Study of Large Scale Structures and Processes

for Biomedicine, Bioengineering, Biofuels

Discoveries Through the Computational Microscope
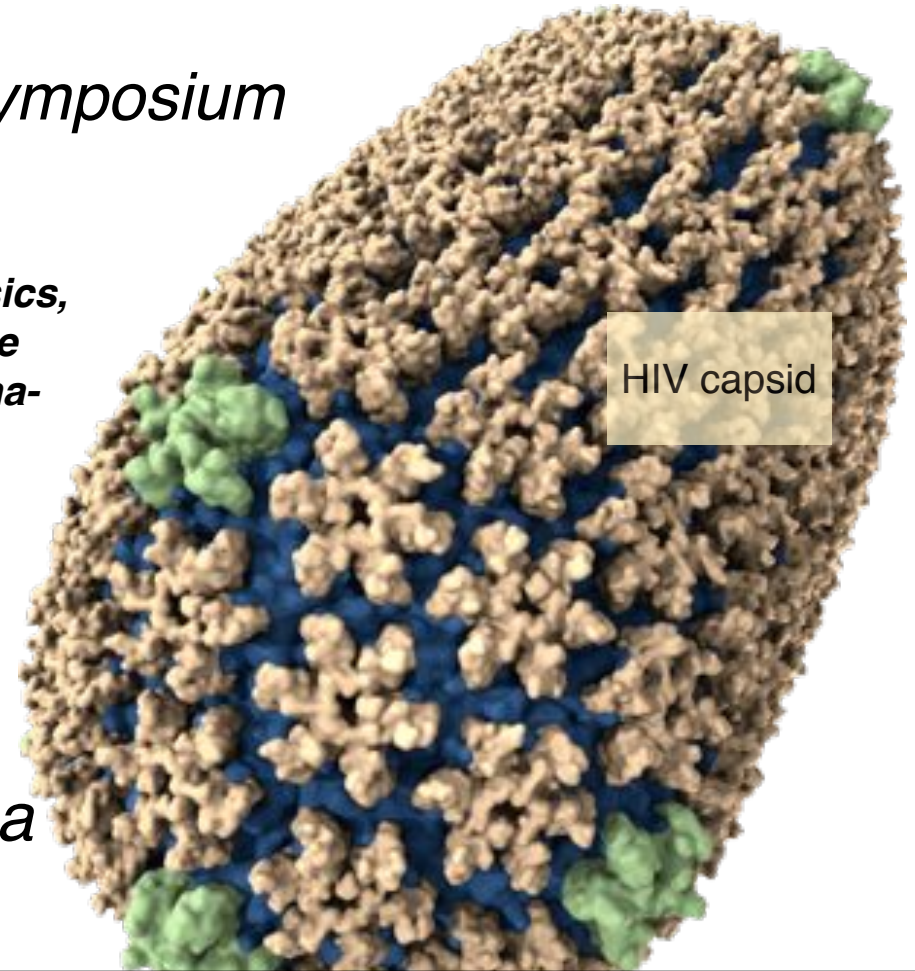
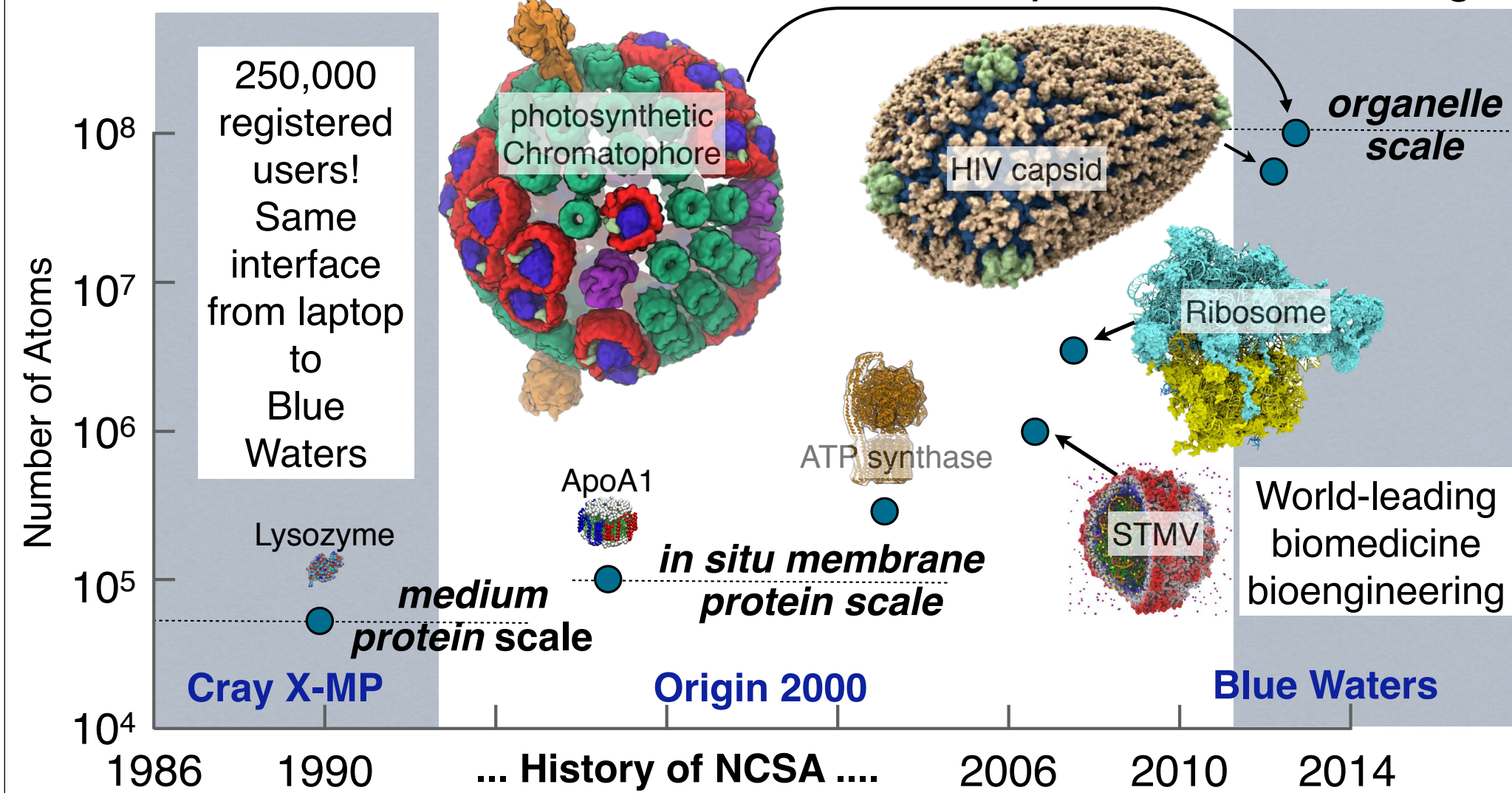*Blue Waters Symposium*

May 14, 2014

Klaus Schulten

Department of Physics, Beckman Institute U. Illinois at Urbana-Champaign

Blue Waters
Research Instrument for a New Era

HIV capsid

NAMD/VMD Effort Towards Cell-scale Computational Modeling
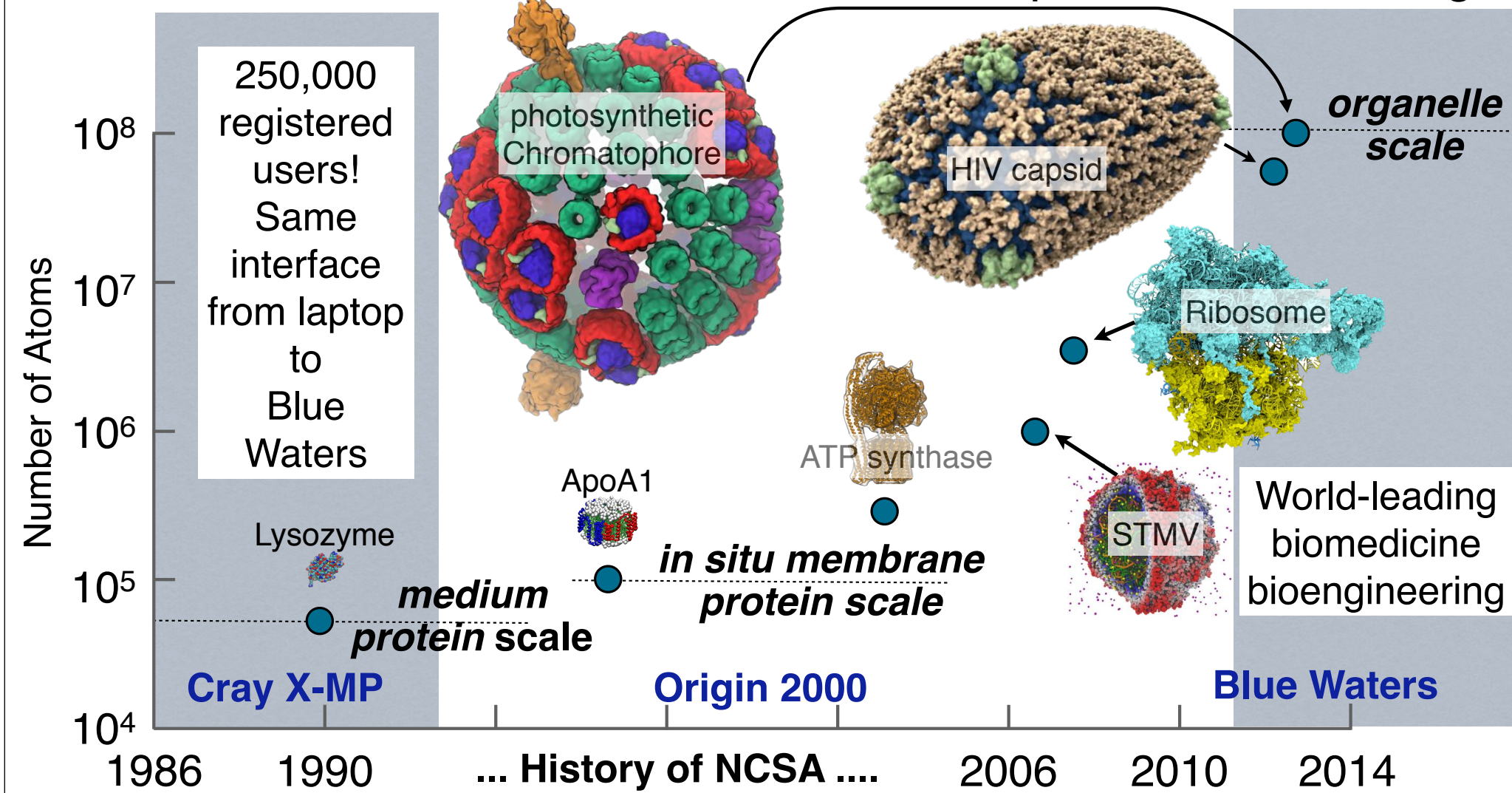
Role of Kale Parallel Programming Lab

