

NAMD - An Exploring Tool

20 years of computer science innovation and collaboration

1993: HP workstation cluster
1994: Writing NAMD in C++
1998: Commodity Linux clusters
2002: Parallel on 3000 cores, 10^5 atoms
2007: Graphics processors (GPUs)
2013: Petascale supercomputers

Enabling ground-breaking simulations on the world's most powerful computers

Integrating experimental data
Scriptable steering and analysis
Free energy calculations
Multiple-copy algorithms
Hundreds of millions of atoms

Phillips et al., *J. Comp. Chem.* **26**, 1781 (2005)

HIV (2013)



Cadherin (2005)



Serving 70,000 users on affordable hardware

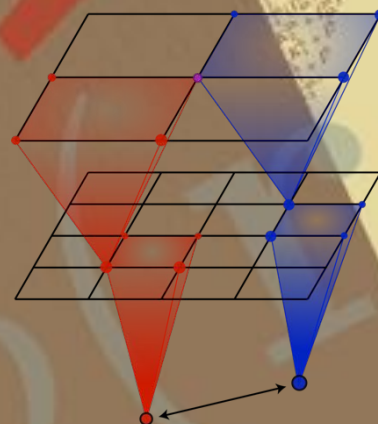
Evolution of computer hardware requires continual algorithmic development...

...over 50 method papers 1995-2014

Multilevel Summation Method

- faster calculation of electrostatic forces
- accelerated using GPUs

D. Hardy, et al., *J. Chem. Theory Comput.* In press. (2015)



: **VMD**

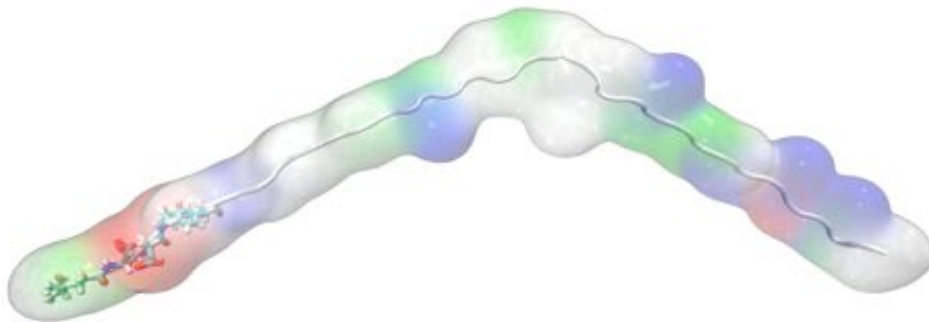
Key person
John Stone
(UIUC)



video: www.lundbeckfoundation.com

VMD: A Thinking Tool

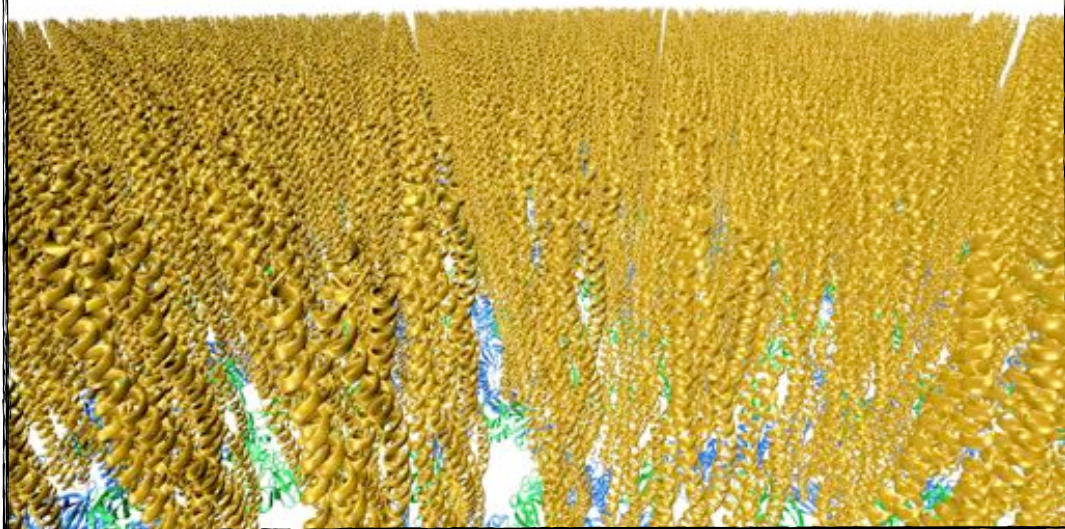
to visualize and analyze trajectories



from small peptides...

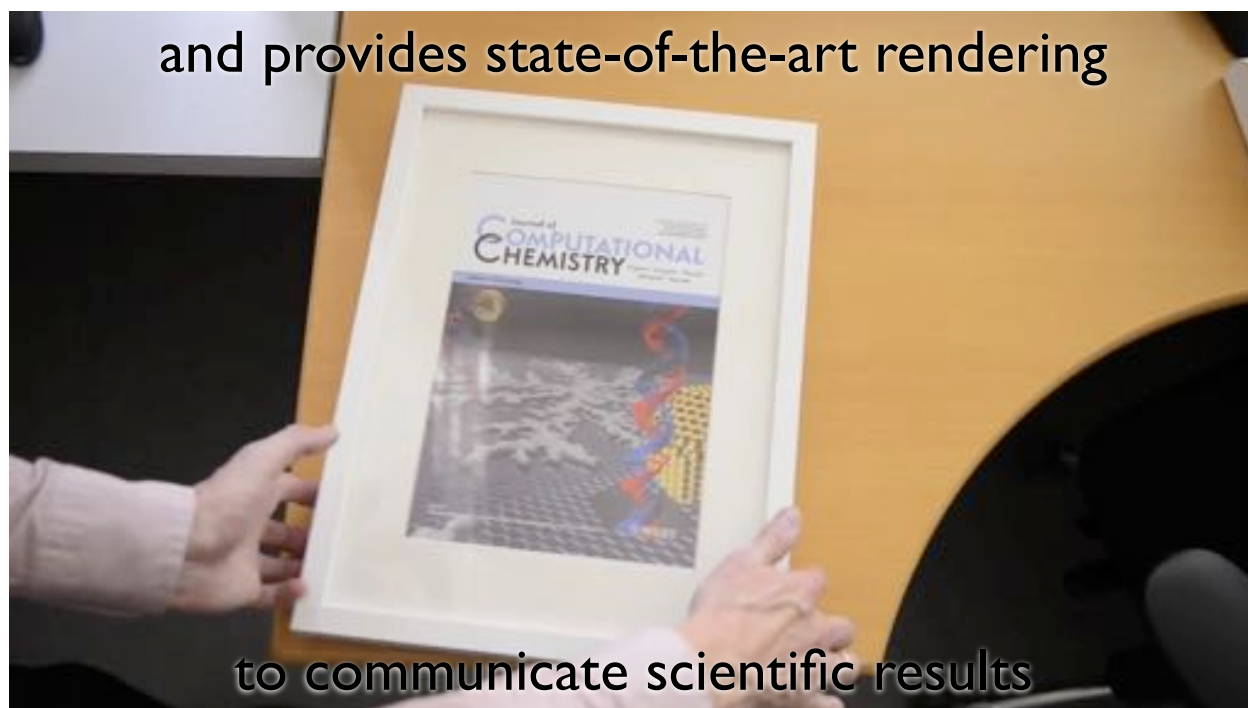
VMD: A Thinking Tool

...to extremely large biological structures



VMD: A Thinking Tool

and provides state-of-the-art rendering



to communicate scientific results

video: www.lundbeckfoundation.com

VMD Plugins

Advanced Tools developed **In-House** and by **External Users**

Analysis

APBSRun
CatDCD
Contact Map
GofRGUI
HeatMapper
ILSTools
IRSpecGUI
MultiSeq
NAMDEnergy
NAMDPLOT
NetworkView
NMWiz
ParseFEP
PBCTools
PMEpot
PropKa GUI
RamaPlot
RMSD Tool
RMSD Trajectory Tool
RMSD Visualizer Tool
Salt Bridges
Sequence Viewer
Symmetry Tool
Timeline
VolMap

Modeling

Autonize
AutoPSF
Chirality
Cionize
Cispeptide
CGTools
Dowser
Force Field Toolkit
Inorganic Builder
MDFF
Membrane
Merge Structs
Molefacture
Mutator
Nanotube
Paratool
Psfgen
RESPTool
RNAView
Solvate
SSRstraints
Topotools

Visualization

Clipping Plane Tool
Clone Rep
DemoMaster
Dipole Watcher
Intersurf
Navigate
NavFly
MultiMolAnim
Color Scale Bar
Remote
Palette Tool
ViewChangeRender
ViewMaster
Virtual DNA Viewer
VMD Movie Maker

Simulation

AutoIMD
IMDMenu
NAMD GUI
NAMD Server
QMTTool

Collaboration

BioCoRE Chat
BioCoRE Login
BioCoRE VMD Shared Views
Remote Control

Data Import and Plotting

Data Import
Multiplot
PDBTool
MultiTex

MolFile I/O Plugins

Externally Hosted Plugins

Check sidechains
MultiMSMS
Interactive Essential Dynamics
Mead Ionize
Clustering Tool
iTrajComp
Swap RMSD
Intervor
SurfVol
vmdlCE

