Introduction to Molecular Dynamics, NAMD and VMD, and Examples

Klaus Schulten, Dept. Physics, U. Illinois at Urbana-Champaign

Chicago

Indianapolis

University of Illinois at Urbana-Champaign

St. Louis

NIH Resource for Macromolecular Modeling and Bioinformatics

NSF Physics Frontier Center for the Physics of Living Cells

http://www.nasa.gov/sites/default/files/thumbnails/image/iss042e024272.jpg

Thanks guys!

Theoretical and Computational Biophysics Group
Beckman Institute, UIUC

NAMD - An Exploring Tool

20 years of computer science innovation and collaboration

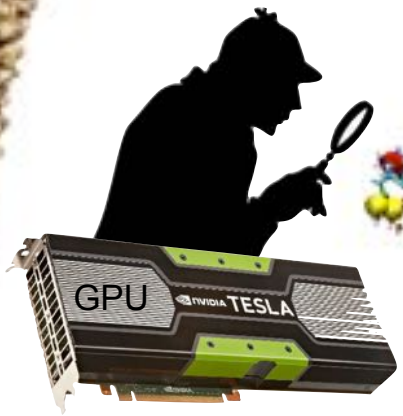
1993: HP workstation cluster
1994: Writing NAMD in C++
1998: Commodity Linux clusters
2002: Parallel on 3000 cores, 10^5 atoms
2007: Graphics processors (GPUs)
2013: Petascale supercomputers

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)

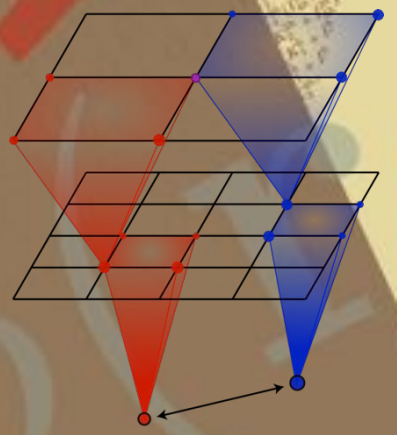
Serving 70,000 users on affordable hardware

Evolution of computer hardware requires continual algorithmic development...

...over 50 method papers 1995-2014

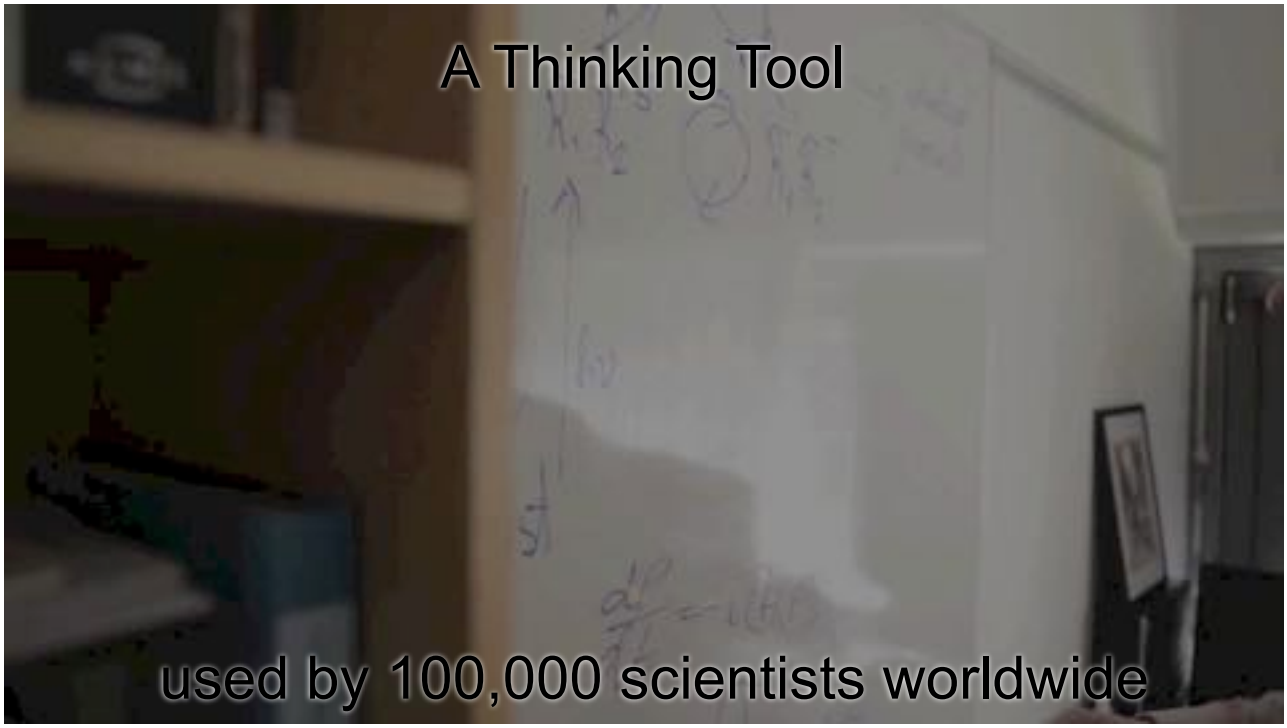
Multilevel Summation Method
- faster calculation of electrostatic forces
- accelerated using GPUs

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



: VMD

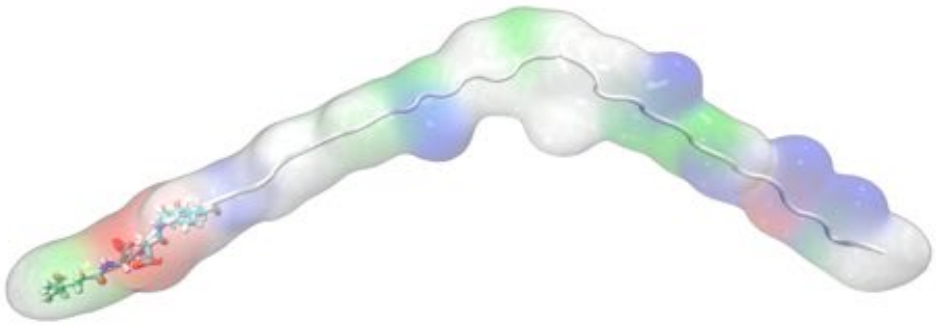
Key person
John Stone
(UIUC)