NAMD/VMD Effort Towards Cell-scale Computational Modeling

Number of Atoms

10^8

10^7

10^6

10^5

10^4

250,000 registered users! Same interface from laptop to Blue Waters

photosynthetic Chromatophore

HIV capsid

organelle scale

Ribosome

ApoA1

ATP synthase

in situ membrane protein scale

STMV

World-leading biomedicine bioengineering

Lysozyme

medium protein scale

Cray X-MP

Origin 2000

Blue Waters

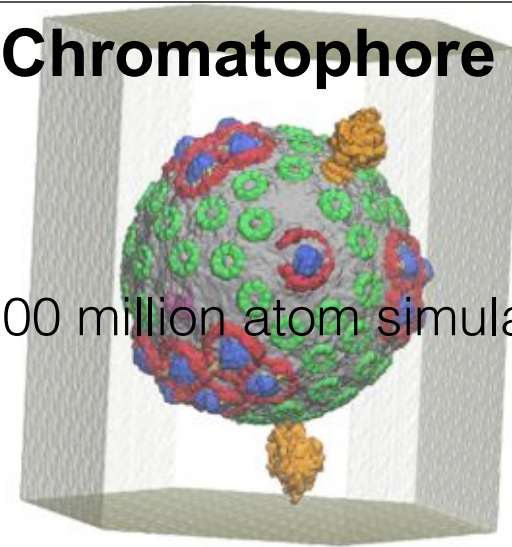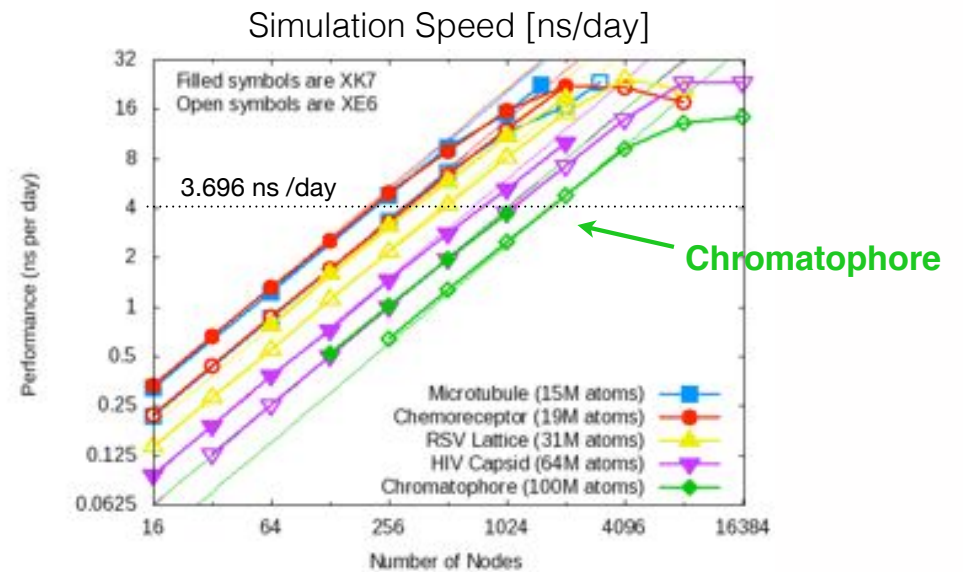1986   1990   ... History of NCSA   2006   2010   2014

A Habitat of Purple Bacteria
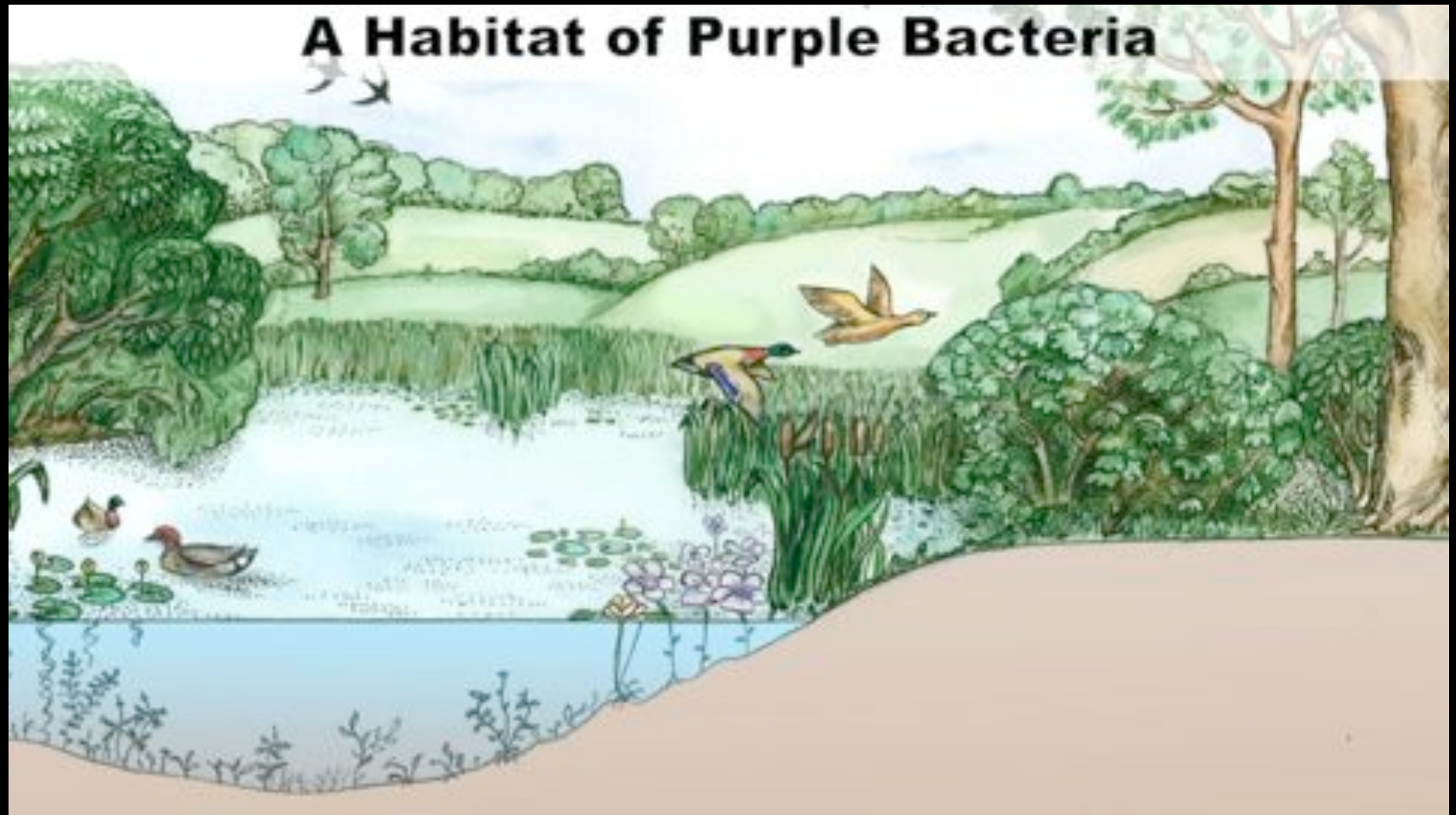
100-million Atom Simulation of Chromatophore
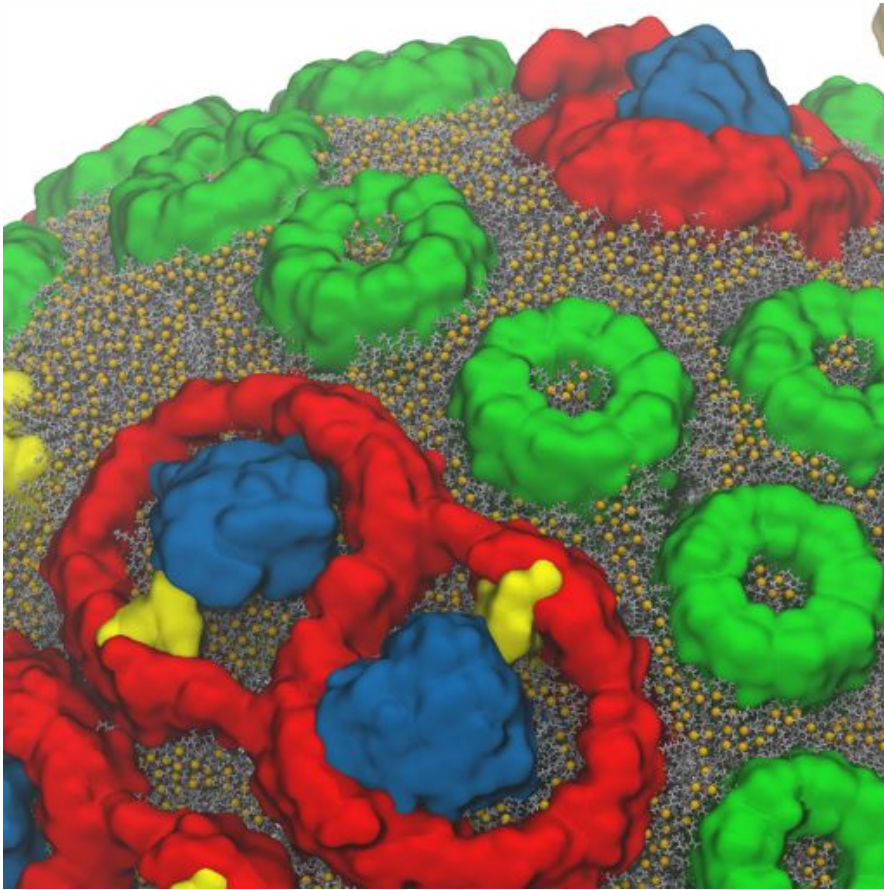
segment of simulated chromatophore
showing lipids