VMD Plugins

Advanced Tools developed **In-House** and by **External Users**

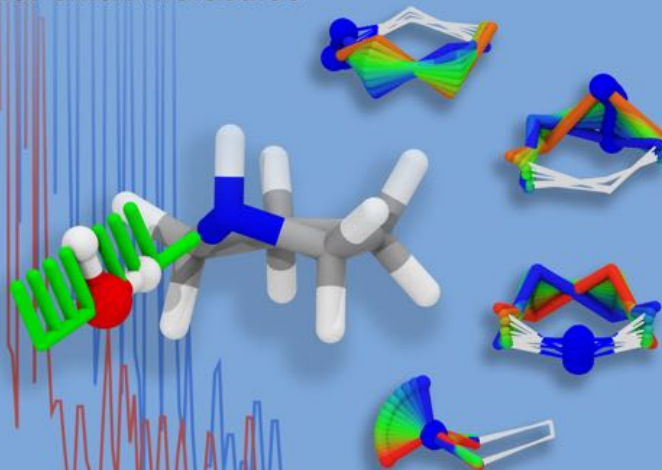
Analysis

APBSRun
CatDCD
Contact Map
GofRGUI
HeatMapper
ILSTools
IRSpecGUI
MultiSeq
NAMDEnergy
NAMDPLOT
NetworkView
NMWiz
ParseFEP
PBCTools
PMEpot
PropKa GUI
RamaPlot
RMSD Tool
RMSD Trajectory Tool
RMSD Visualizer Tool
Salt Bridges
Sequence Viewer
Symmetry Tool
Timeline
VolMap



Dowser
Force Field Toolkit
Inorganic Builder
MDFF
Membrane
Merge Structs
Molefacture
Mutator
Nanotube
Paratool
Psfgen
RESPTool
RNAView
Solvate
SSRstraints
Topotools

Tool to compute force field parameters for small molecules



J. Comput. Chem. **2013**, 34, 2757-2770.

List of Top-Ten Most Accessed Articles for 2014

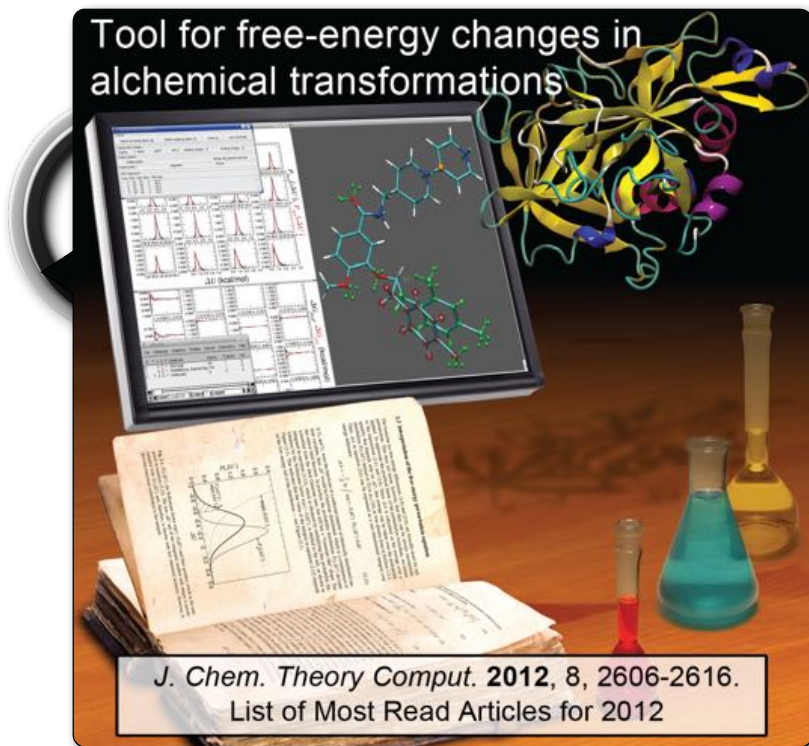
VMD Plugins

Advanced Tools developed In-House and by **External Users**

Analysis

- APBSRun
- CatDCD
- Contact Map
- GofRGUI
- HeatMapper
- ILSTools
- IRSpecGUI
- MultiSeq
- NAMD Energy
- NAMD Plot
- NetworkView
- NMWiz
- ParseFEP
- PBCTools
- PMEpot
- PropKa GUI
- RamaPlot
- RMSD Tool
- RMSD Trajectory Tool
- RMSD Visualizer Tool
- Salt Bridges
- Sequence Viewer
- Symmetry Tool
- Timeline
- VollMap

Tool for free-energy changes in alchemical transformations



Plotting

ns

Plugins

VMD Plugins

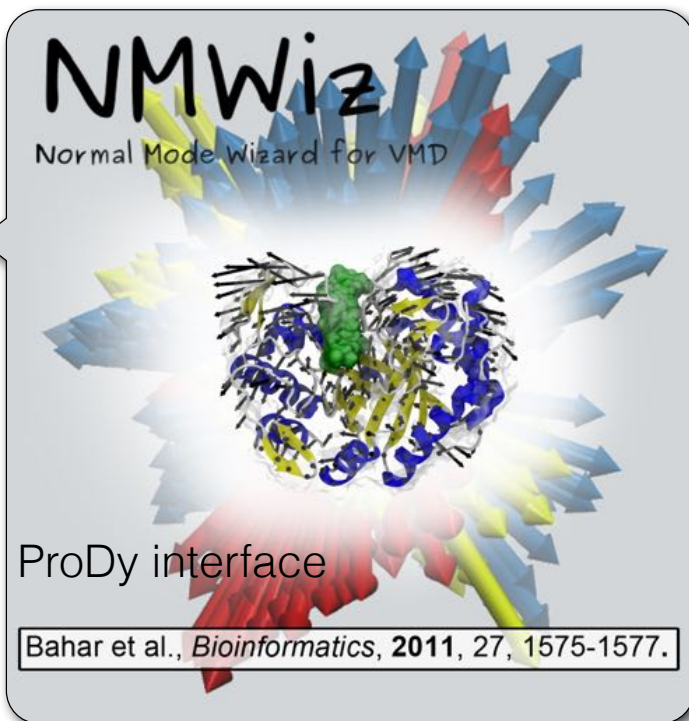
Advanced Tools developed In-House and by **External Users**

Analysis

- APBSRun
- CatDCD
- Contact Map
- GofRGUI
- HeatMapper
- ILSTools
- NMWiz
- ParseFEP
- PBCTool
- RMSD Visualizer Tool
- Salt Bridges
- Sequence Viewer
- Symmetry Tool
- Timeline
- VollMap



NMWiz
Normal Mode Wizard for VMD



ews

and Plotting

Plugins

osted Plugins

omics

ProDy interface

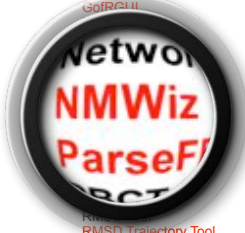
Bahar et al., *Bioinformatics*, 2011, 27, 1575-1577.

VMD Plugins

Advanced Tools developed **In-House** and by **External Users**

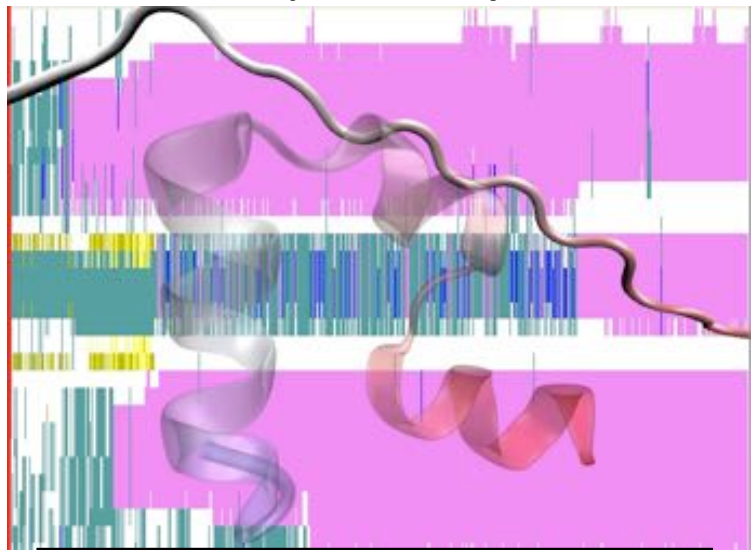
Analysis

- APBSRun
- CaDCD
- Contact Map
- GoRGUI



- RMSD Trajectory Tool
- RMSD Visualizer Tool
- Salt Bridges
- Sequence Viewer
- Symmetry Tool
- Timeline
- VollMap

A tool to identify events in molecular dynamics trajectories



Plotting

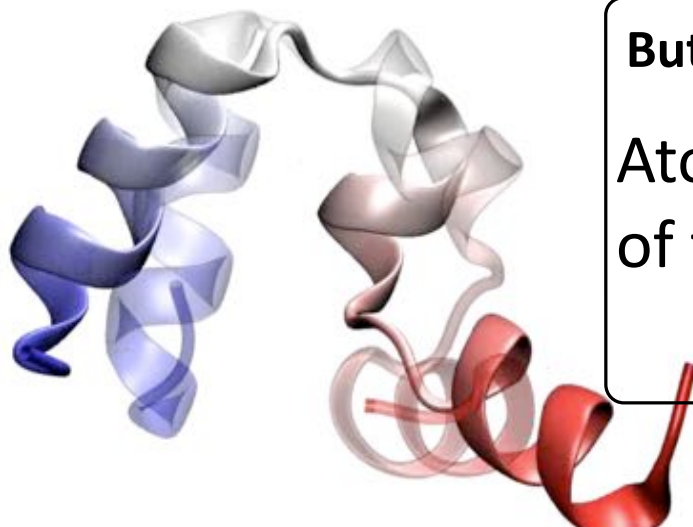
Plugins

Extreme Scaling Workshop, 2013, 43-50.

MD simulations can now fold proteins

Schulten et al. *Nature Physics* **6**: 751, 2010; Pande et al *JACS* **133**:664, 2011; Shaw et al *Science* **334**:517, 2011

Villin Headpiece
(26 a.a.)