video: www.lundbeckfoundation.com

VMD: A Thinking Tool

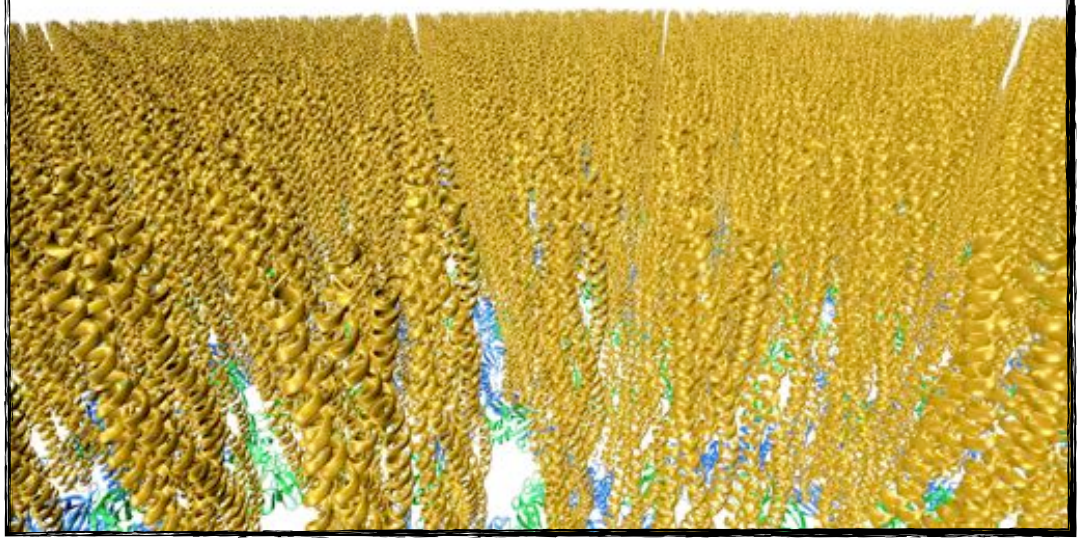
to visualize and analyze trajectories



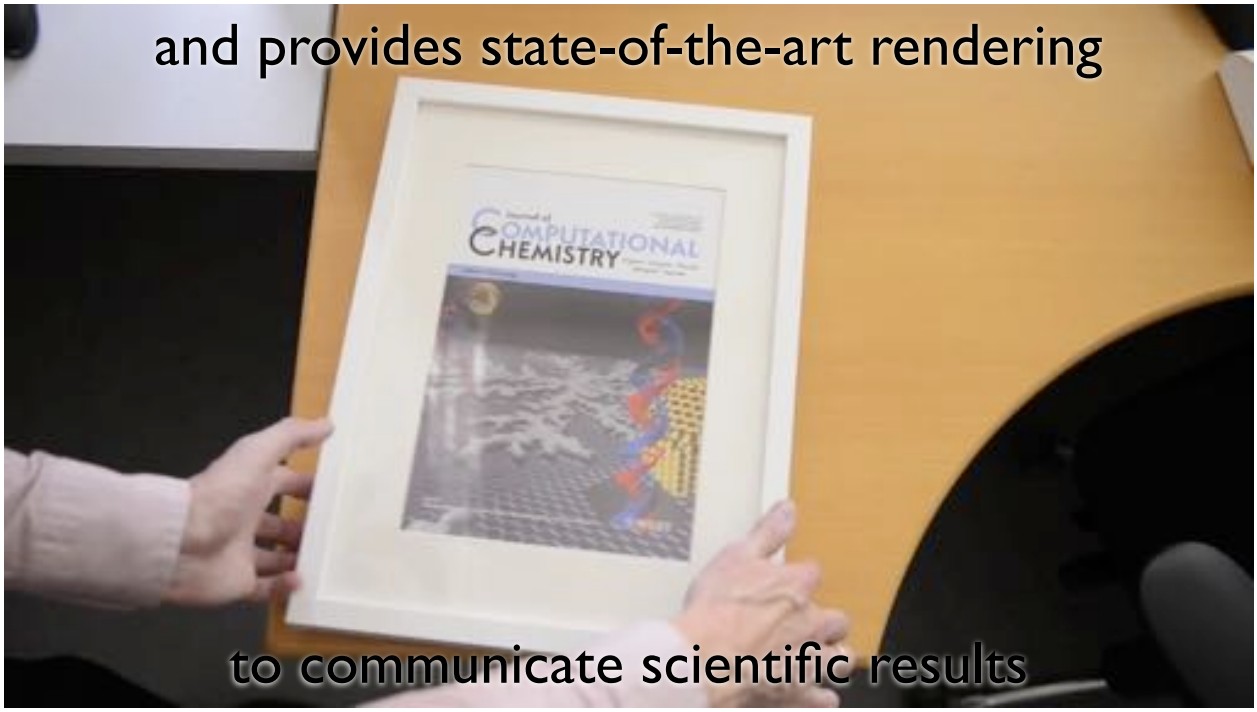
from small peptides...

VMD: A Thinking Tool

...to extremely large biological structures



VMD: A Thinking Tool



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
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
VolMap

Modeling

AutoIonize
AutoPSF
Chirality
Cionize
Cispeptide
CGTools
Dowser
Force Field Toolkit
Inorganic Builder
MDFF
Membrane
Merge Structs
Molefacture
Mutator
Nanotube
Paratool
Psfgen
RESPTool
RNAView
Solvate
SSRestraints
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
QMTool

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
vmdICE

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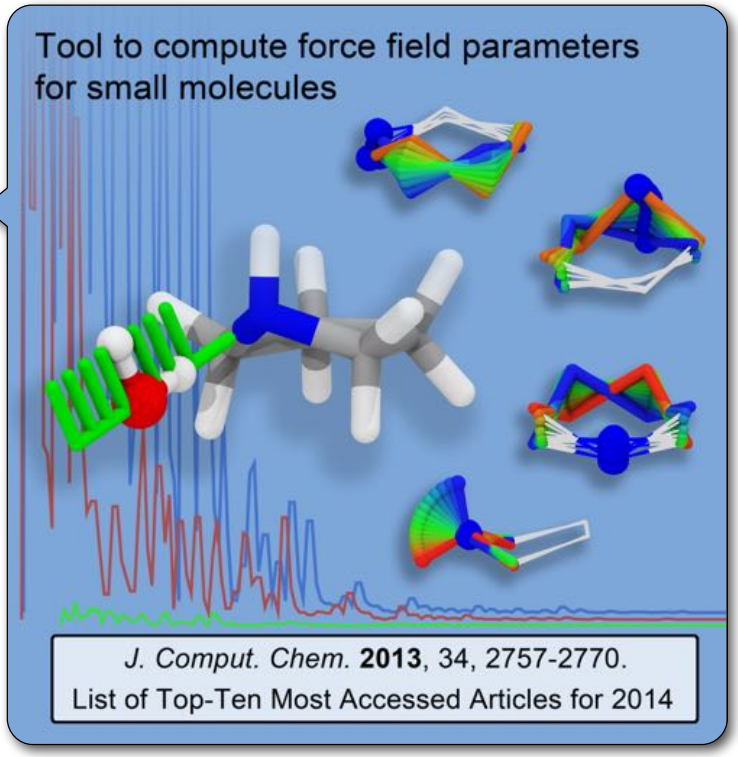

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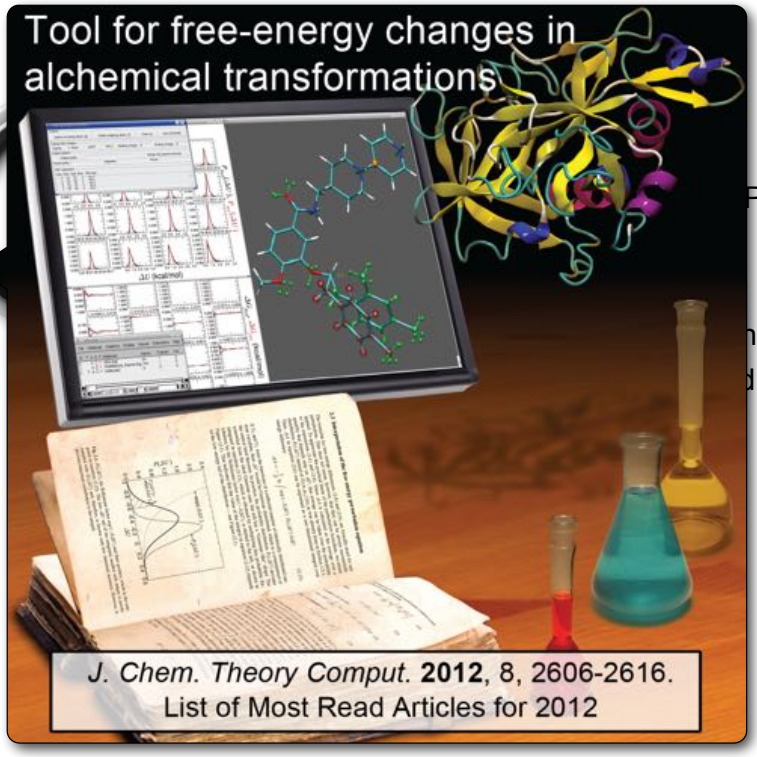