100 million atom simulation

Simulation Speed [ns/day]

Filled symbols are XK7
Open symbols are XE6

3.696 ns /day

Chromatophore

Performance (ns per day)

Microtubule (15M atoms)
Chemoreceptor (19M atoms)
RSV Lattice (31M atoms)
HIV Capsid (64M atoms)
Chromatophore (100M atoms)

Number of Nodes

Blue Waters - A Key Instrument for US Life Science
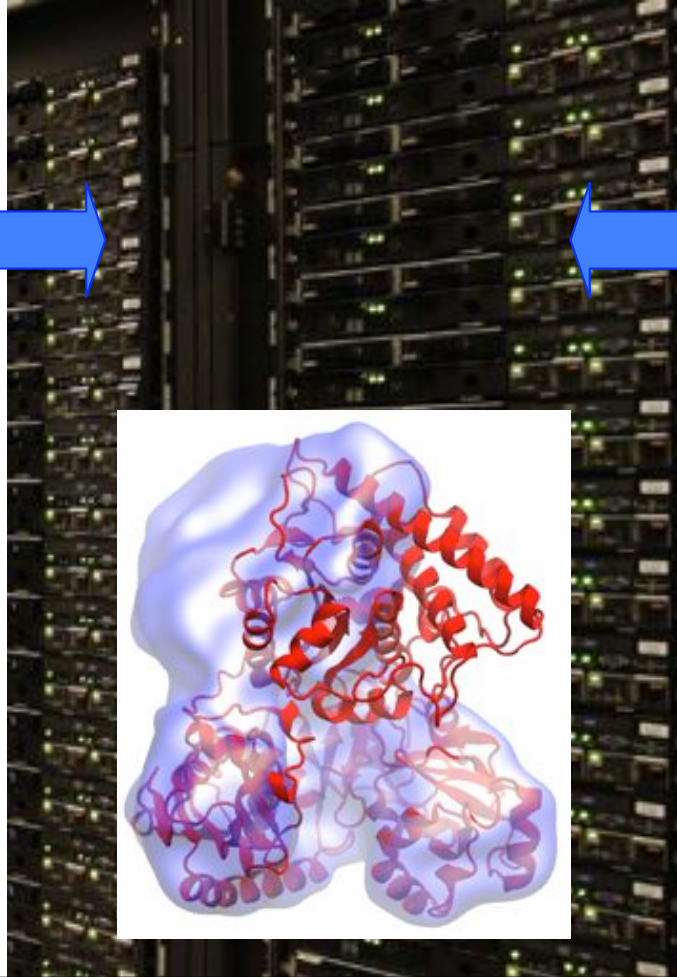## *BW Solves Structures from X-ray Crystallography and Cryo-EM*

Electron microscopy
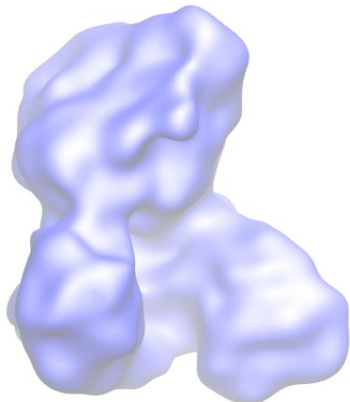
FEI microscope

electron density of protein in action
at low resolution

X-ray crystallography

APS at Argonne

ideal protein structure at high resolution
Acetyl – CoA Synthase

BW Solves Structures from X-ray Crystallography and Cryo-EM

Electron microscopy

FEI microscope

electron density of protein in action at low resolution

The Antibiotic Resistance Crisis

2,000,000 Americans fall ill from antibiotic-resistant infections each year of whom at least 23,000 die.
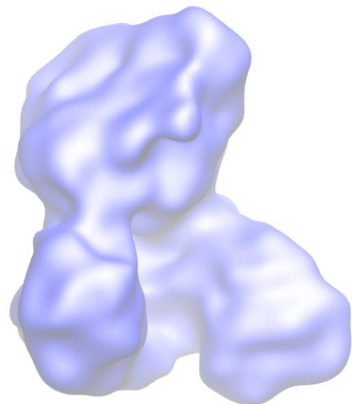
50% antibiotics target the bacterial ribosome

Erythromycin Tablets BP 250mg

- wide antimicrobial spectrum
- eye and respiratory tract infections
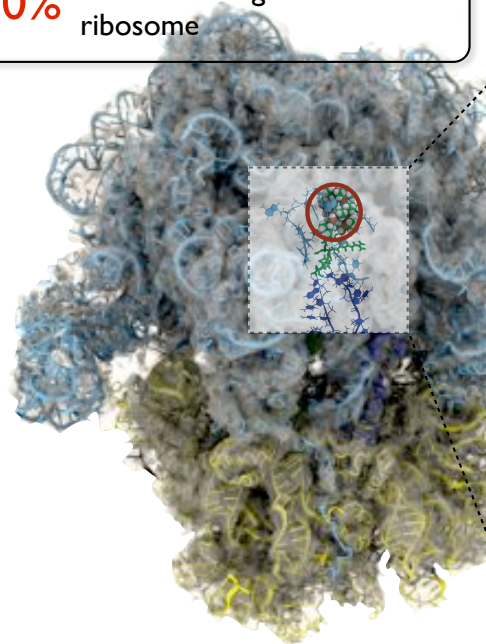
ERY antibiotics

nascent protein
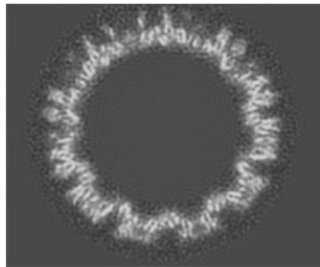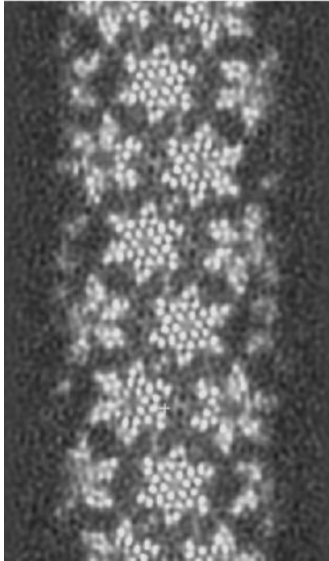
tRNA

X-ray crystallography

APS at Argonne

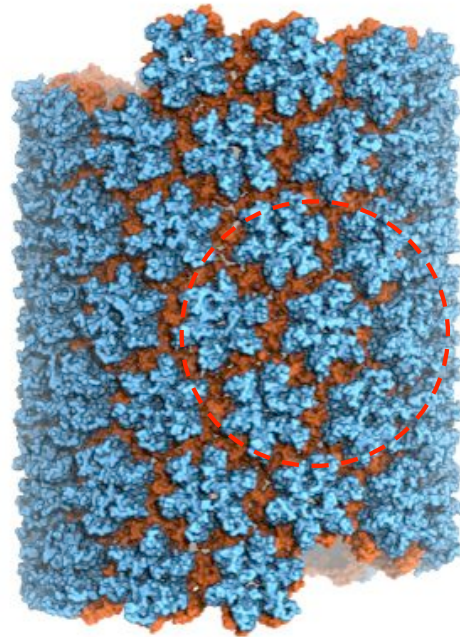ideal protein structure at high resolution