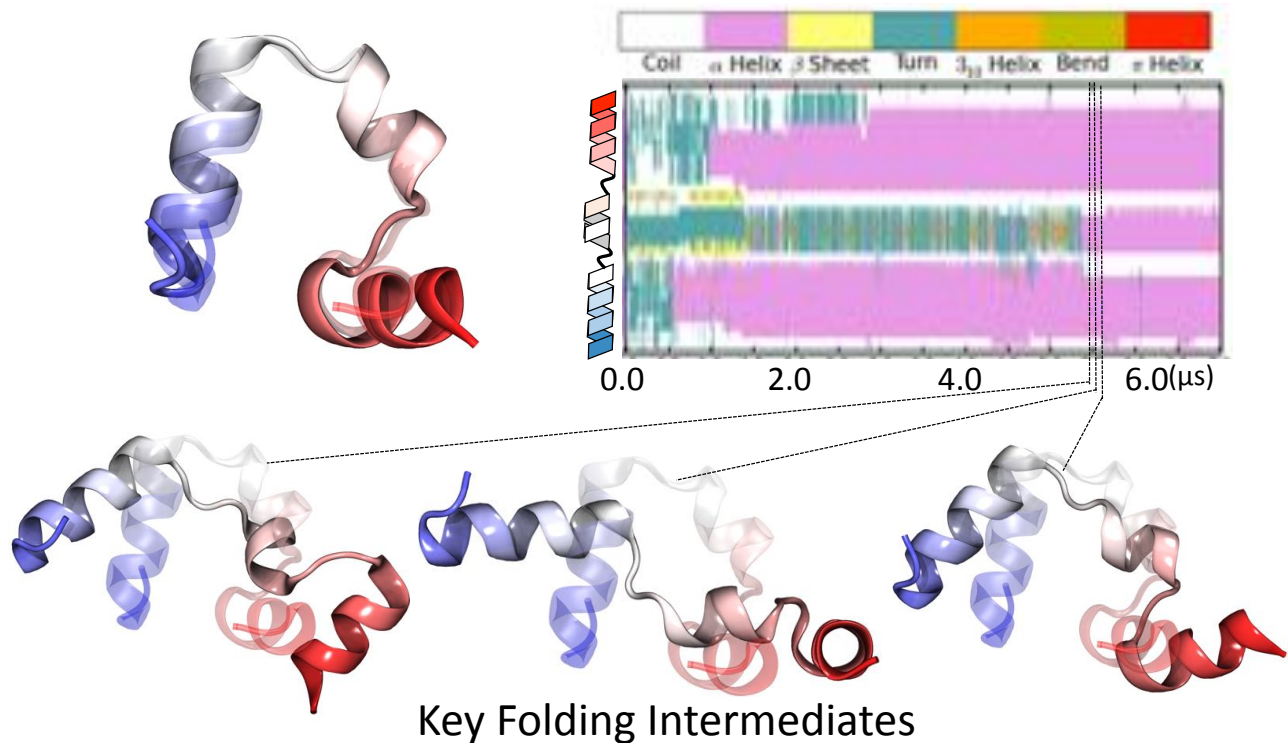
But what do we learn?
Atomic-level detail
of folding dynamics

Key person
Peter Freddolino
(now U. Michigan)

Folding Dynamics of Villin Headpiece Unveiled

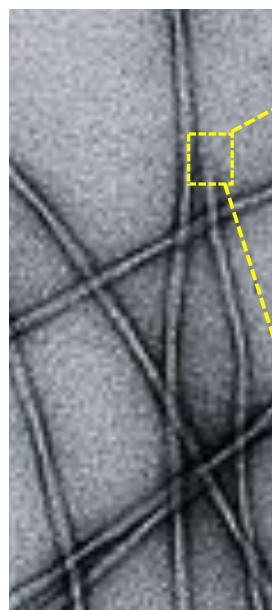
MD simulations explored key folding transitions not seen before

Schulten et al. *Biophys J* **94**:L75, 2008, **97**: 2009



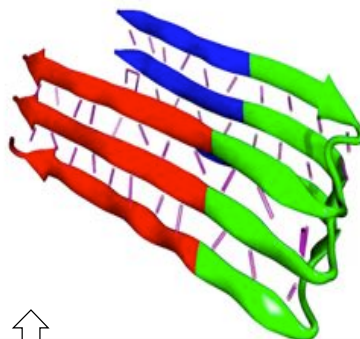
Folding Simulations (1.3 ms) Unravel Growth Mechanism of Disease Causative Amyloid

Wei Han and Schulten *JACS*, 136:12450-12460, 2014



EM Image
Amyloid- β Fibril

“+” Tip



“-” Tip

What do we learn?

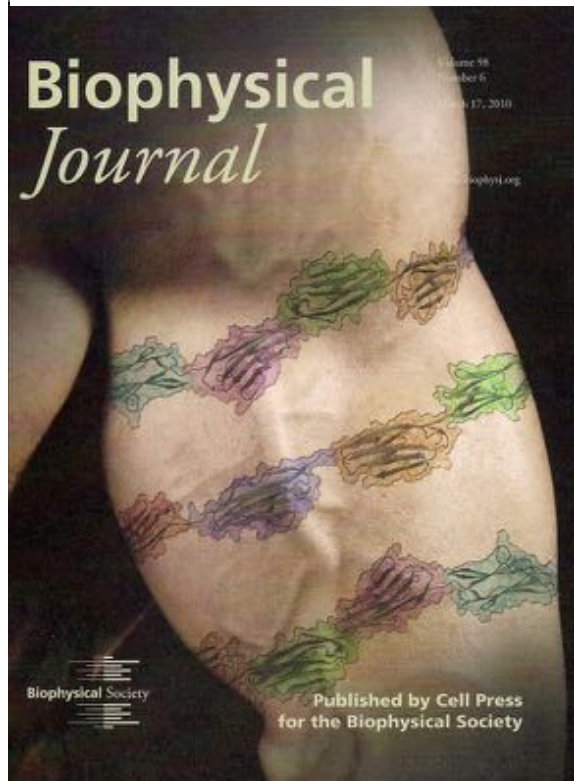
Similar affinity to both tips

Faster kinetics at “+” tip

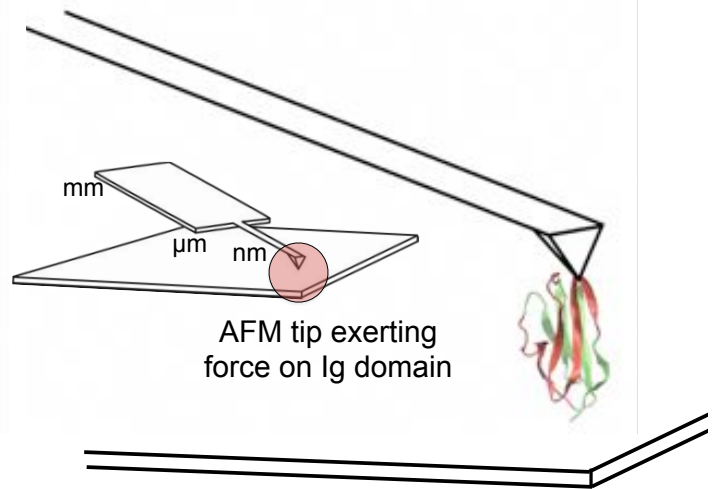
“+” tip catalyzes structural change of monomer

Reconstructed from **1.3 millisecond** atomic/coarse-grained simulations using the PACE force field.

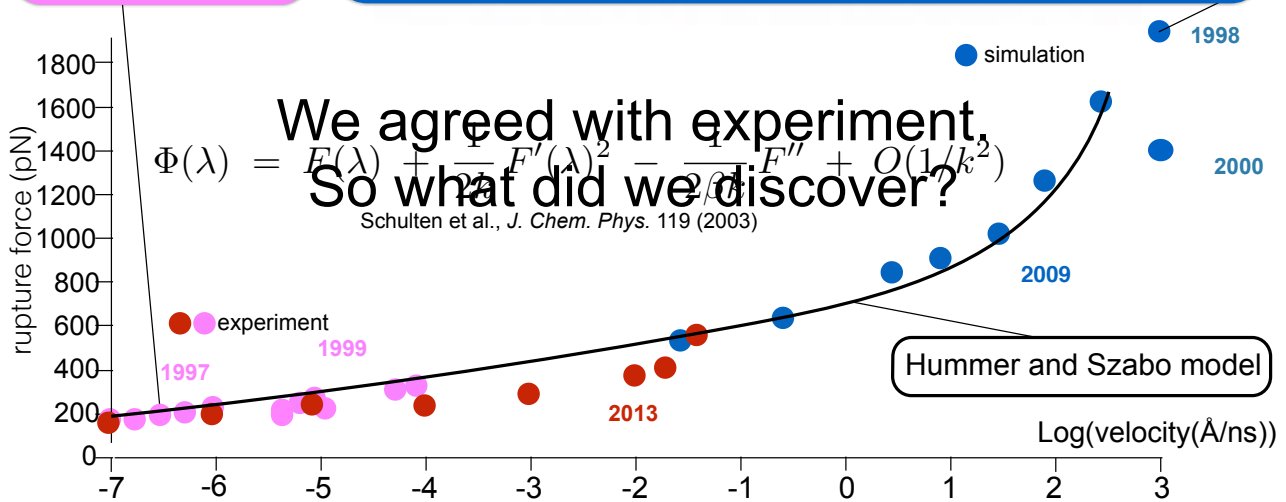
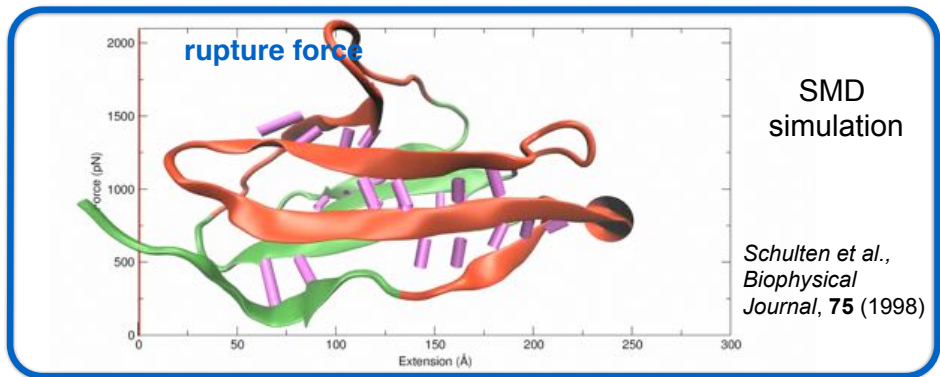
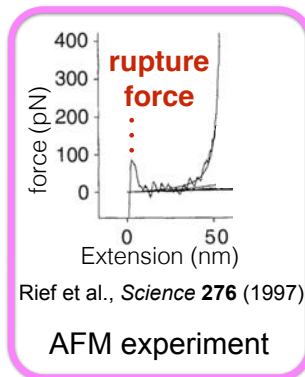
Forced Unfolding of Titin Ig Domain



