nm

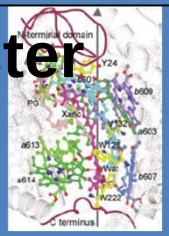
Exascale

spin echo

10PF

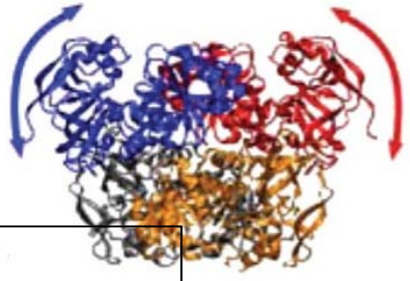
Petascale

Cluster



vibrational

backscattering



1 *fs* 1 *ps* 1 *ns* **1 μs**