Plotting

ns

d Plugins

VMD Plugins

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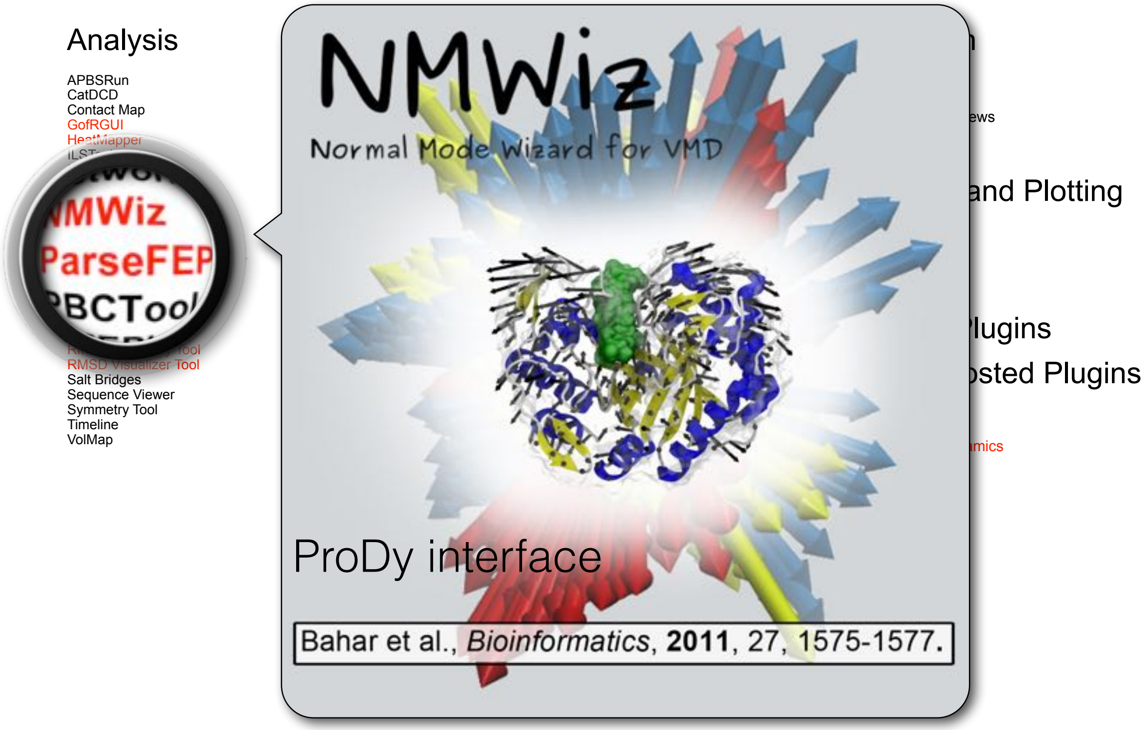
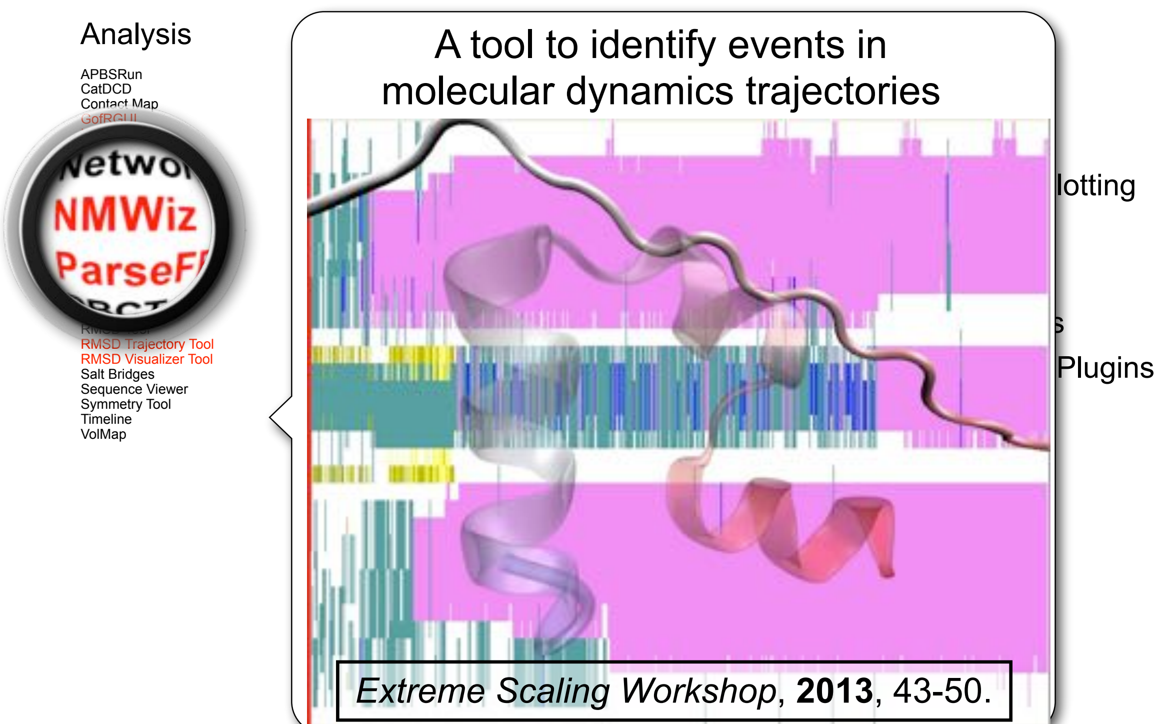


VMD Plugins

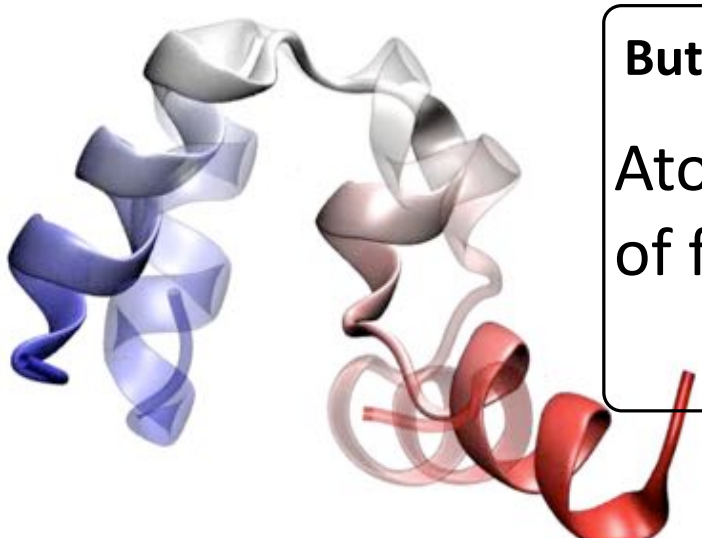
Advanced Tools developed **In-House** and by **External Users**



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

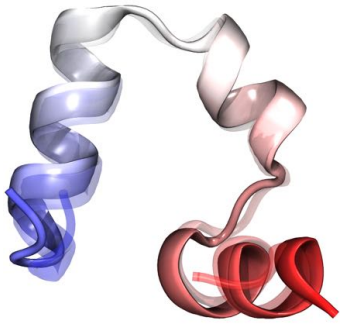
Key person
Peter Freddolino
(now U. Michigan)

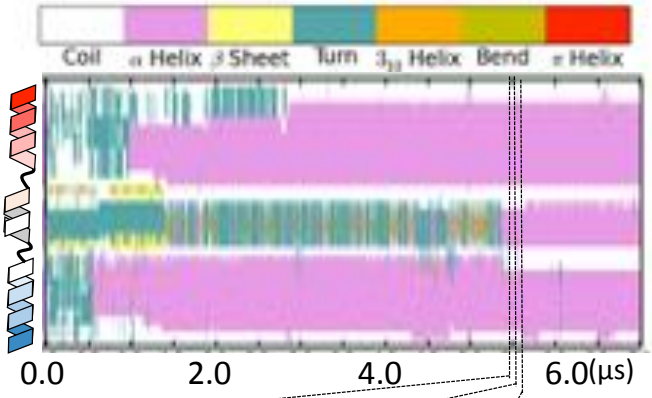
Schulten et al. *Biophys J* **94**:**L**75, 2008, **97**: 2009

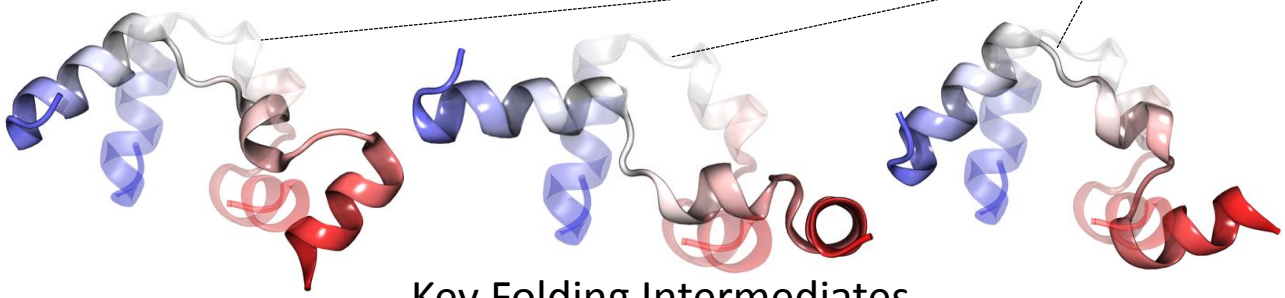
Folding Dynamics of Villin Headpiece Unveiled

MD simulations explored key folding transitions not seen before

Schulten et al. *Biophys J* **94**:**L**75, 2008, **97**: 2009



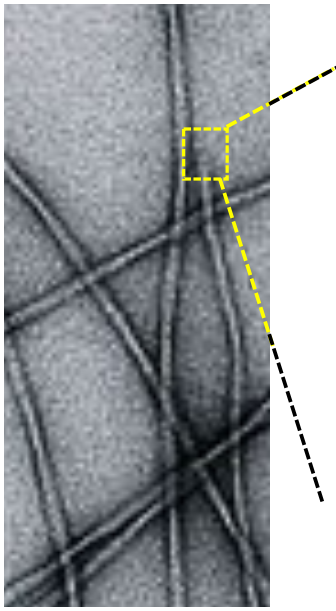




Key Folding Intermediates

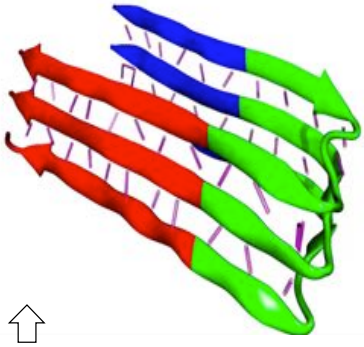
Folding Simulations (1.3 ms) Unravel Growth Mechanism of Disease Causative Amyloid

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



EM Image
Amyloid-β Fibril

"+" Tip



"-" Tip

What do we learn?