Titin =
muscle's
third protein

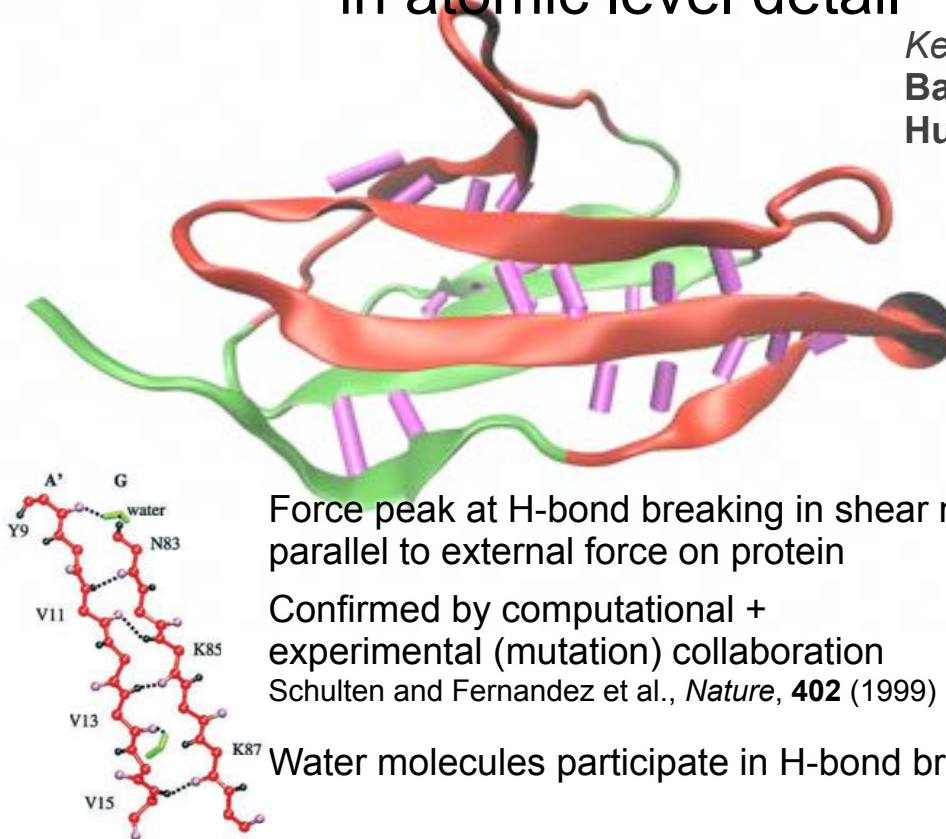


Forced Unfolding of Titin Ig Domain



Our simulation revealed the unfolding process in atomic level detail

Key persons
Barry Izralev (UIUC)
Hui Lu (now UIC)



Force peak at H-bond breaking in shear mode, in parallel to external force on protein

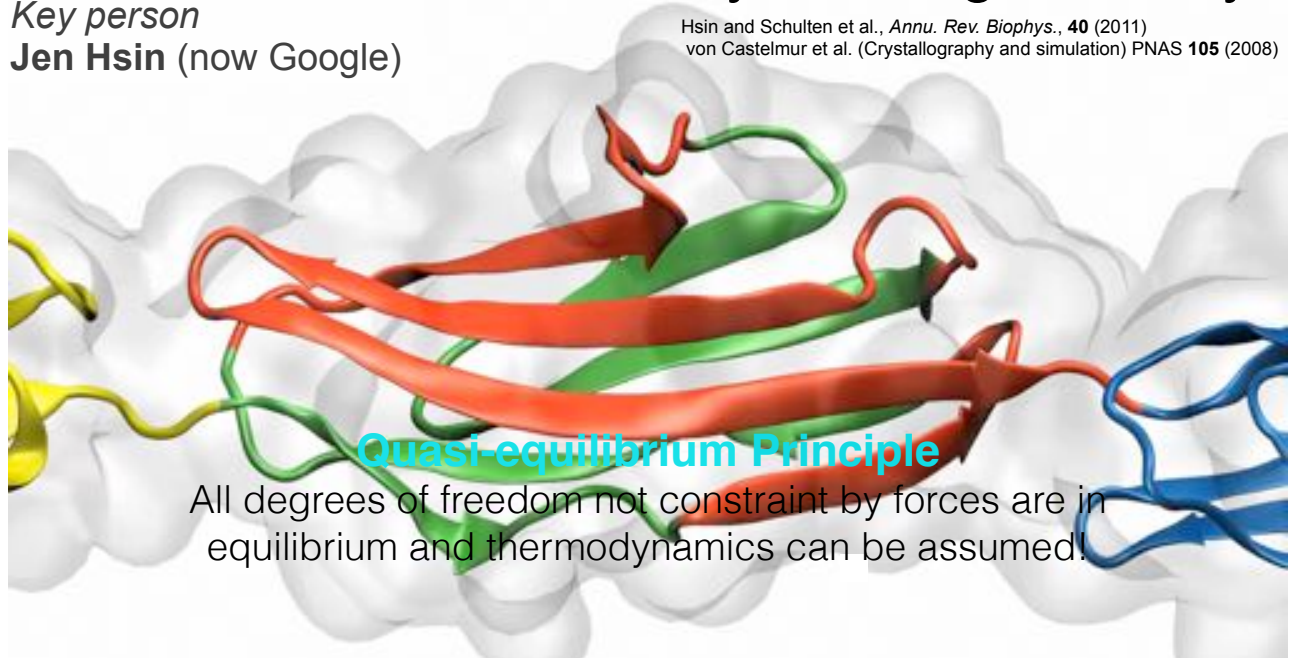
Confirmed by computational + experimental (mutation) collaboration
 Schulten and Fernandez et al., *Nature*, **402** (1999)

Water molecules participate in H-bond breaking

From one domain to many: multi-Ig elasticity

Key person
Jen Hsin (now Google)

Hsin and Schulten et al., *Annu. Rev. Biophys.*, **40** (2011)
 von Castelmur et al. (Crystallography and simulation) *PNAS* **105** (2008)



Quasi-equilibrium Principle

All degrees of freedom not constraint by forces are in equilibrium and thermodynamics can be assumed!

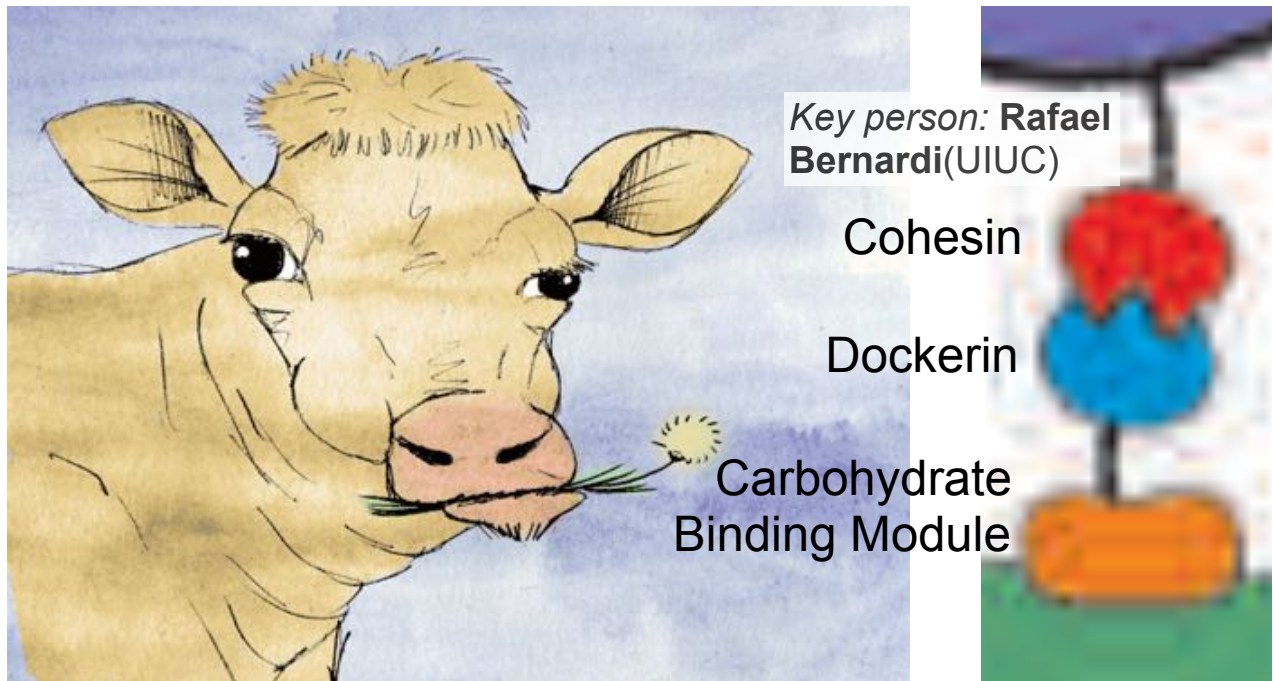
$$\text{Extension} = \sum_j \langle x_j \exp[f x_j / k_B T] \rangle_{V_j} / \langle \exp[f x_j / k_B T] \rangle_{V_j} = g(f)$$

Crystallography and simulation with 3000 investigations into how the system functions.
 We look at six domains.

$$\text{Force} = g^{-1}(\text{Extension})$$

Ultrastable Biomass Adhesion Complex

Single Molecule AFM and Steered Molecular Dynamics (SMD) combined to detail Bacterium-Biomass Adhesion Complex