5-2
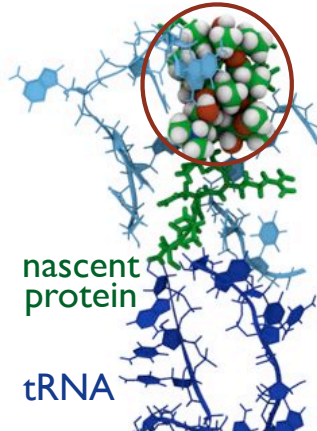
BLUE WATERS SOLVES STRUCTURE OF AIDS VIRUS

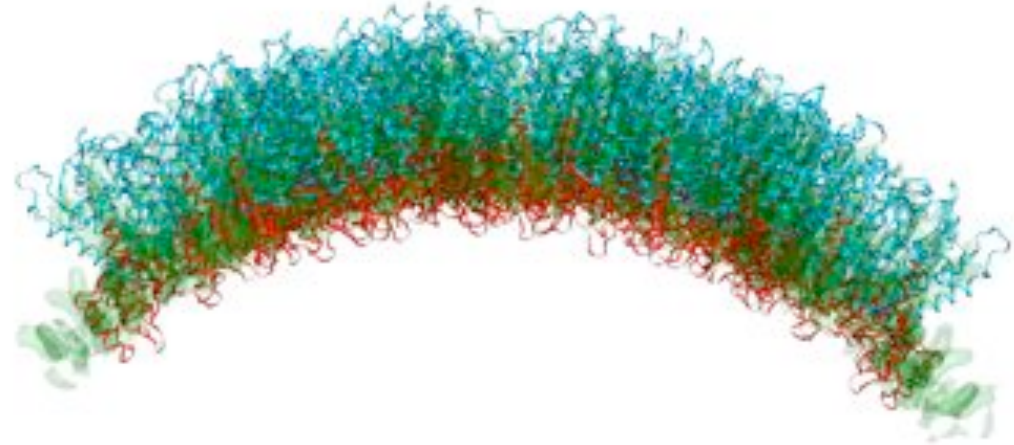## Blue Waters Early Science Project

cylindrical capsid density 8 A resolution

Gongpu Zhao and Peijun Zhang

MDFF provides structural information on CA elements involved in hexamer-hexamer interactions

MDFF fitted all-atom structure to EM density and identified residues at the trimer interface that are critical for capsid stability

# Unveiling the Structure of the HIV Capsid

Theoretical and Computational Biophysics Group
University of Illinois at Urbana-Champaign
www.ks.uiuc.edu

Capsid Response to Electrical Field

$\vec{E}$
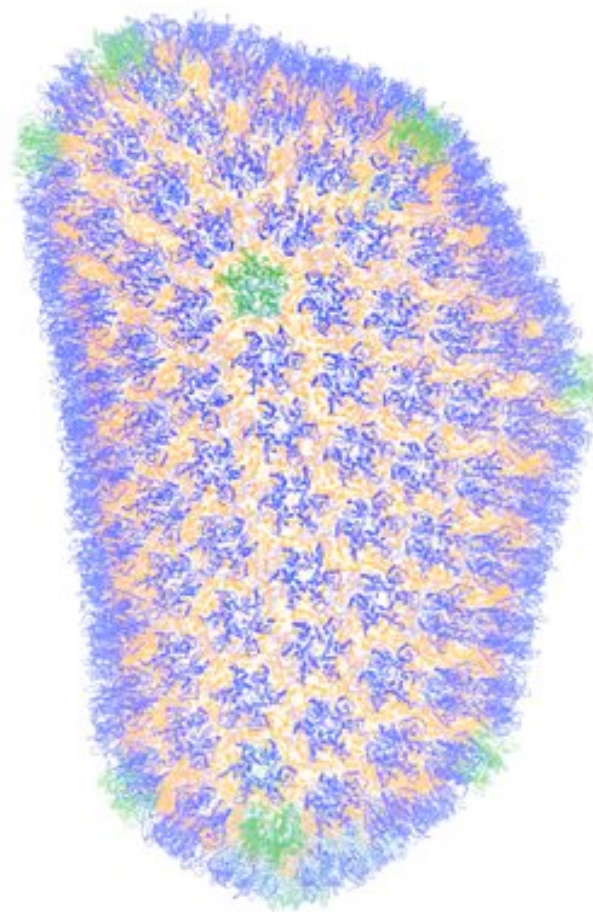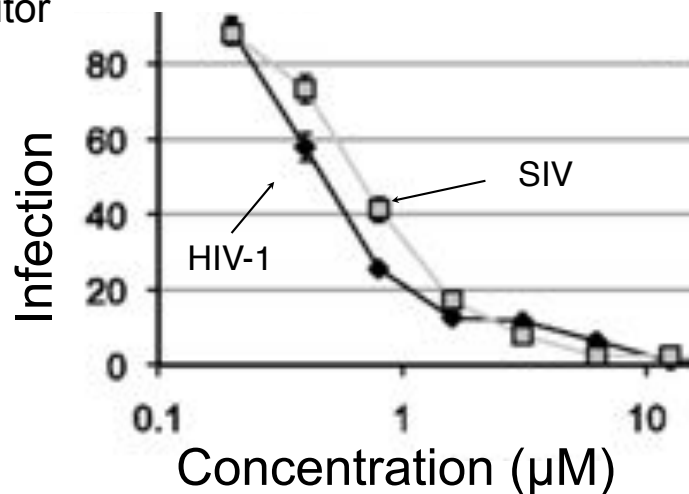
Chloride Channel

Hydrophobic interactions
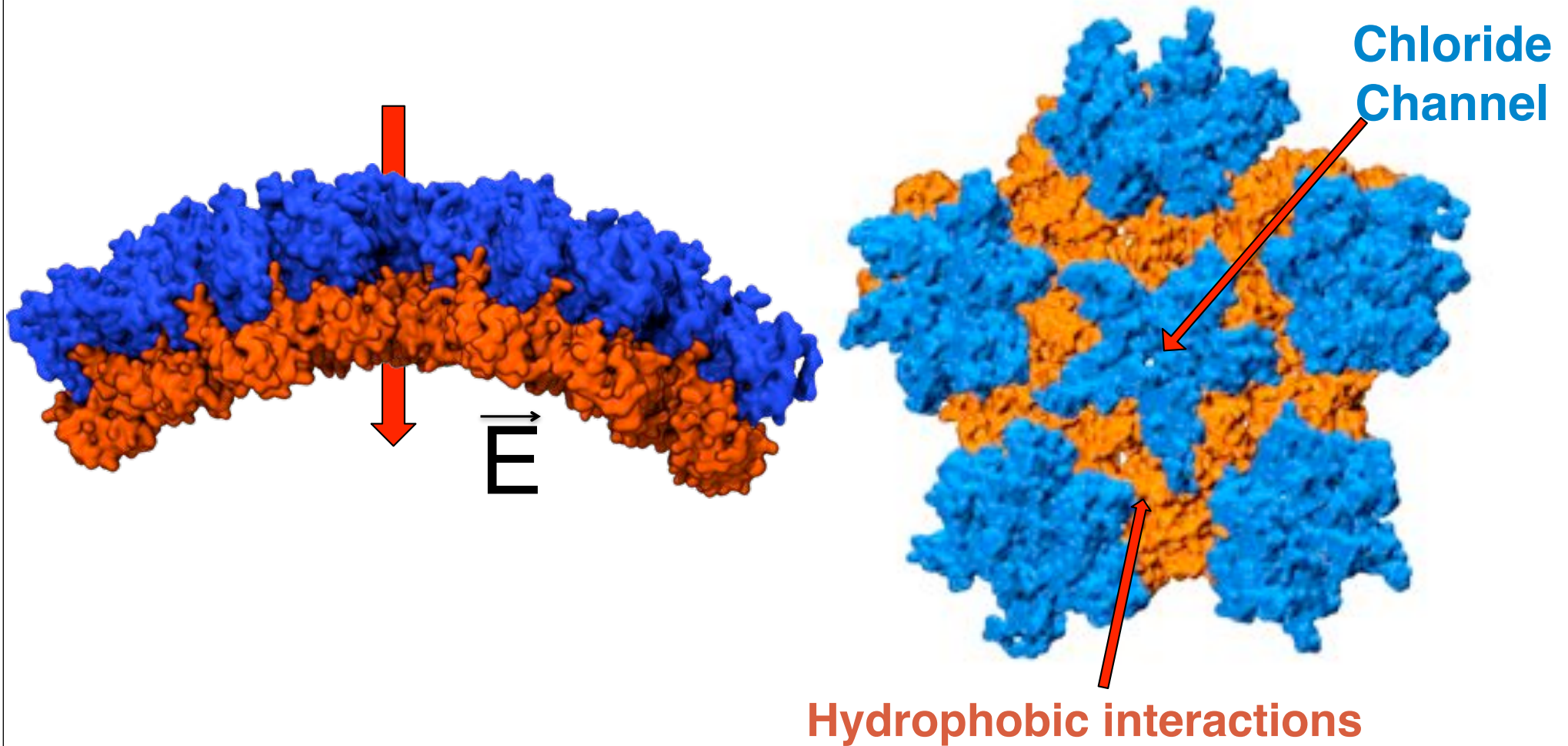
Blue Waters Simulation Results Guide Drug Development