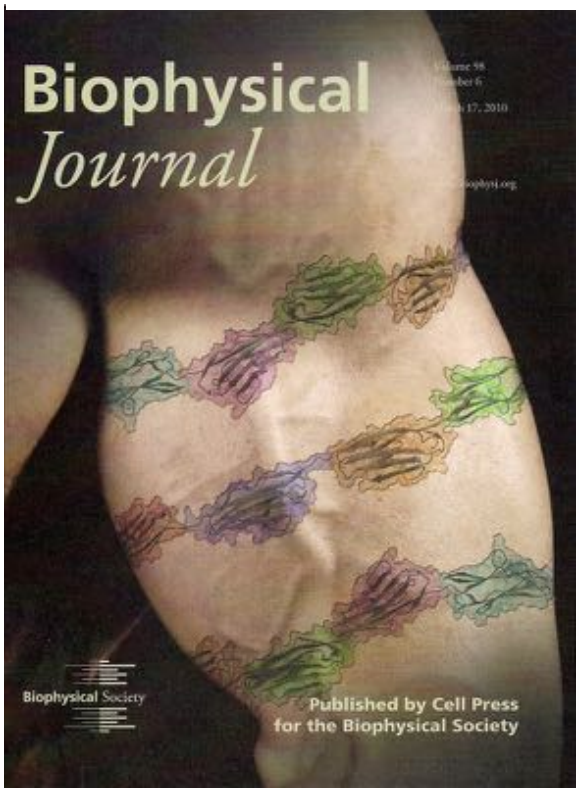
Similar affinity to both tips

Faster kinetics at "+" tip

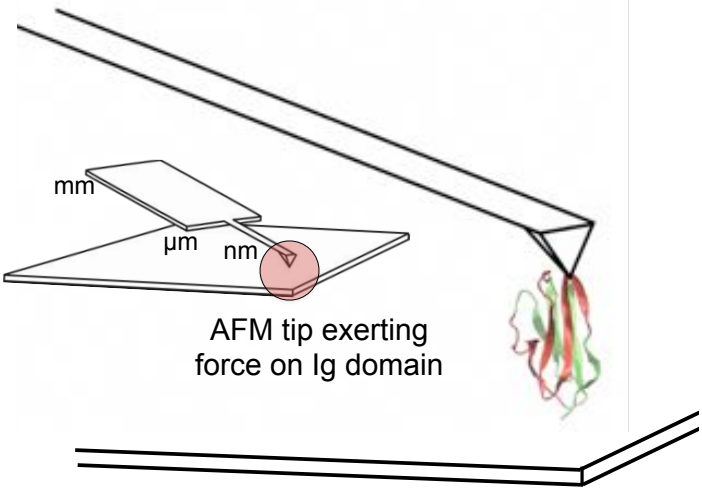
"+" tip catalyzes structural change of monomer

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

Forced Unfolding of Titin Ig Domain

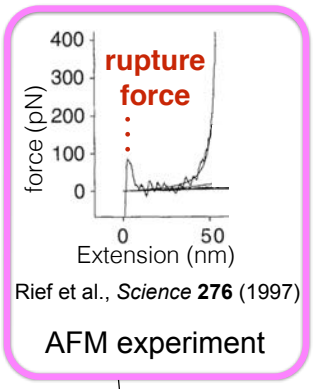


Titin = muscle's third protein



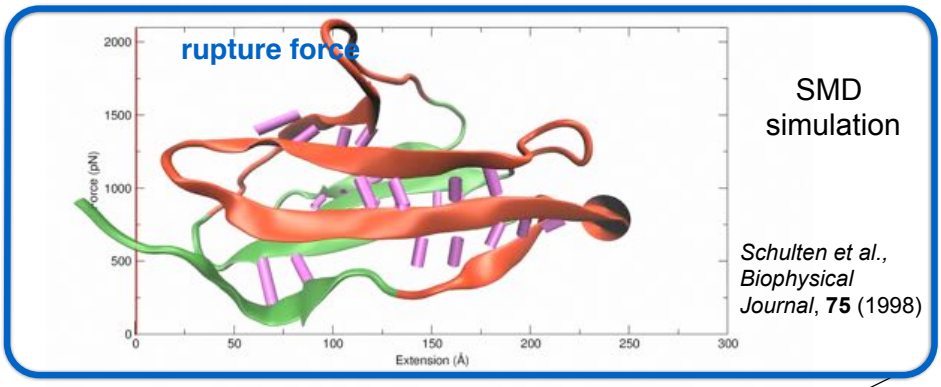
AFM tip exerting force on Ig domain

Forced Unfolding of Titin Ig Domain



Rief et al., *Science* **276** (1997)

AFM experiment



SMD simulation

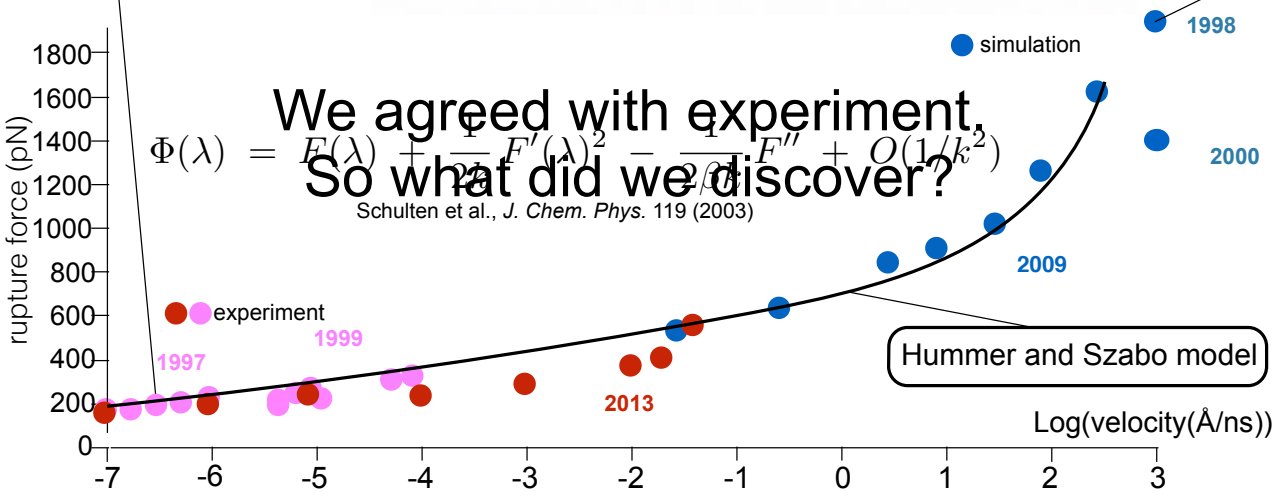
Schulten et al., Biophysical Journal, **75** (1998)

We agreed with experiment.

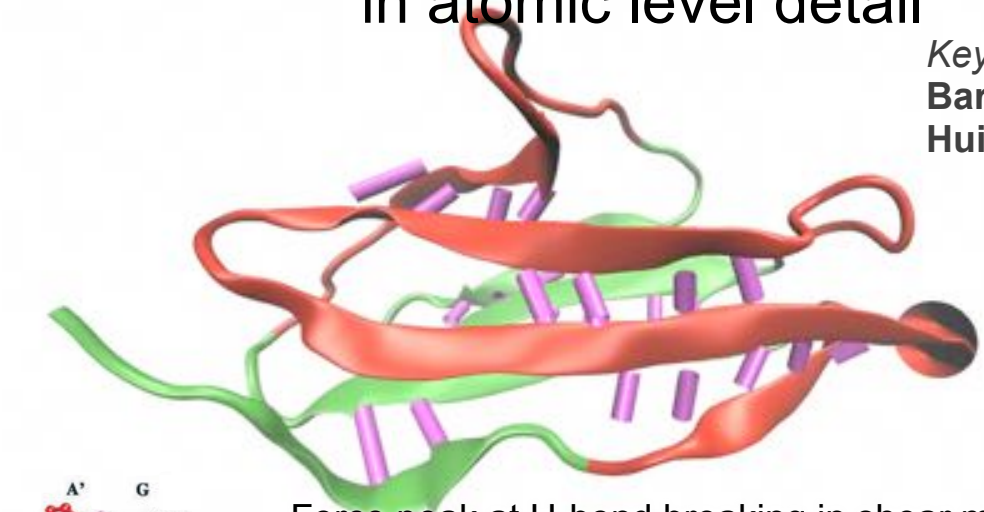
So what did we discover?