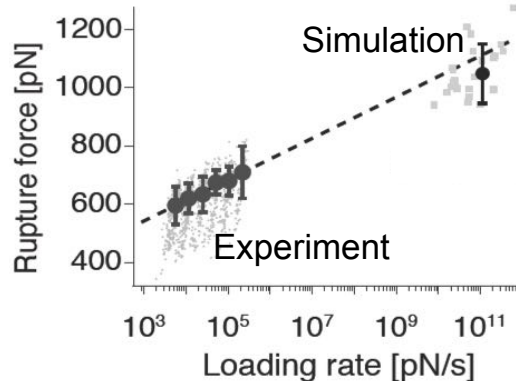


Challenging environments guided nature in the development of ultrastable protein complexes

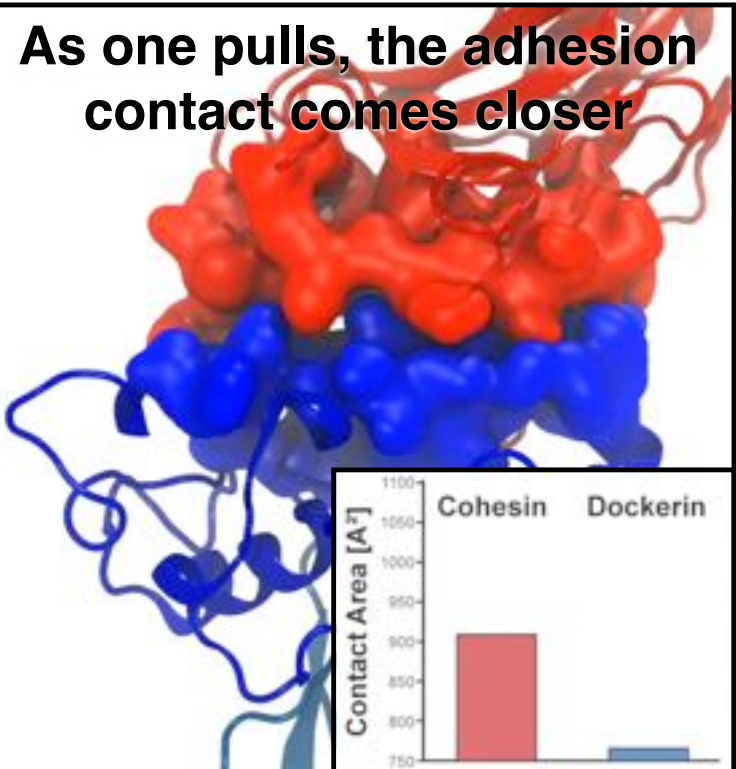
Strongest Measured Adhesion Bond

Adhesion becomes stronger when force is applied

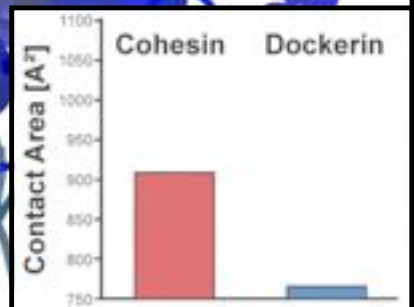
Collaboration w/ **Hermann Gaub** (Munich)
Nat. Commun. **5**, 5635 (2014)



As one pulls, the adhesion contact comes closer



Cohesin
Dockerin



From the Strongest to the Softest

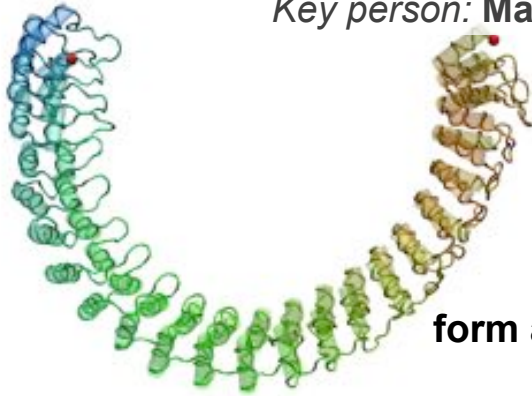
Ankyrin are very common protein motifs related to mechano-gating

PREDICTIONS FROM SIMULATIONS

Spring constant ~ 5 mN/m
 340,000 atoms – 20 nanoseconds
 M. Sotomayor, et. al. , *Structure* 13, 669 (2005)

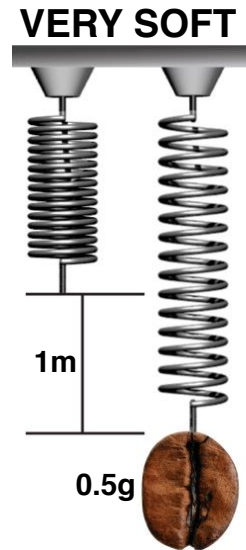
AFM MEASUREMENTS

Spring constant ~ 2.4 mN/m
 G. Lee, et. al. , *Nature* 440, 246 (2006)



Key person: Marcos Sotomayor (now OSU)

Ankyrin repeats
 form an extremely soft spring

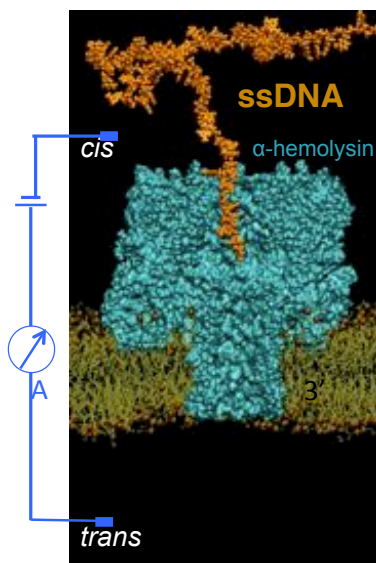


Ankyrin activates mechano-gating of TRPN1 channels
 for hearing and touch in flies

A spring characterized by the
 constant of 5mN/m is stretched
 1m with by a 0.5g weight.

Simulations Assist in the Design of Nanopore Devices for DNA Sensing

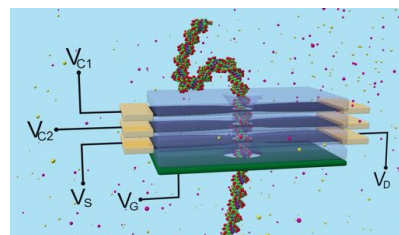
Protein Nanopore Conducts ssDNA



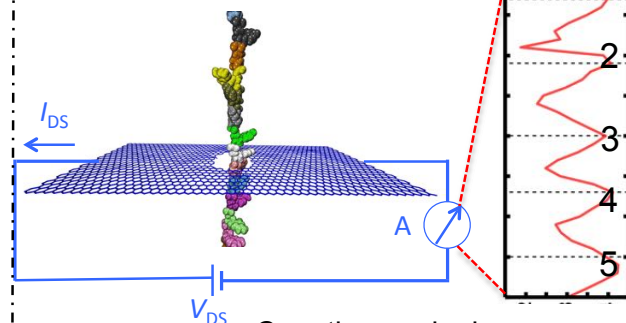
Klaus
 asks
 Amit
 Meller:
 Can I
 simulate
 for you?

Amit Meller tests Klaus:
 Which end threads faster,
 3' or 5'?

Graphene Nanopore Sensing Device



MD simulations combined with
 quantum mechanics calculations

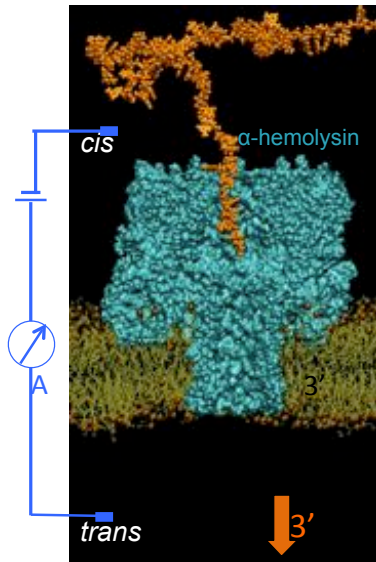


Counting nucleobases

A. Girdhar, C. Sathe, K. Schulten, J.-P. Leburton,
Nanotechnology, in press (2015)

Simulations Assist in the Design of Nanopore Devices for DNA Sensing

Protein Nanopore Conducts ssDNA

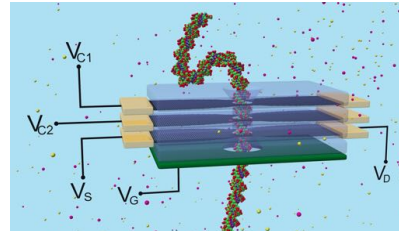


Key person:
Aleksei Aksimentiev
(UIUC)

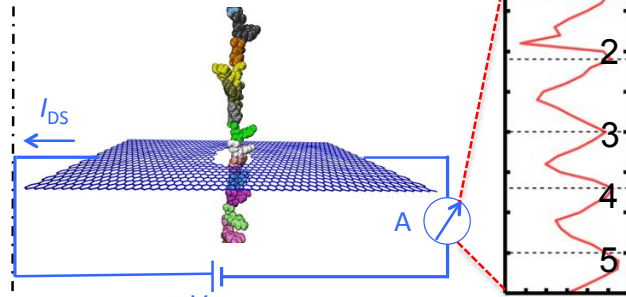
Klaus:
(after 3 weeks)
Faster when 3' enters first!

Amit: Yes, yes!
But why? But why?