Pfizer PF74 efficiently inhibits HIV-1 infection at an early step during infection.
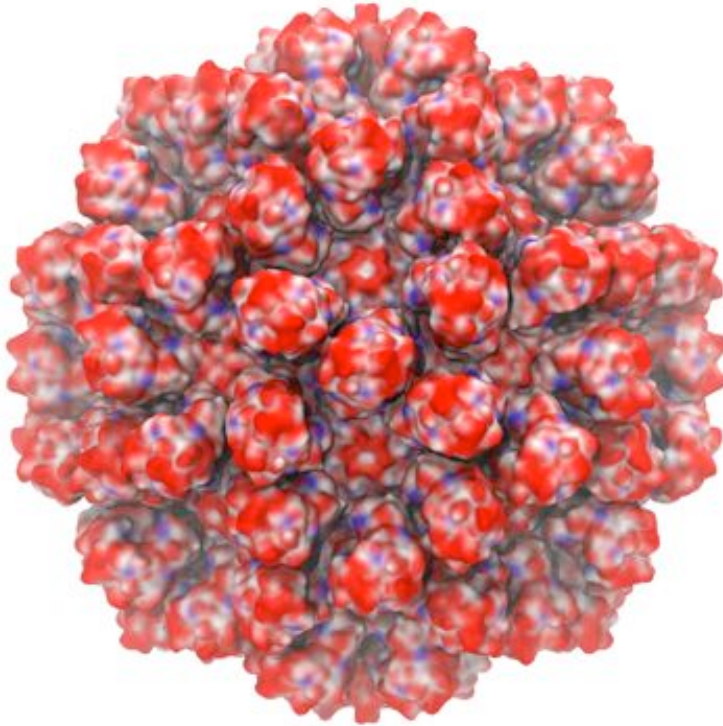

Pfizer's **PF74**
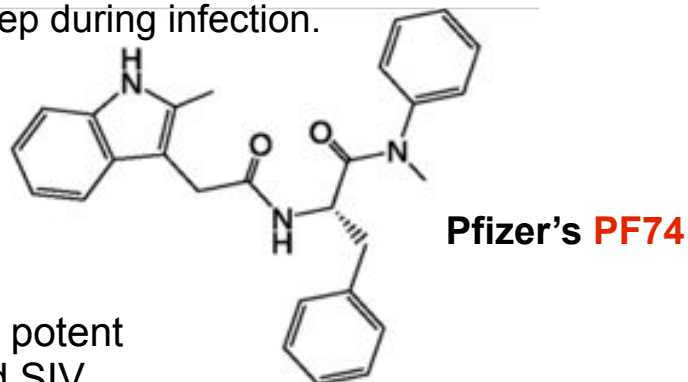
PF74 is a potent HIV-1 and SIV inhibitor

Wade Blair et al. PLoS Pathog 6: e1001220 (2010).   Computational modeling of PF74 bound to HIV-1 capsid.

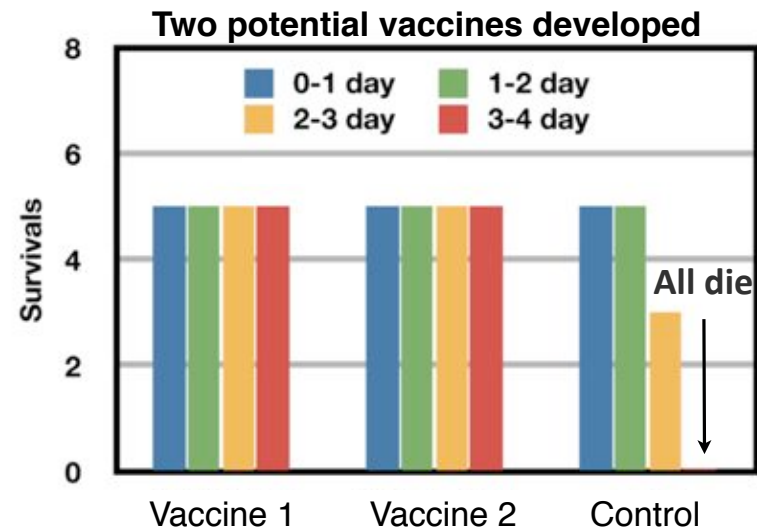# Blue Waters Helps Develop Vaccine for Rabbit Hemorrhagic Disease Virus

Rabbit Hemorrhagic Disease Virus Capsid
180 capid proteins, **10 million atoms**

Our first Blue Waters publication!
PLoS Pathogens (2013) 9(1): e1003132
Collaboration with Fei Sun (Chinese Academy of Sciences)

Two potential vaccines developed

- 0-1 day
- 1-2 day
- 2-3 day
- 3-4 day

All die

Vaccine 1   Vaccine 2   Control

- First reported in China in 1983

- 14 million domesticated rabbits died within 9 months
  - **huge** industrial loss

- Blue Waters simulations on Early Science System solved capsid structure, led to vaccine

- Closely related to porcine epidemic diarrhea virus in 2014 - can simulations lead to a new vaccine?

Blue Waters Investigates Microtubules Maintaining Cell Structure, Cell Division, and Intracellular Transport

The Human Protein Atlas Project
www.proteinatlas.org

10 µm
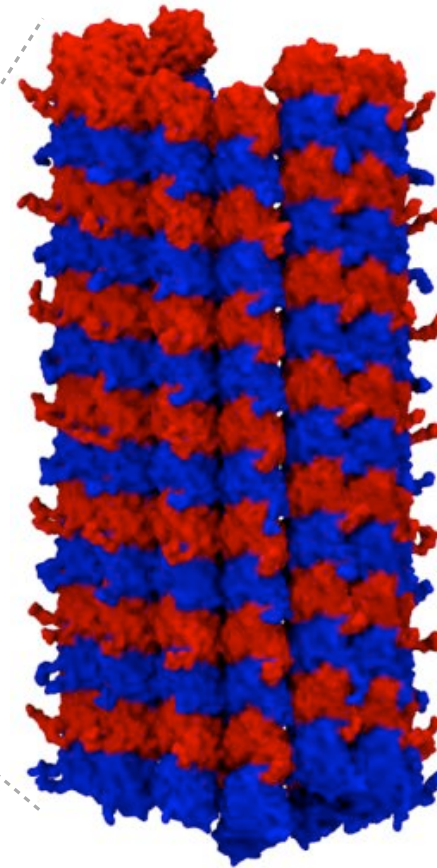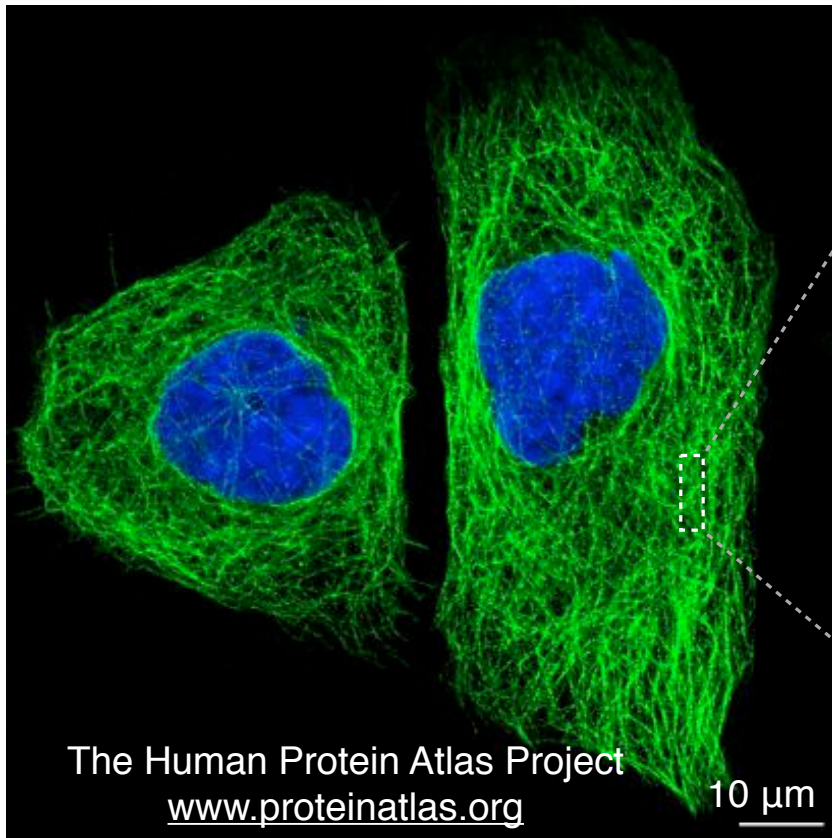
System:

Cytoskeleton

Question:

Microtubule Dynamic Instability:
How do microtubules switch between growth and shrinkage

Significance:

Cancer drugs are targeting microtubules.

microtubule segment

Stabilizing Effect of Microtubule Associated Proteins
- End Binding Protein and Kinesin