$$\Phi(\lambda) = E(\lambda) + \frac{1}{24k}F'(\lambda)^2 - \frac{1}{2\beta k}F'' + O(1/k^2)$$

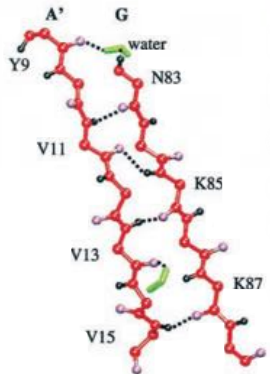
Schulten et al., *J. Chem. Phys.* 119 (2003)



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

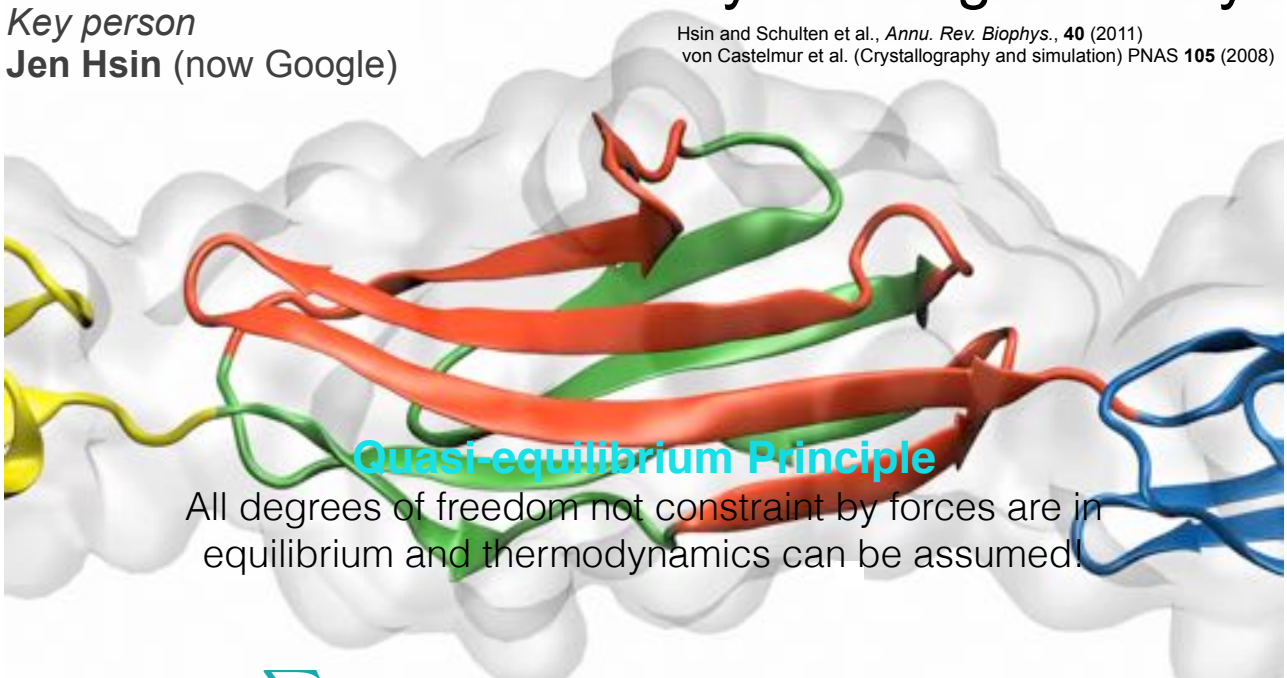
Confirmed by computational + experimental (mutation) collaboration
Schulten and Fernandez et al., *Nature*, **402** (1999)

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!

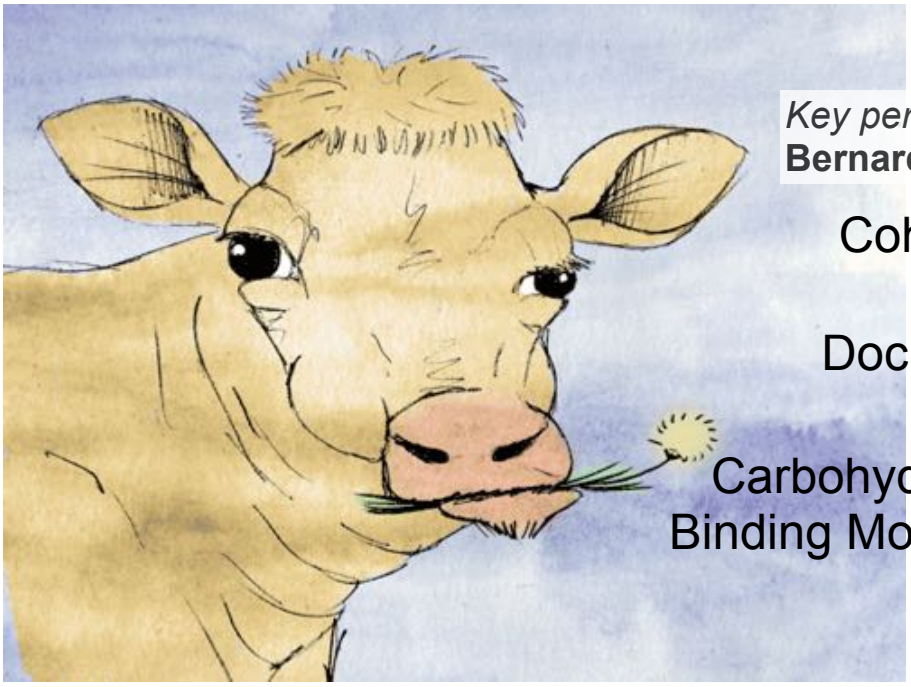
$$\text{Extension} = \sum_j \langle x_j \exp[f x_j / k_\mathrm{B}T] \rangle_{V_j} \,/\, \langle \exp[f x_j / k_\mathrm{B}T] \rangle_{V_j} \;=\; g(f)$$

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

Titin is a muscle protein with 300 domains.
Crystallography and simulation permit investigation into how the system functions.
We look at six domains.

Ultrastable Biomass Adhesion Complex

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



Key person: **Rafael Bernardi**(UIUC)

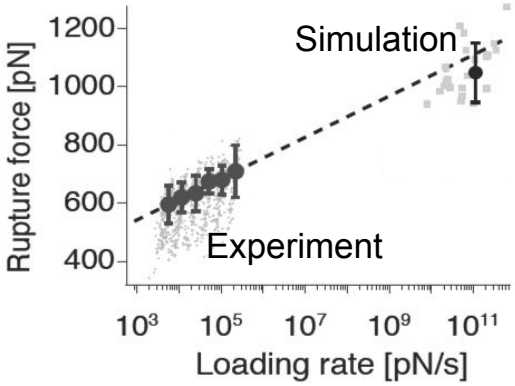
Challenging environments guided nature in the development of ultrastable protein complexes

Strongest Measured Adhesion Bond

Adhesion becomes stronger when force is applied

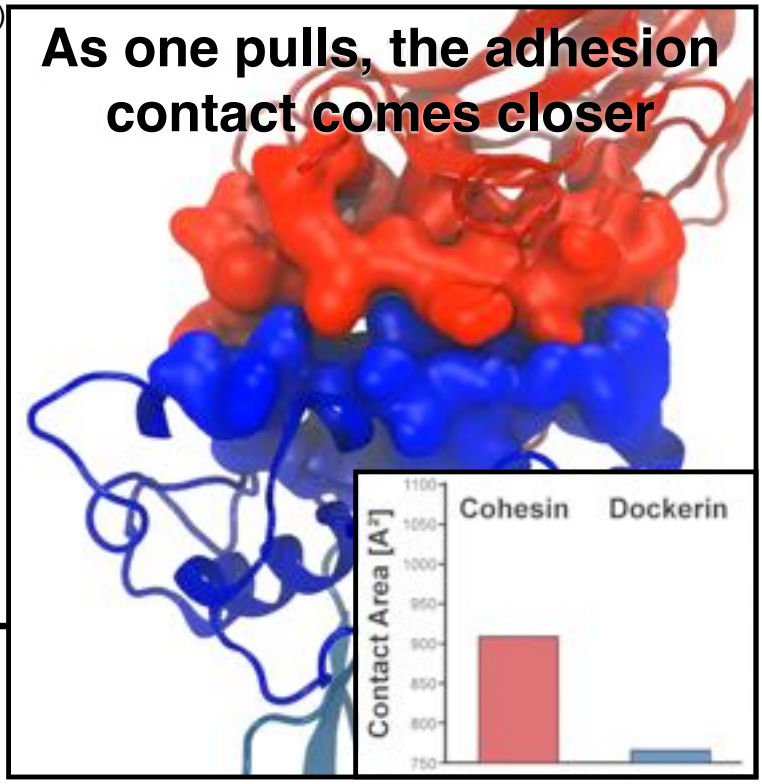
Collaboration w/ **Hermann Gaub** (Munich)