Graphene Nanopore Sensing Device



MD simulations combined with quantum mechanics calculations

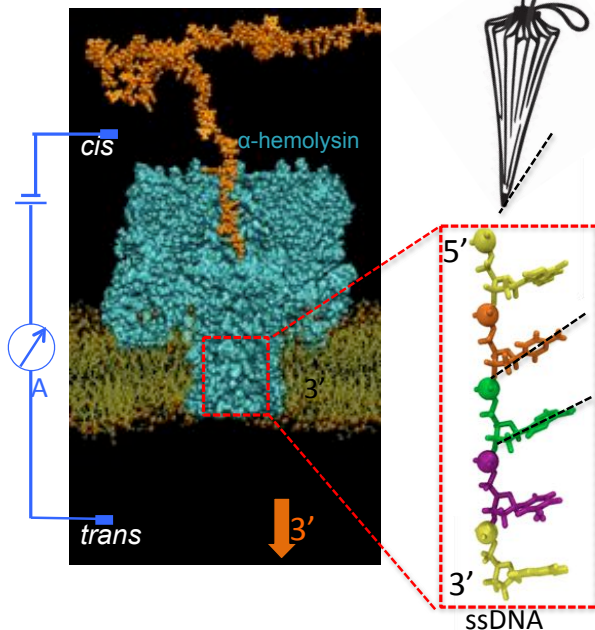


Counting nucleobases

A. Girdhar, C. Sathe, K. Schulten, J.-P. Leburton, *Nanotechnology*, in press (2015)

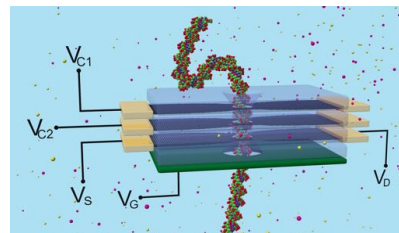
Simulations Assist in the Design of Nanopore Devices for DNA Sensing

J. Mathé, A. Aksimentiev, D. R. Nelson, K. Schulten, A. Meller. *Proc. Natl. Acad. Sci. U.S.A.* **102**, 12377 (2005)

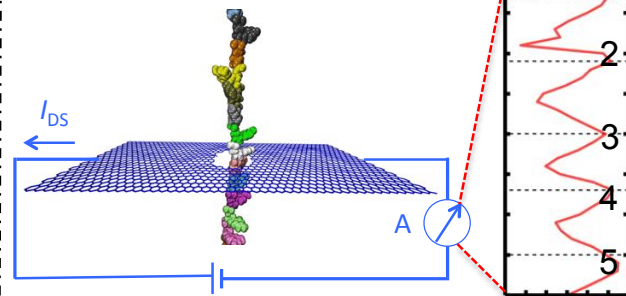


ssDNA bases get tilted one way in narrow pore!

Graphene Nanopore Sensing Device



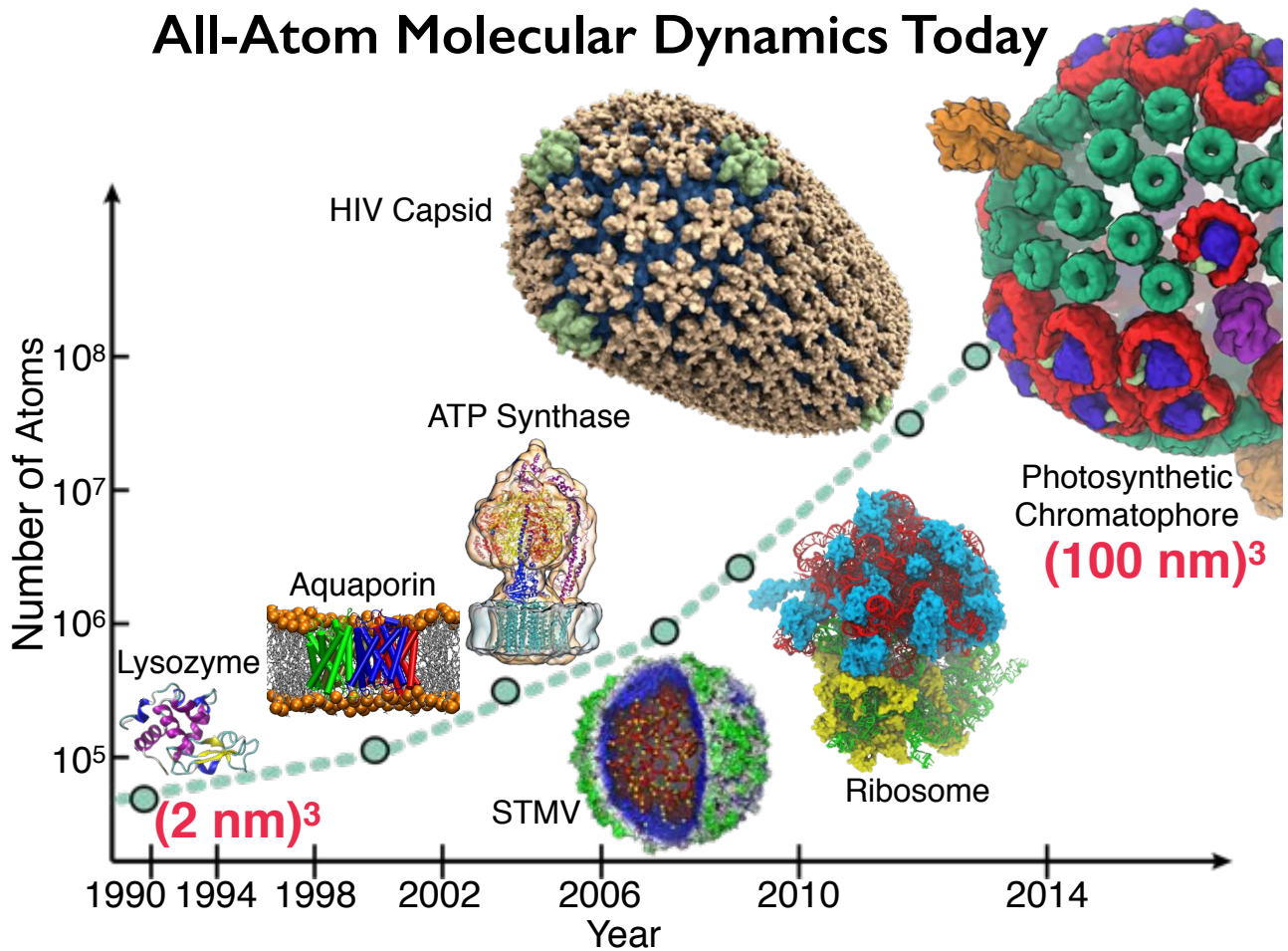
MD simulations combined with quantum mechanics calculations



Counting nucleobases

A. Girdhar, C. Sathe, K. Schulten, J.-P. Leburton, *Nanotechnology*, in press (2015)

All-Atom Molecular Dynamics Today

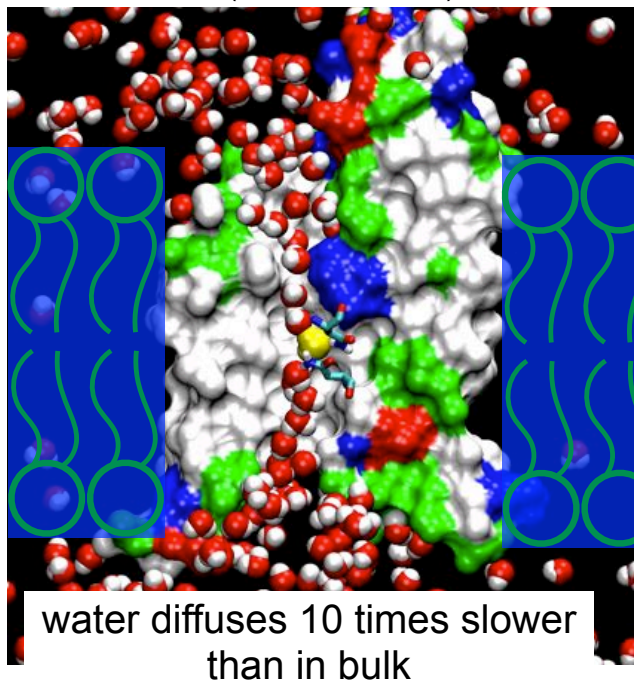


Discover How Membrane Protein Functions - Aquaporin

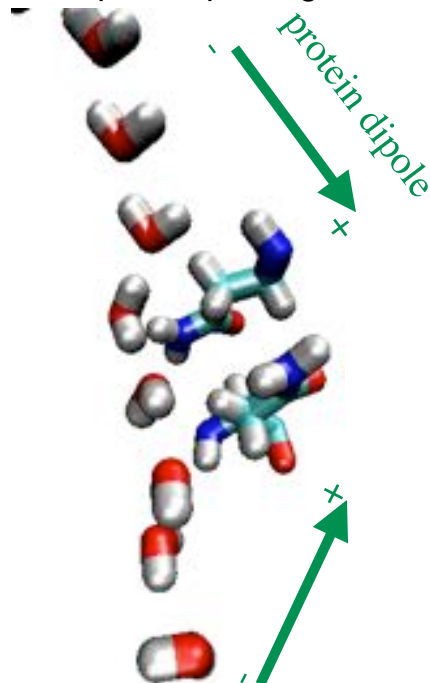
Nobel Prize in 2003 was awarded to Peter Agre

Schulten, R. Stroud, et al. *Science*, 296, 525, (2002)