15 million atoms system

Microtubule

Microtubule + End binding protein

Microtubule + End binding protein + Kinesin
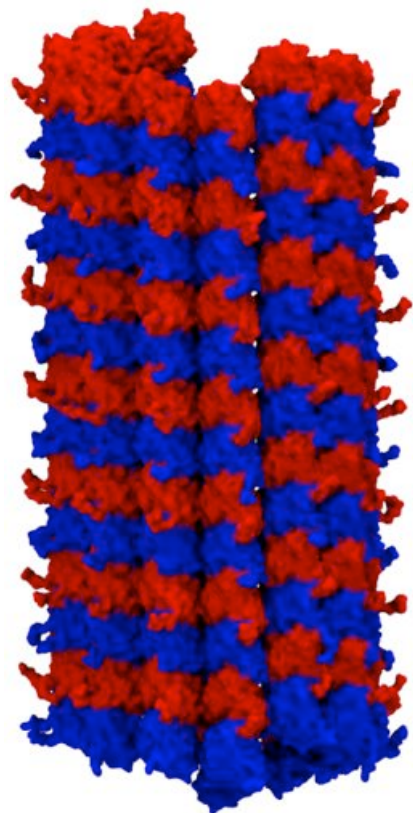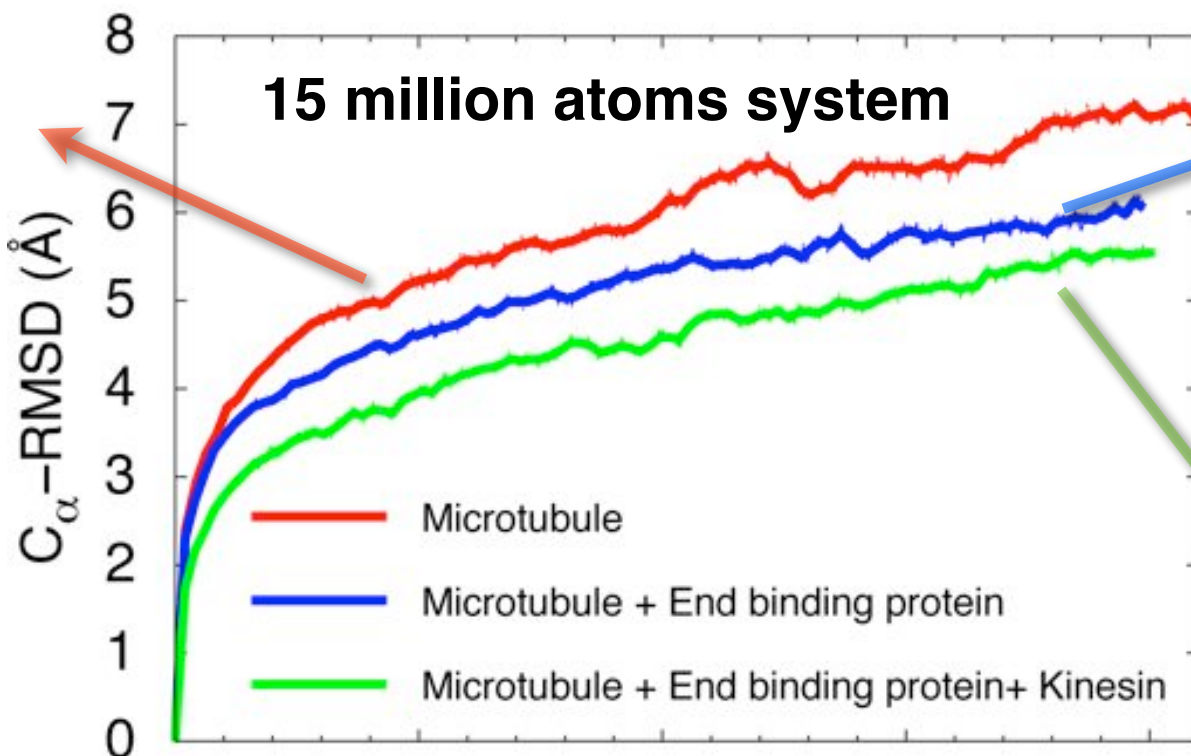
Microtubule

Why Blue Waters:

Investigating chemical details for a **huge** system

Microtubule "frozen" by anti-cancer drug (Taxol)
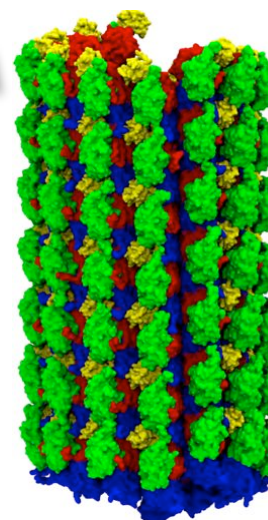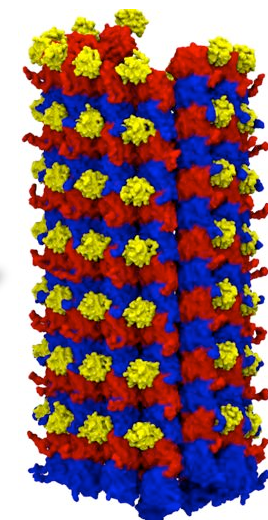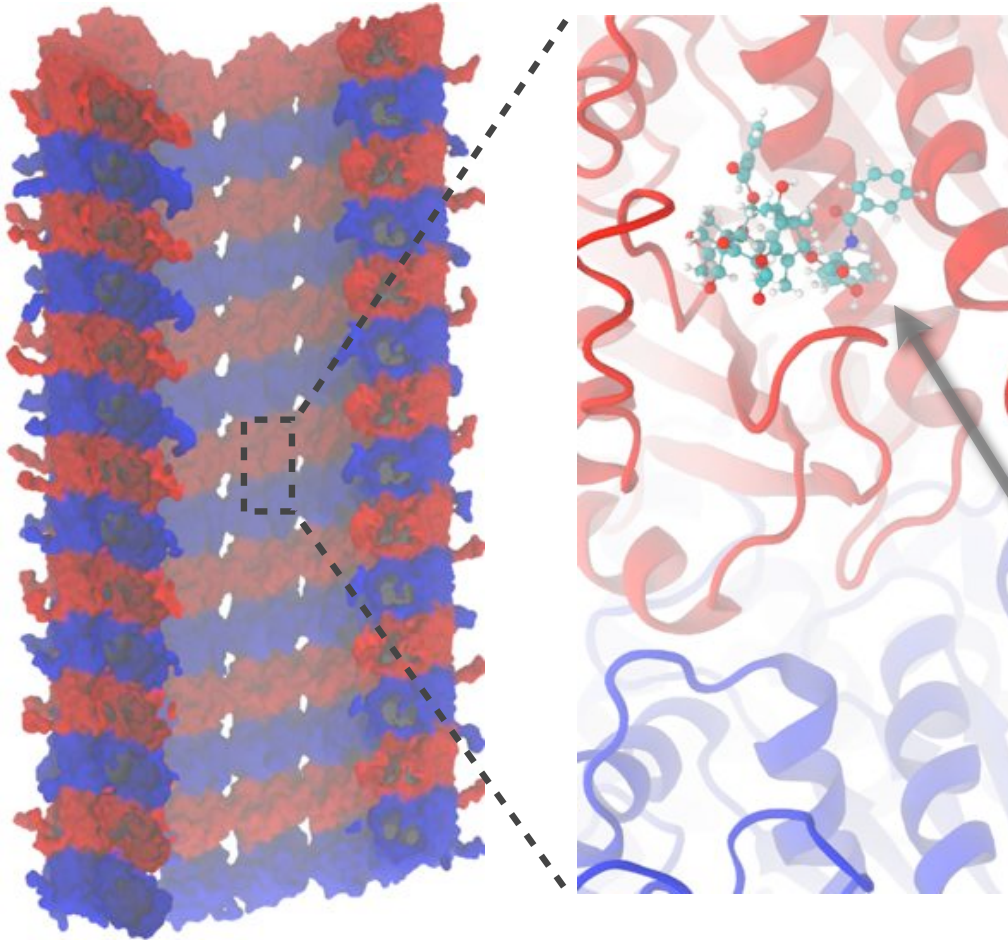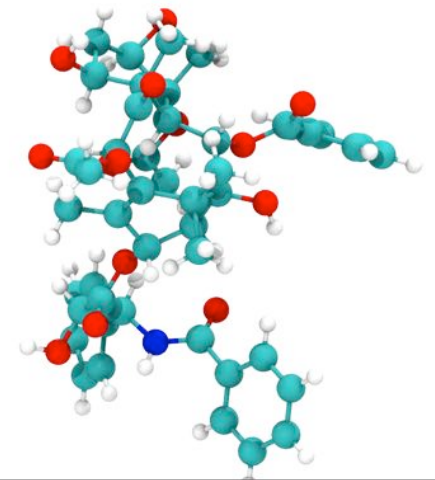
microtubule segment

Questions to answer with Blue Waters:

How does Taxol stabilize microtubules to kill cancer cells?
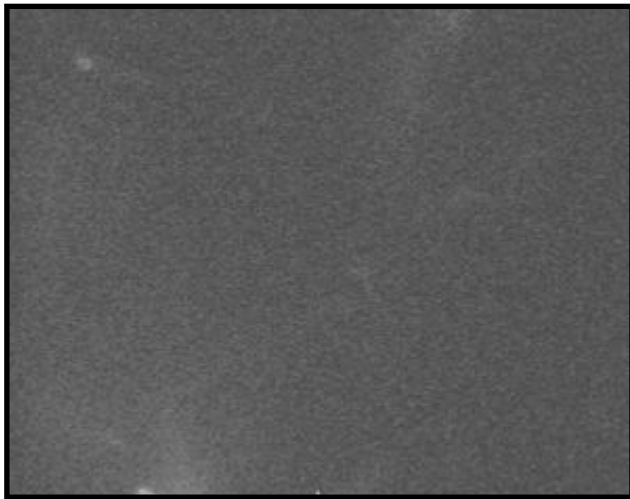
How do microtubules develop resistance to Taxol?

Could lead to development of new cancer drugs

Taxol →

Blue Waters Explores the Bacterial Brain

Bacteria use chemoreception to *decide* where to swim.