Nat. Commun. **5**, 5635 (2014)



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

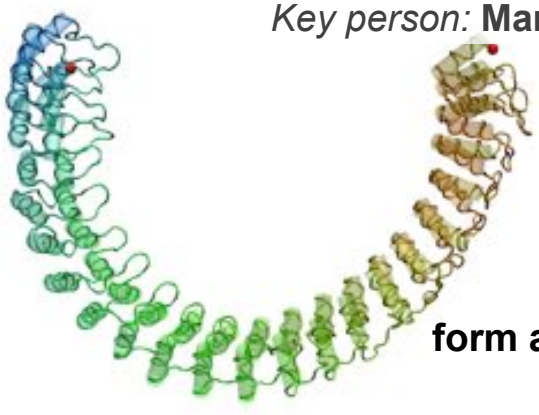
M. Sotomayor, et. al. , *Structure* **13**, 669 (2005)

AFM MEASUREMENTS

Spring constant ~ 2.4 mN/m

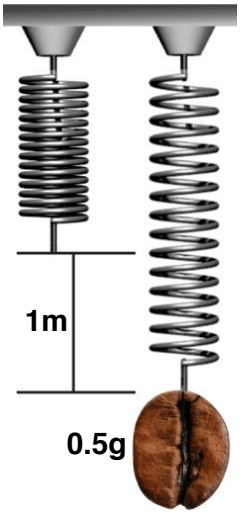
G. Lee, et. al. , *Nature* **440**, 246 (2006)

Key person: **Marcos Sotomayor** (now OSU)



Ankyrin repeats form an extremely soft spring

VERY SOFT



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.

Calcium Controlled Elasticity

Cadherin is a key player in cell adhesion - the glue between the cells

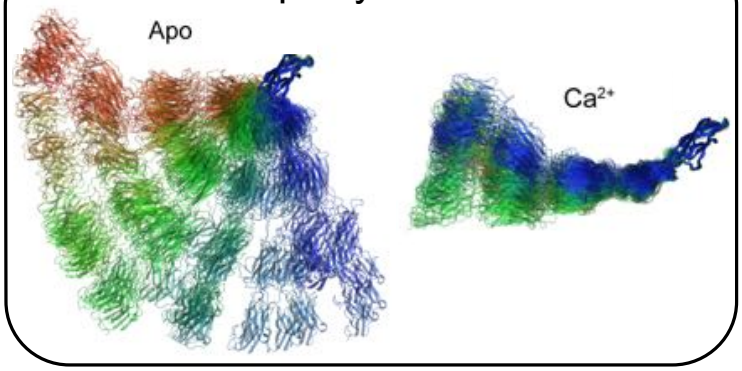
At least 110 different cadherins in human tissue

Classical cadherins are essential for epithelial tissue, like the human gut

Deletion in specific cadherin genes causes deafness

Key person: **Marcos Sotomayor** (now OSU)

Calcium keeps system more stable

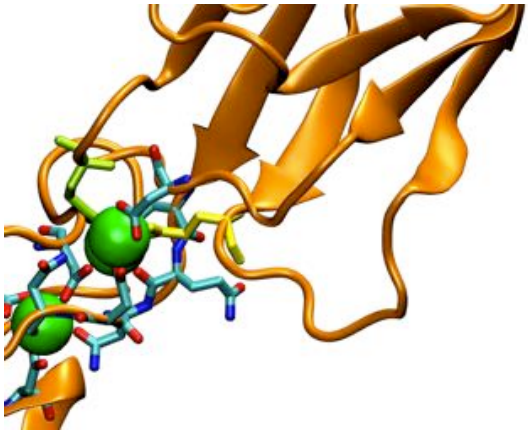


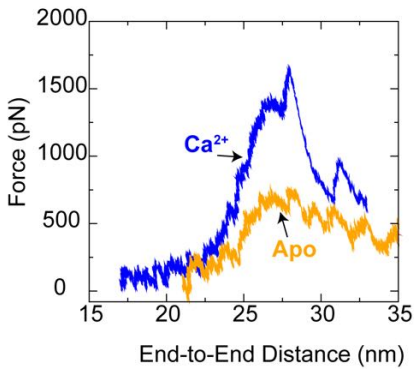
Calcium Controlled Elasticity

Calcium prevents unfolding of Cadherin domains

PREDICTIONS FROM SIMULATIONS
Unfolding force doubles adding calcium
M. Sotomayor, et. al., *Biophys. J.* **94**, 4621 (2008)

AFM MEASUREMENTS
Unfolding force doubles adding calcium
J. Oroz, et. al., *J. Bio. Chem.* **286**, 9405 (2011)

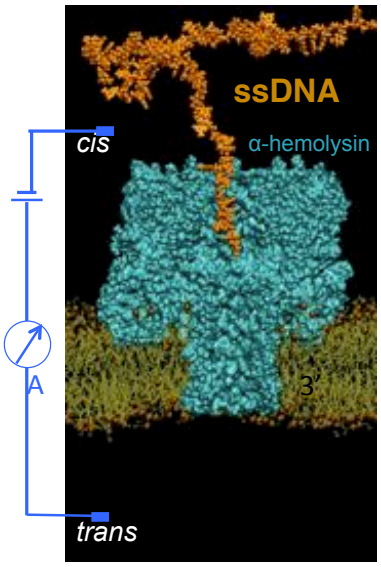




Cadherin-Catenin complex plays a key role in **learning** and **memory** mechanisms through long-term potentiation, maintaining synaptic plasticity.

Simulations Assist in the Design of Nanopore Devices for DNA Sensing

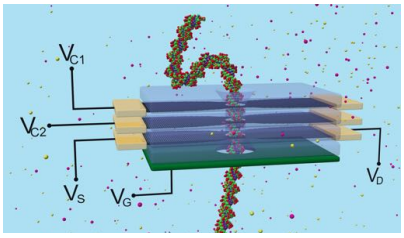
Protein Nanopore Conducts ssDNA



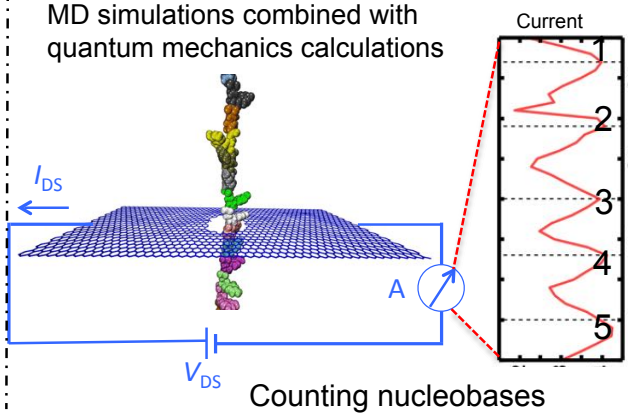
Klaus asks Amit Meller: Can I simulate for you?

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)**

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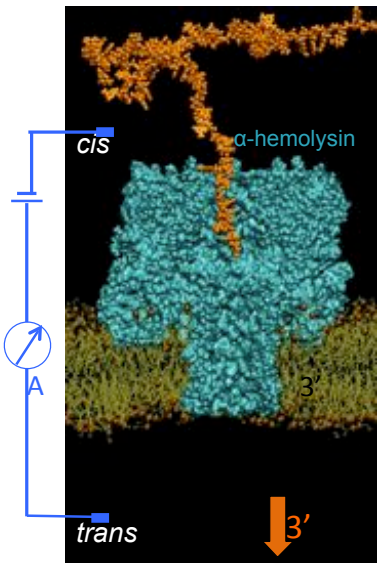
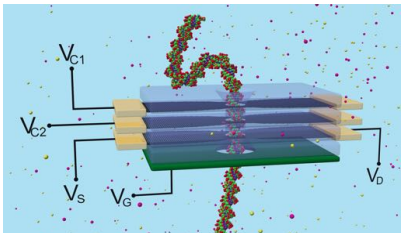


Key person: **Aleksei Aksimentiev** (UIUC)