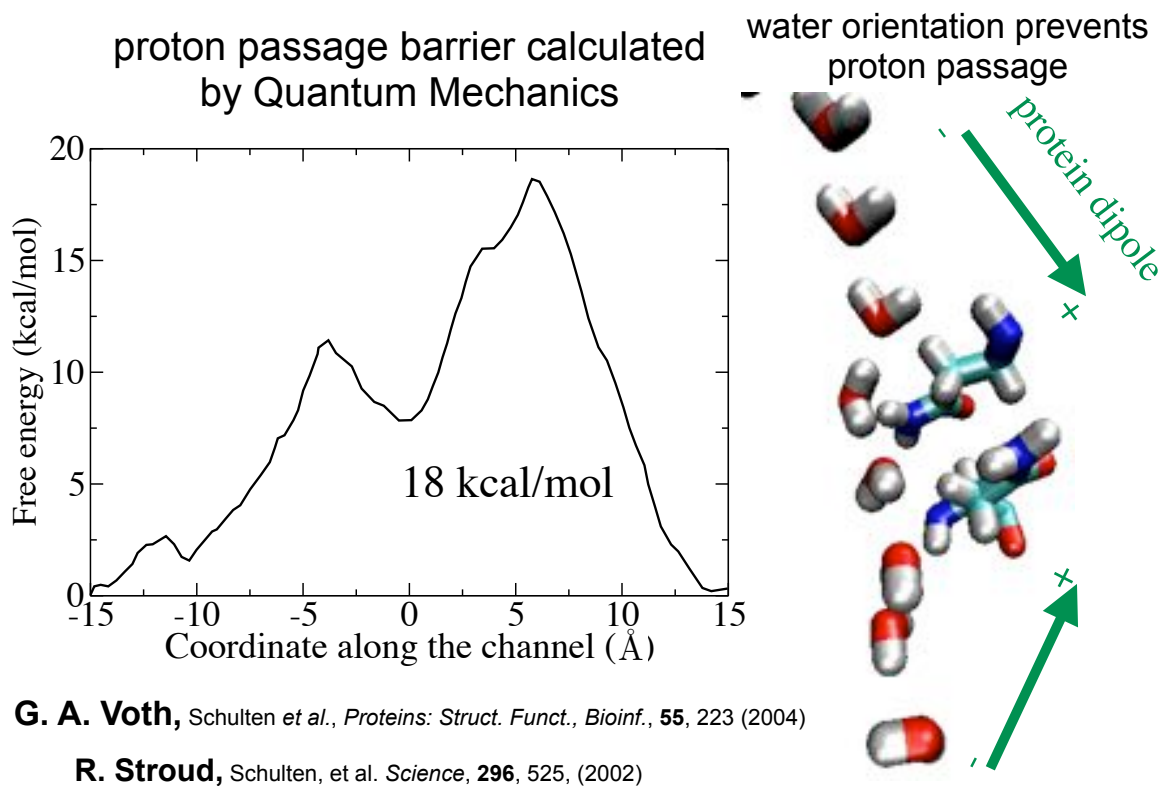
Key persons: Emad Tajkhorshid (UIUC),
Morten Jensen (now Shaw Res.)



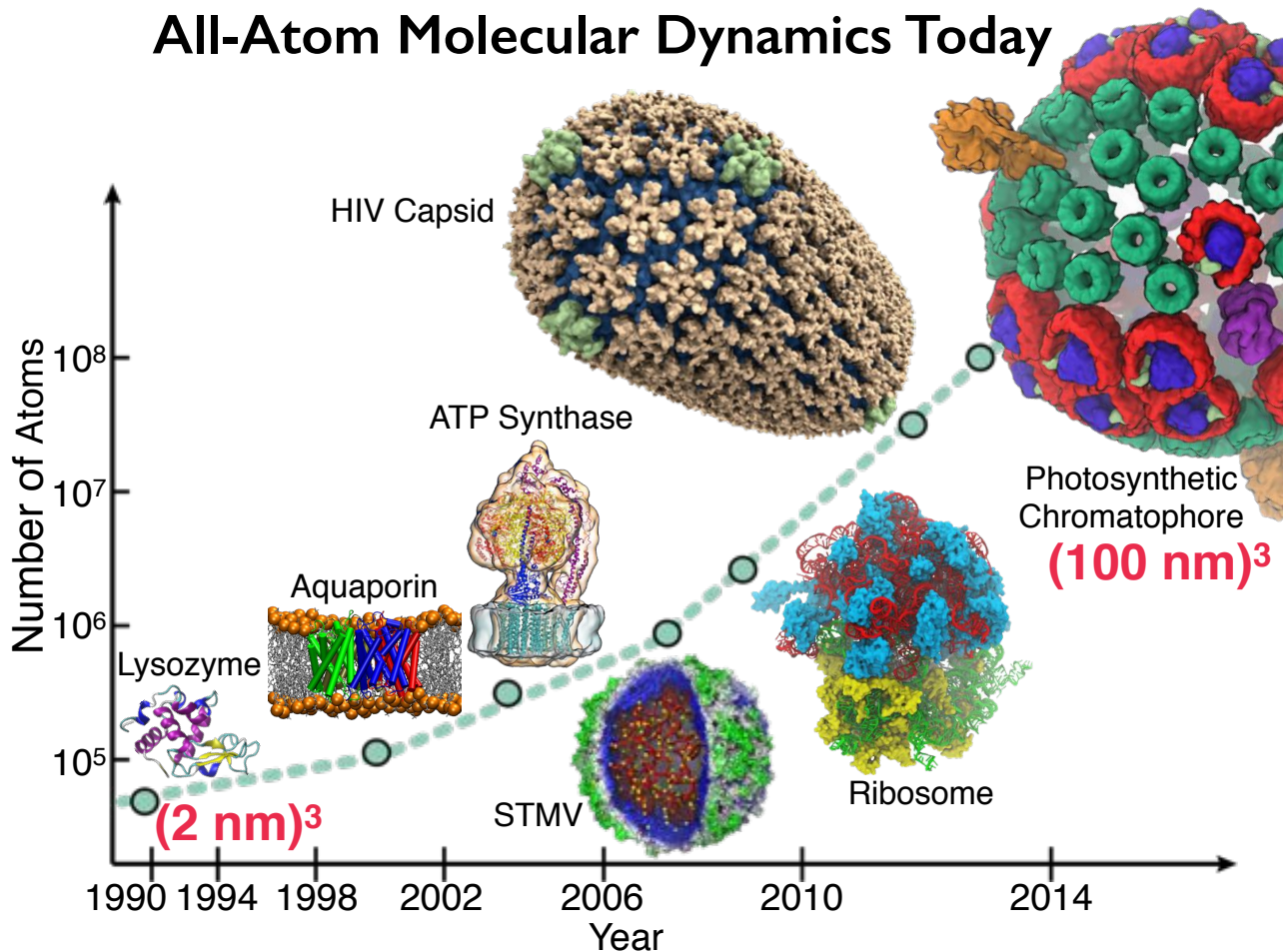
water orientation prevents proton passage



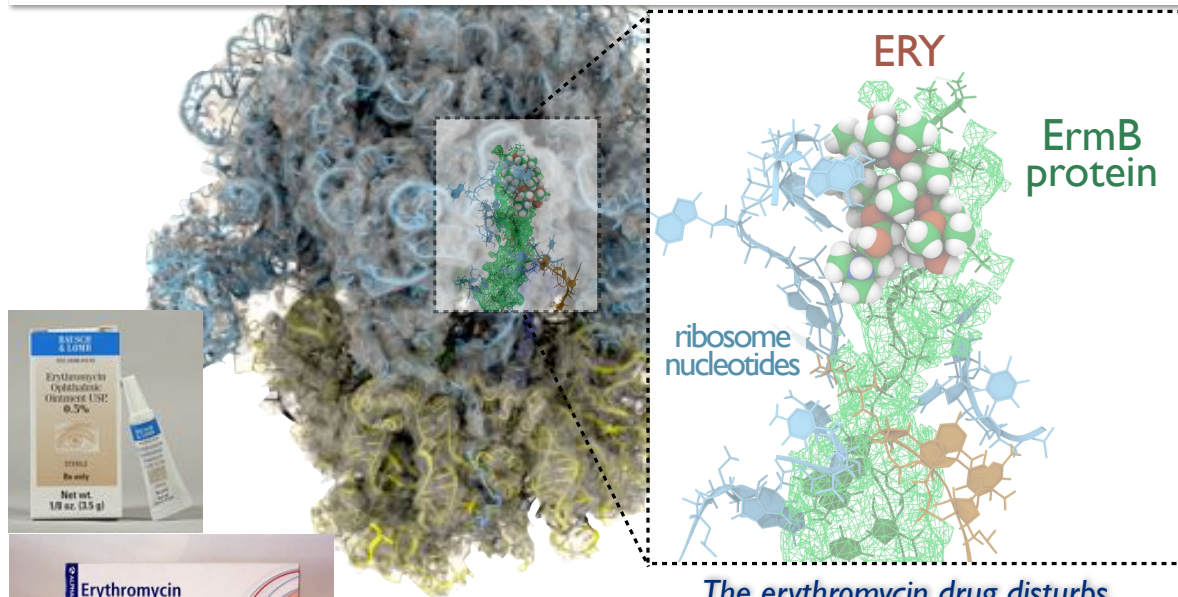
Aquaporin Conducts Water, But Not Protons



All-Atom Molecular Dynamics Today



Blue Waters Fights Antibiotic Drug Resistance - Today's Medical Emergency No. One



The erythromycin drug disturbs bacterial protein synthesis.

Macrolide antibiotics allosterically predispose the ribosome for translation arrest. *PNAS* 111:9804-9809, 2014.

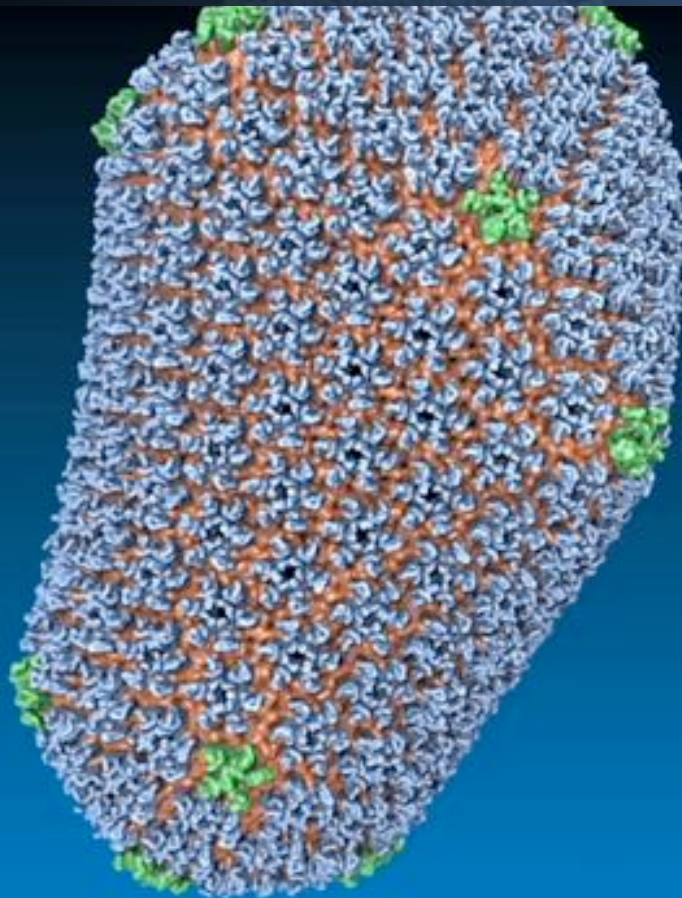
Collaborators: Mankin (UIC), Wilson (LMUM)

- wider antimicrobial spectrum than penicillin
- treats eyes, respiratory tract infections.