Free-swimming *E. coli*

Video: Berg, Howard (Harvard U.)
http://www.rowland.harvard.edu/labs/bacteria/movies/ecoli.php
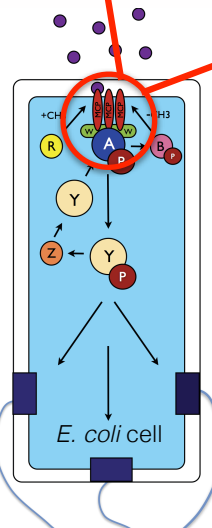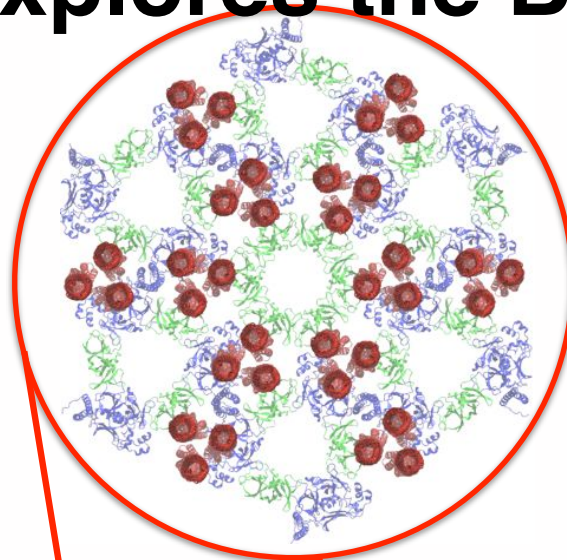
Thousands of proteins cluster to form the chemoreceptor array.

E. coli **chemotaxis protein network.**

E. coli cell

Significance

Central to understanding the fundamental molecular mechanism through which bacteria sense their environment and optimize their location.

Target for new antibiotics and fungicides

Why Blue Waters?

The Chemoreceptor array is a ***petascale*** system as the decision making emerges from the collective interactions of many proteins.

Chemoreceptor array. **100 million atoms**

Ribosome. ~3 million atoms

Blue Waters Assists Second-generation Biofuels Production

ENERGY BIOSCIENCES INSTITUTE.org

Second-generation biofuels
Uses agricultural waste: bagasse, corncob, woodchip, …

First-generation biofuels
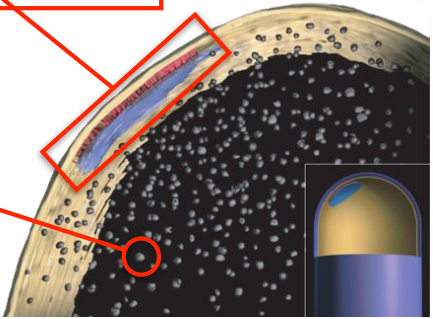Uses food sources as the carbohydrates monomers source

Enzymatic Degradation → Carbohydrates Monomers → Yeast Fermentation

Cellulosomes are highly efficient in biomass degradation.

Single Molecule Experiments:

AFM cantilever
PEG — CBM
Coh — Doc
XMod — Xyn
PEG — Glass surface

Force (pN): 600, 300, 0
Config. I
PEG Xylanase CBM
Complex rupture
1
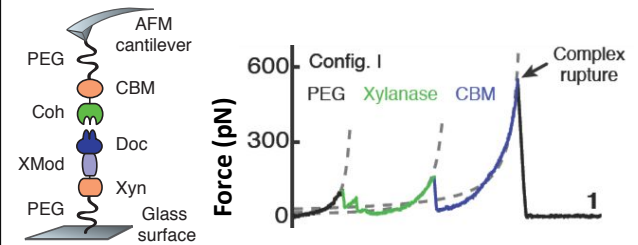
Combining Simulations and Experiments
we demonstrated Cellulosomes are built
from protein modules that adhere through
extremely strong complexes

1 scaffoldin
9 enzymes
SdbA   ClpA

13 million atoms

Blue Waters allowed us to build the First Complete Atomistic Cellulosome Model
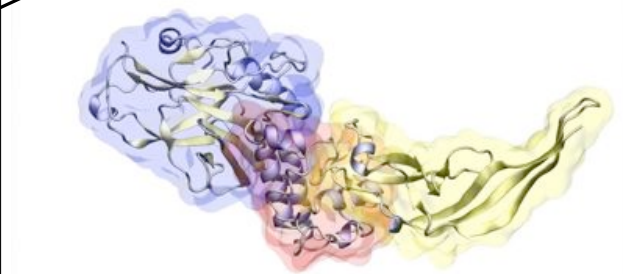
Cohesin : Dockerin - XMod

Large Memory Remote Visualization & Analysis Nodes Would Broaden User Base and Accelerate Discovery

Blue Waters Publications 2013-2014
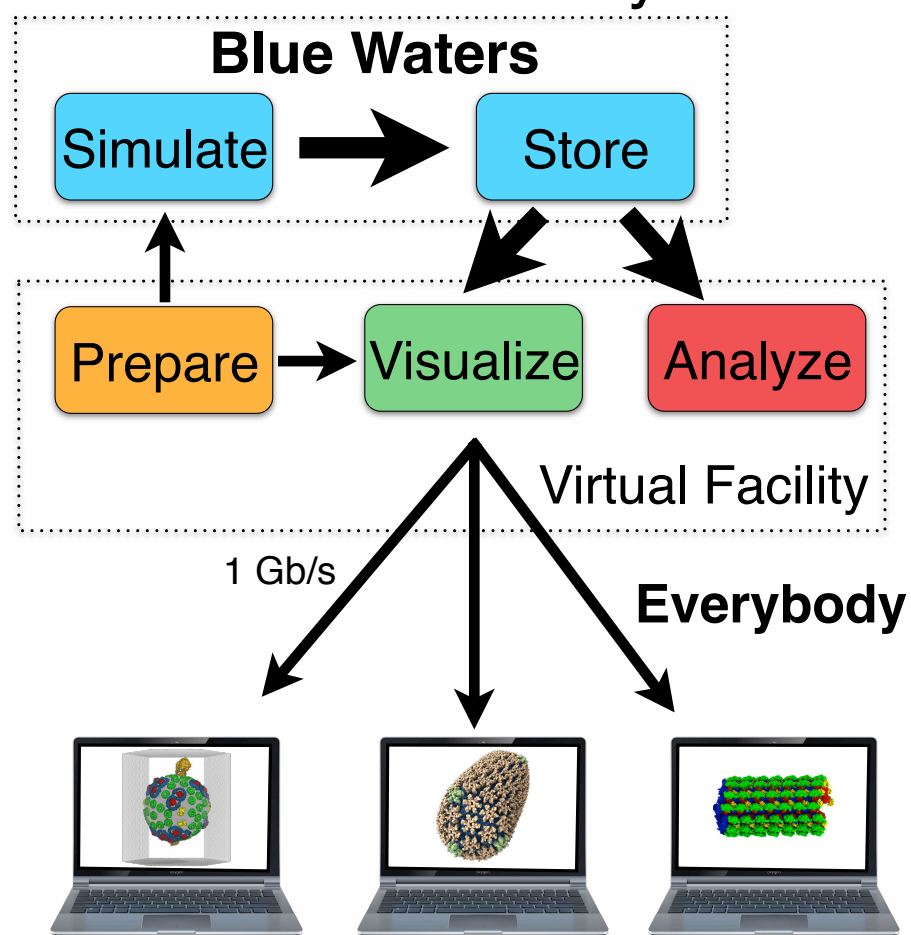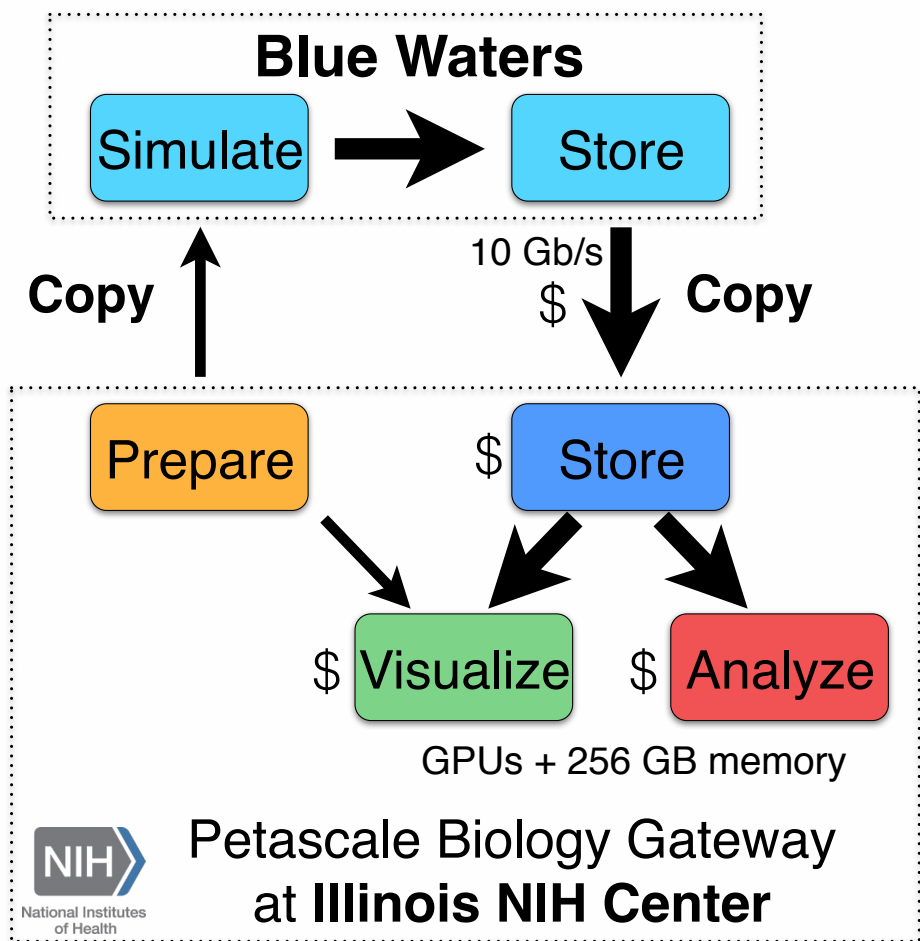
Atomic model of rabbit hemorrhagic disease virus by cryo-electron microscopy and crystallography. Xue Wang, Fengting Xu, Jiasen Liu, Bingquan Gao, Yanxin Liu, Yujia Zhai, Jun Ma, Kai Zhang, Timothy S. Baker, Klaus Schulten, Dong Zheng, Hai Pang, and Fei Sun. *PLoS Pathogens*, 9:e1003132, 2013.