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

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

Graphene Nanopore Sensing Device



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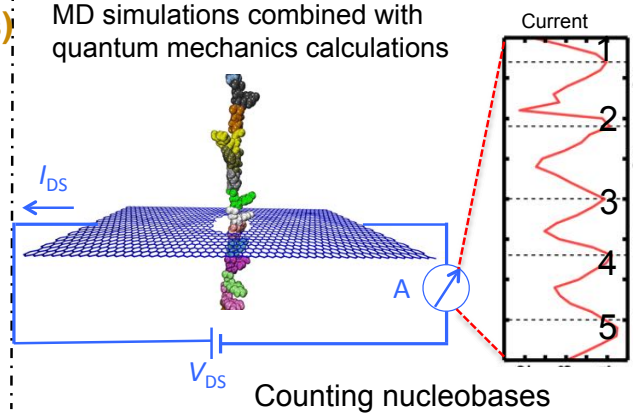

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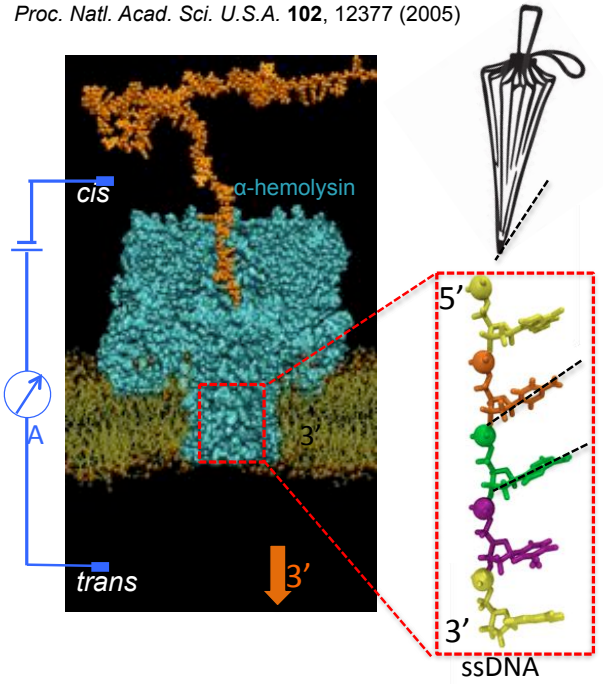
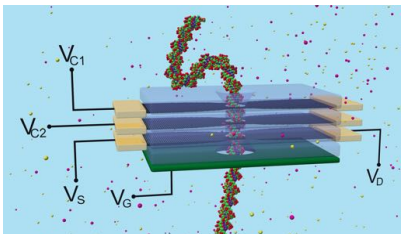
J.Mathé, A. Aksimentiev, D. R. Nelson, K. Schulten, A. Meller.
Proc. Natl. Acad. Sci. U.S.A. **102**, 12377 (2005)

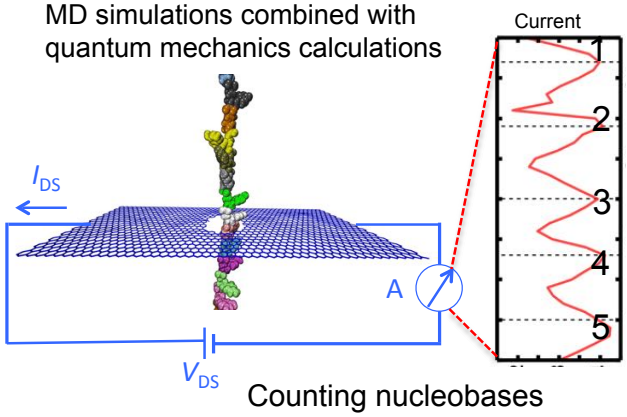


ssDNA bases get tilted one way in narrow pore!

Graphene Nanopore Sensing Device



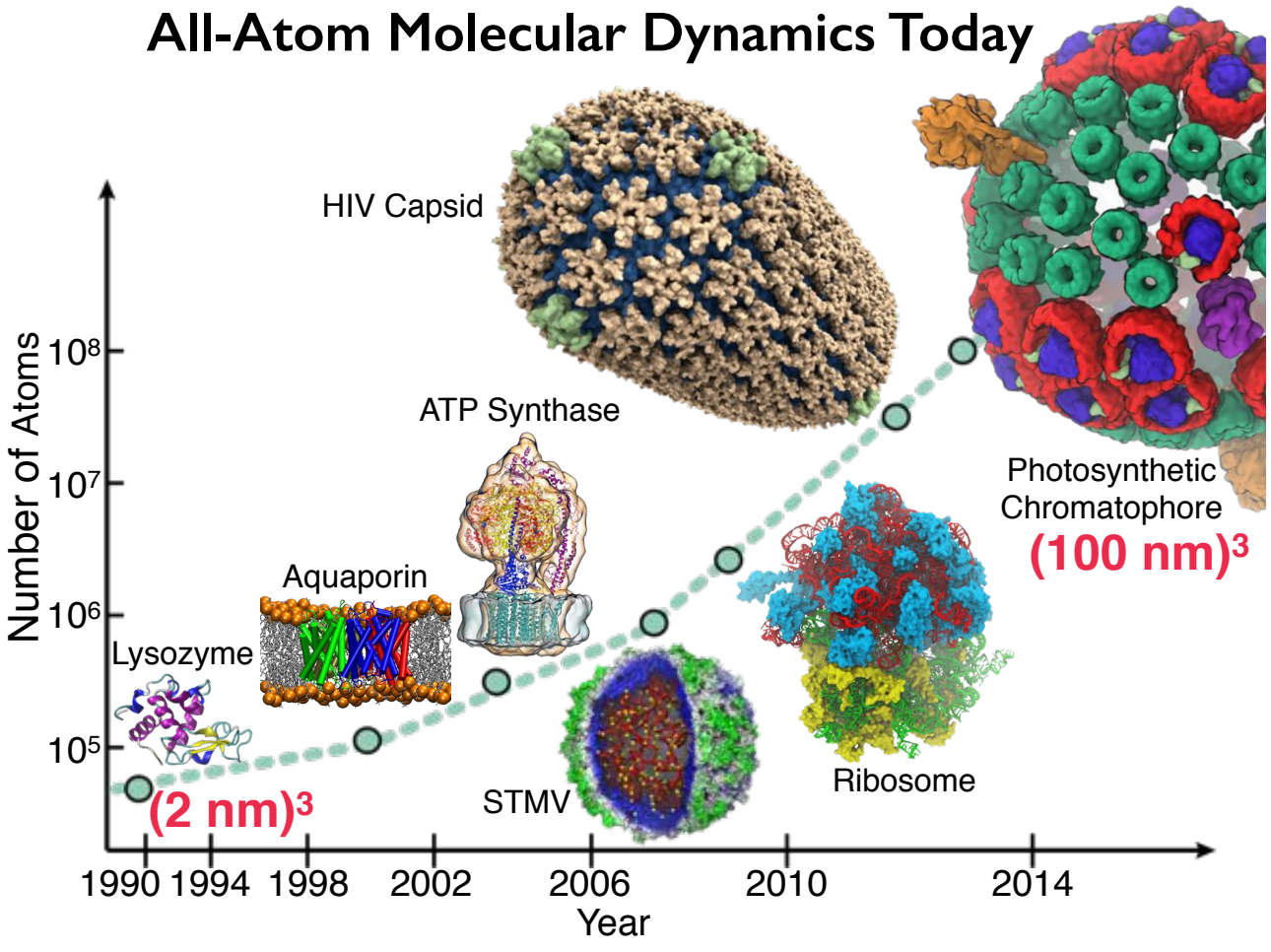
MD simulations combined with quantum mechanics calculations