BlueWaters Opens New Chapter in HIV Treatment

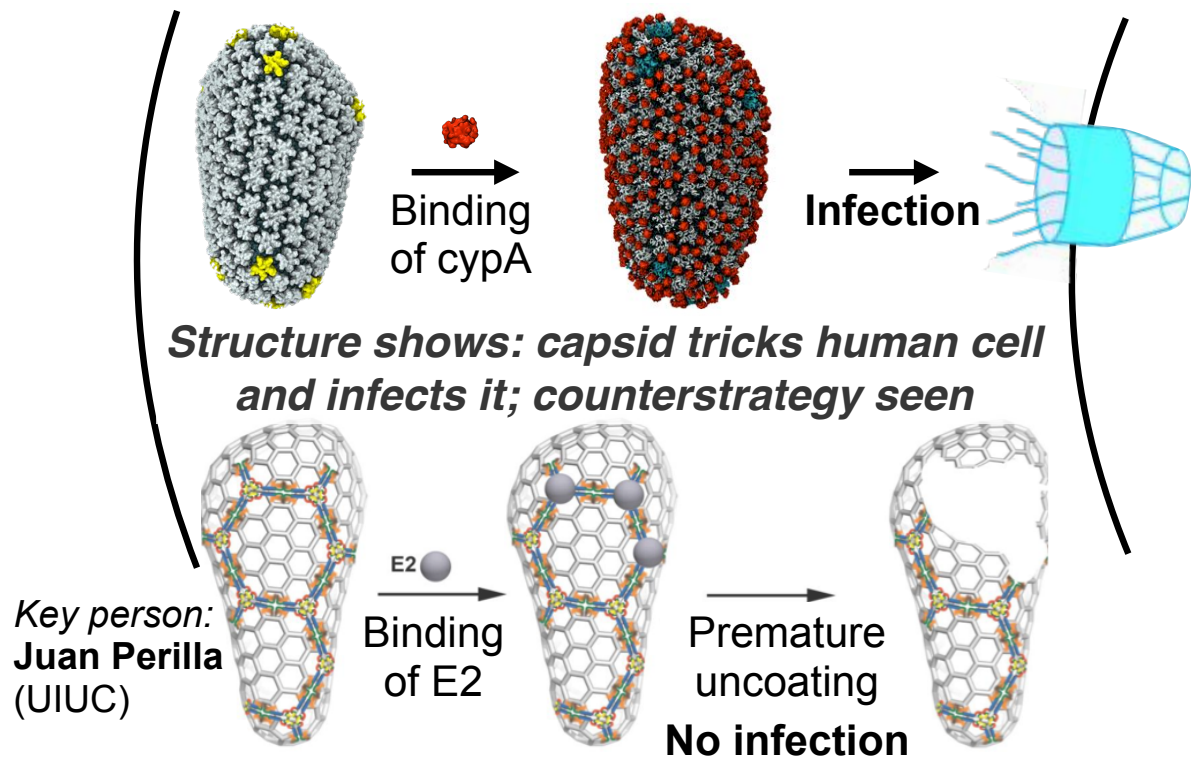


BW One-Microsecond Simulation Includes 64 Million Atoms



Key person:
Juan Perilla
(UIUC)
Structure
Discovered
on Blue Waters:
Nature 497 (2013)

Blue Waters Reveals Structure of HIV Capsid

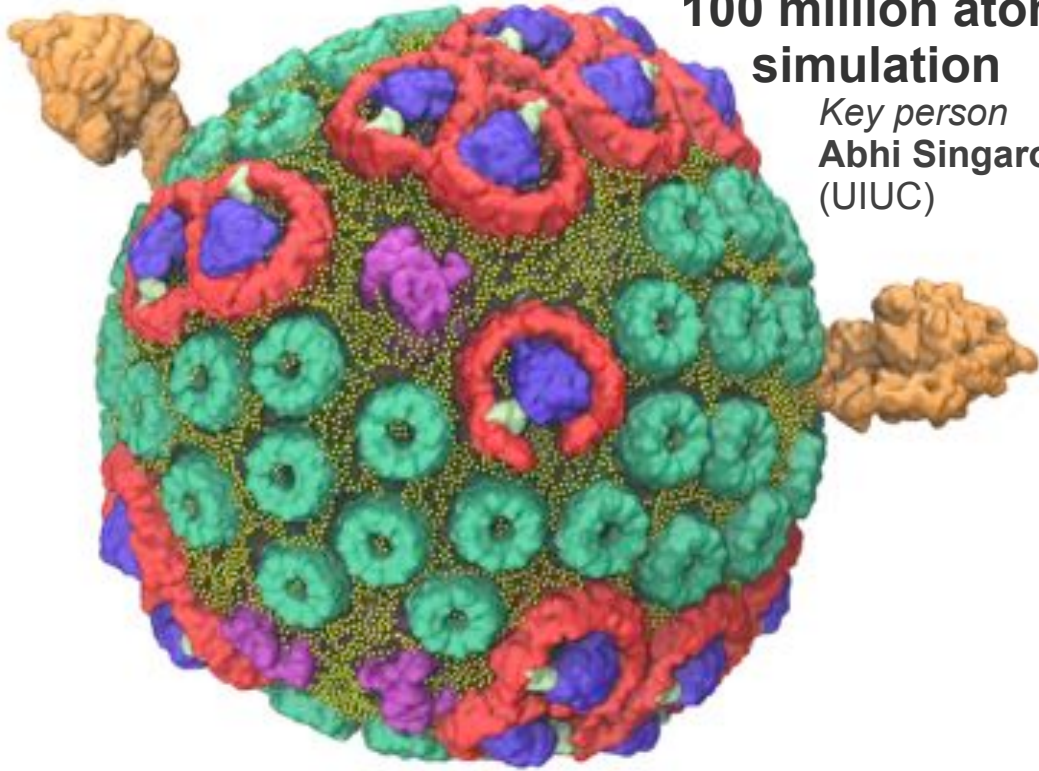


F. Diaz-Griffero, *Viruses* (2011)

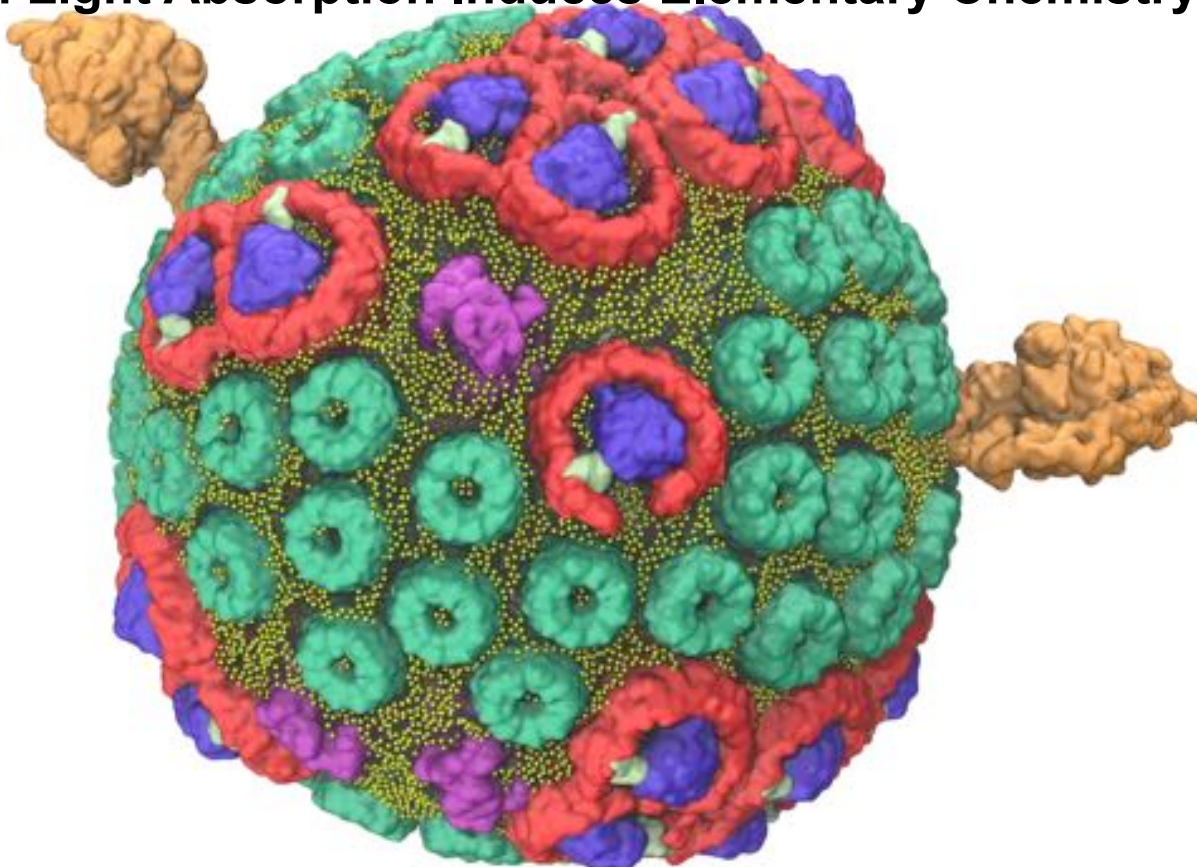
Blue Waters Uncovers Photosynthesis

100 million atom
simulation

Key person
Abhi Singaroy
(UIUC)



Sun Light Absorption Induces Elementary Chemistry



Finally Sun Light Produces Biological Fuel ATP