Mature HIV-1 capsid structure by cryo-electron microscopy and all-atom molecular dynamics. Gongpu Zhao, Juan R. Perilla, Ernest L. Yufenyuy, Xin Meng, Bo Chen, Jiying Ning, Jinwoo Ahn, Angela M. Gronenborn, Klaus Schulten, Christopher Aiken, and Peijun Zhang. *Nature*, 497:643-646, 2013.

Early experiences scaling VMD molecular visualization and analysis jobs on Blue Waters. John E. Stone, Barry Isralewitz, and Klaus Schulten. *In Proceedings of the XSEDE Extreme Scaling Workshop*, 2013.

GPU-Accelerated Molecular Visualization on Petascale Supercomputing Platforms. John E. Stone, Kirby L. Vandivort, and Klaus Schulten. *In Proceedings of the 8th International Workshop on Ultrascale Visualization, UltraVis '13*, pp. 6:1-6:8, New York, NY, USA, 2013.
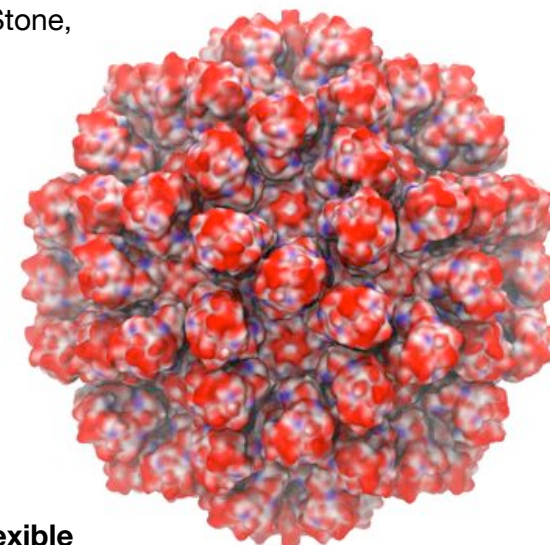
Assembly of Nsp1 nucleoporins provides insight into nuclear pore complex gating. Ramya Gamini, Wei Han, John E. Stone, and Klaus Schulten. *PLoS Computational Biology*, 10:e1003488, 2014.

Generalized scalable multiple copy algorithms for molecular dynamics simulations in NAMD. Wei Jiang, James Phillips, Lei Huang, Mikolai Fajer, Yilin Meng, James Gumbart, Yun Luo, Klaus Schulten, and Benoit Roux. *Computational Physics Communications*, 185:908-916, 2014.

GPU-Accelerated Analysis and Visualization of Large Structures Solved by Molecular Dynamics Flexible Fitting. John E. Stone, Ryan McGreevy, Barry Isralewitz, and Klaus Schulten. *Faraday Discussion 169*, 2014. In press. doi:10.1039/C4FD00005F.
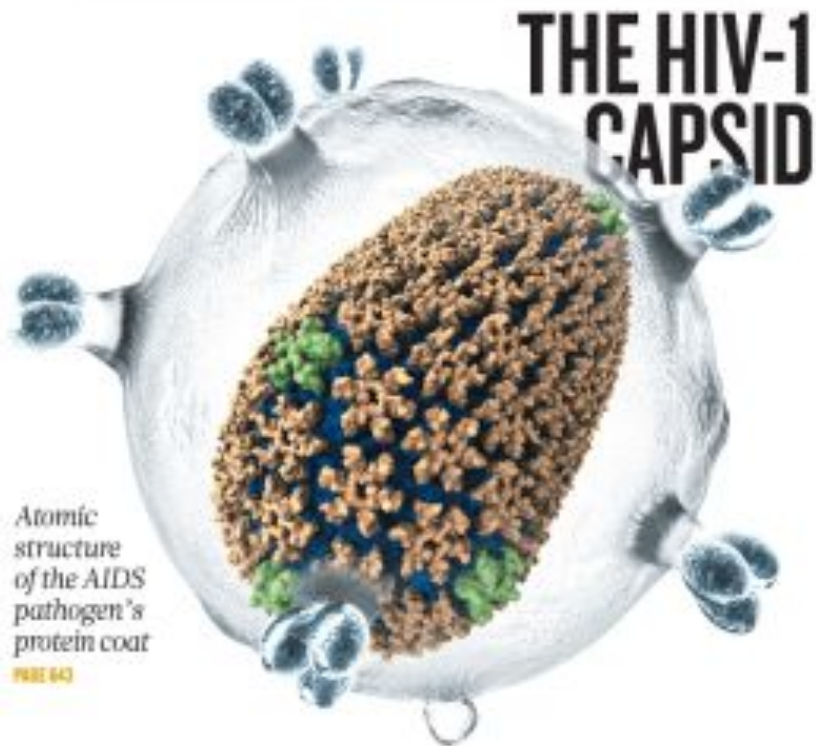
Light harvesting by lamellar chromatophores in Rhodospirillum photometricum. Danielle Chandler, Johan Strumpfer, Melih Sener, Simon Scheuring, and Klaus Schulten. *Biophysical Journal*, 2014. In press.

Unlocking the Full Potential of the Cray XK7 Accelerator. Mark D. Klein and John E. Stone. *Cray Users Group*, 2014. In press.

nature

THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

THE HIV-1 CAPSID

Atomic structure of the AIDS pathogen's protein coat

PAGE 643

NATURE.COM/NATURE

THE FIRST LIGHT
In pursuit of the most distant galaxies
PAGE 554

CROSSING THE BORDERS
International collaborations make the most impact
PAGE 557

A SITTING TARGET
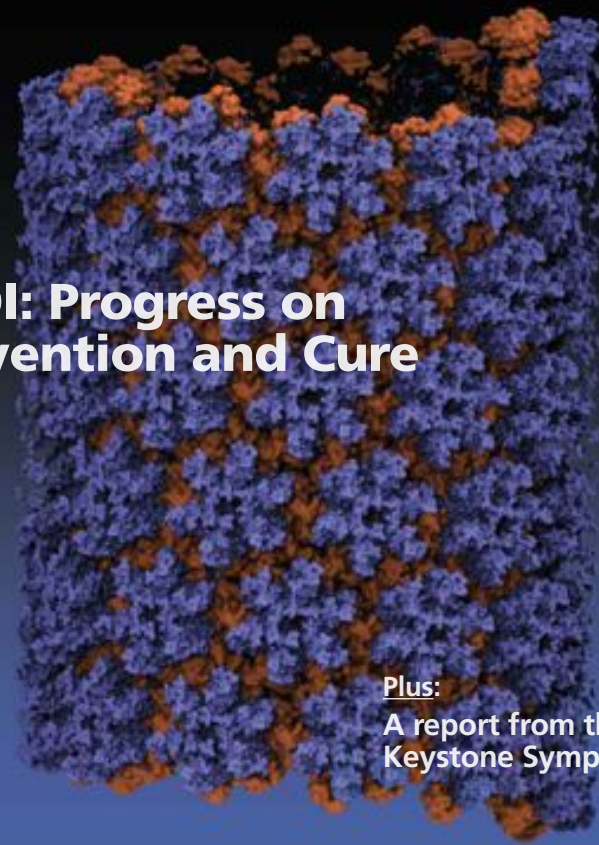An indirect hit on 'undruggable' KRAS proteins
PAGES 577 & 609
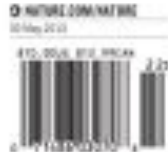
IAVIReport

The Publication on AIDS Vaccine Research

CROI: Progress on Prevention and Cure

Plus:

A report from the Keystone Symposium

Thank you NSF!

Thank you NCSA!

Very Large Biosystem Simulation Workshop

Topics Include:

Preparing Large-Scale Simulations

- Opportunities for Large System Simulations Today: Science, Software, Hardware
- Large System Assembly from Multi-Resolution Crystallographic and Cryo-EM Data
- Setting Up Large Simulations with VMD
- Running Large Simulations with NAMD

Building Multi-Protein Complexes

- Determining Large Structures through Hybrid Methods using Molecular Dynamics Flexible Fitting
- Preparing Large-Scale Simulations: Membrane Modeling

Analysis of Multi-Protein Complexes

- NAMD Tuning on Petascale Supercomputers
- Analyzing Large Scale Simulations: Electrostatics, Interaction Energies, Radial Distribution, Solvent Accessible Surface Area, Contacts, Principle Component Analysis
- Hands-on Training: Analyzing Large Scale Simulations with VMD

Beckman Institute
August 11-15, 2014
Application deadline: July 23, 2014
http://www.ks.uiuc.edu/Training/Workshop/vlss/

Very Large System Simulation Workshop
Beckman Institute, Urbana, Illinois
August 11-15, 2014
Now Enrolling! Apply Today!