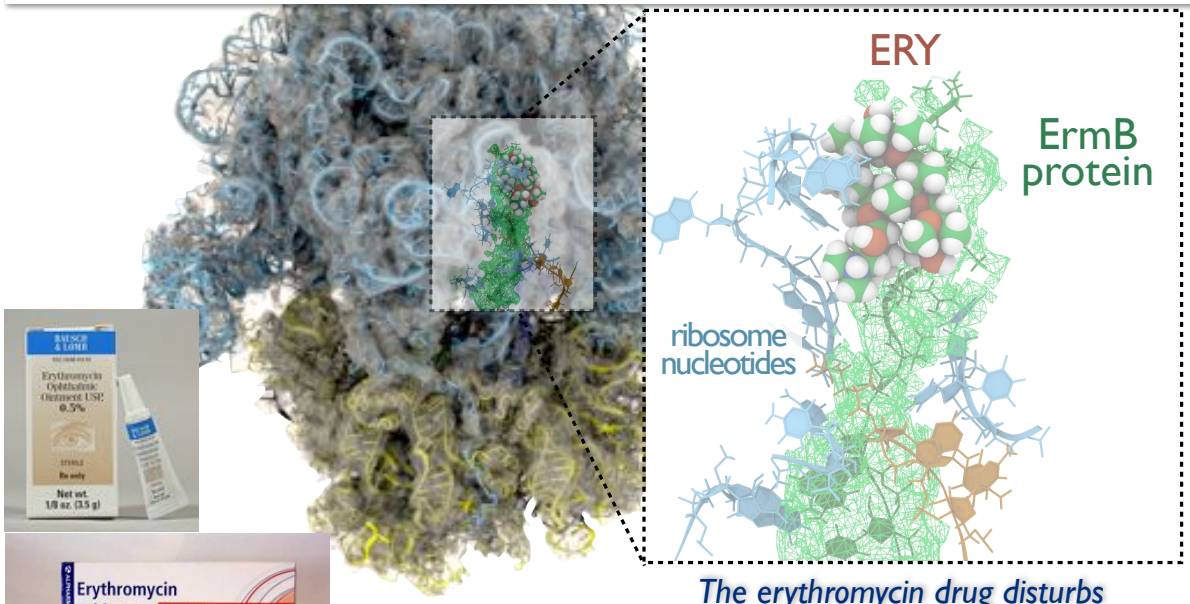
Counting nucleobases

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

All-Atom Molecular Dynamics Today



Blue Waters Fights Antibiotic Drug Resistance - Todays Medical Emergency No. One



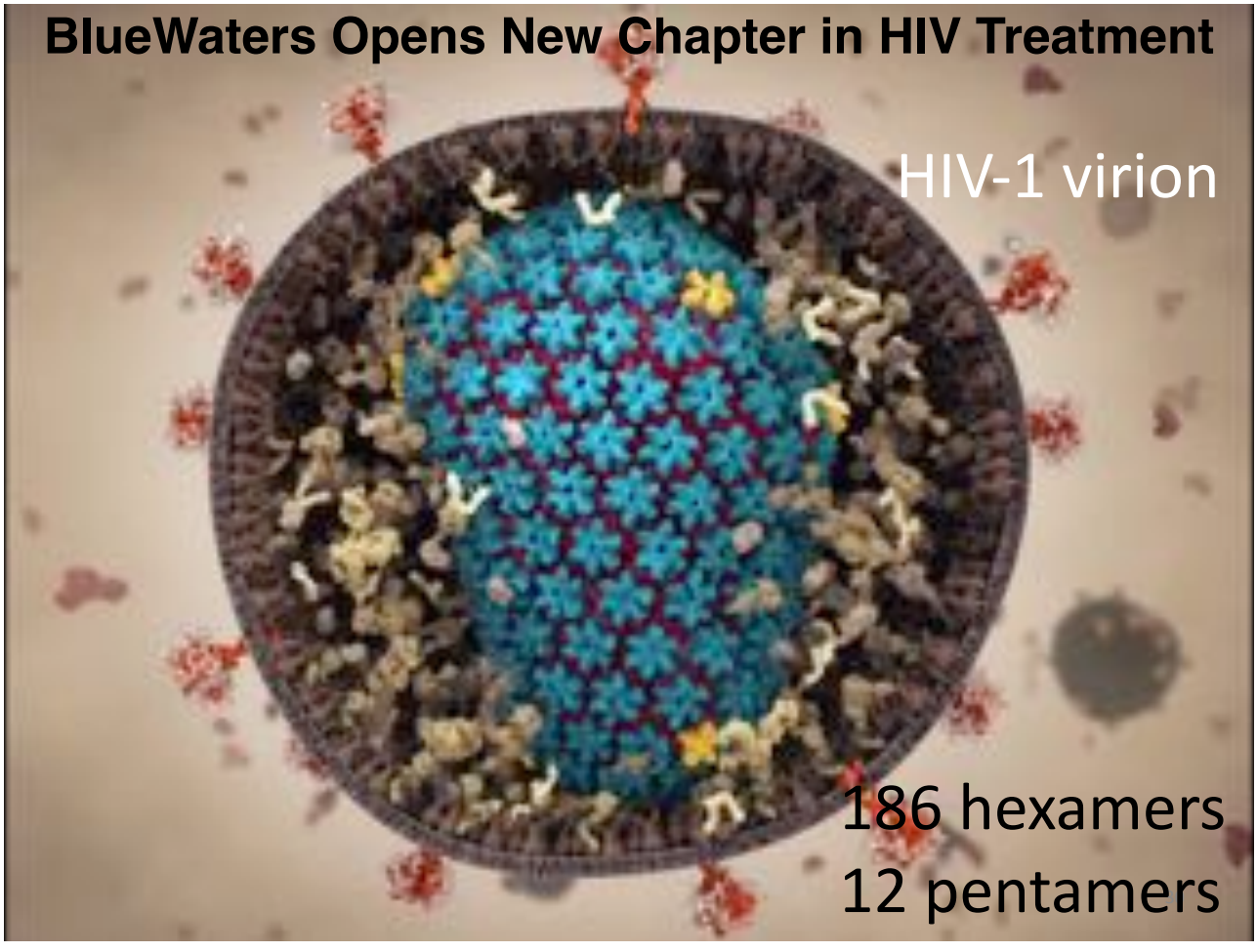
- wider antimicrobial spectrum than penicillin
- treats eyes, respiratory tract infections.

The erythromycin drug disturbs bacterial protein synthesis.

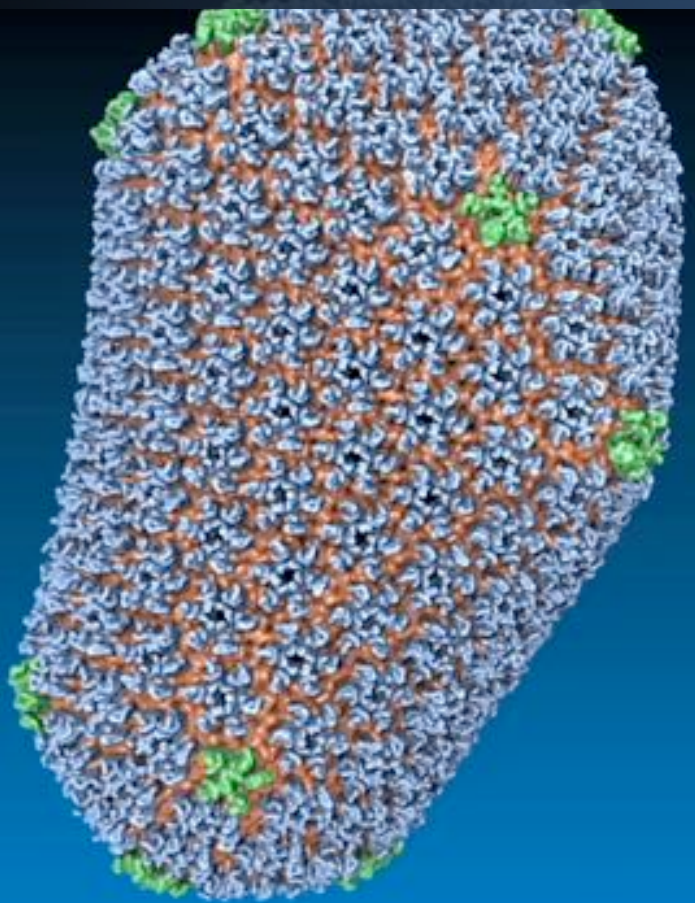
Macrolide antibiotics allosterically predispose the ribosome for translation arrest. *PNAS* **111**:9804-9809, 2014.

Collaborators: Mankin (UIC), Wilson (LMUM)

BlueWaters Opens New Chapter in HIV Treatment

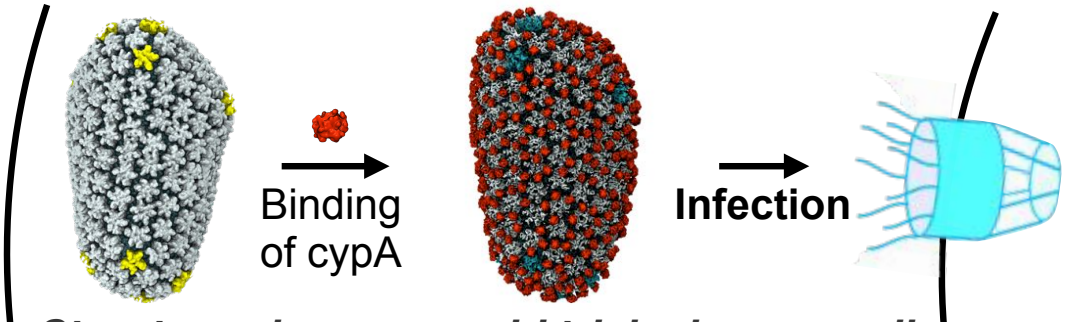


BW One-Microsecond Simulation Includes 64 Million Atoms

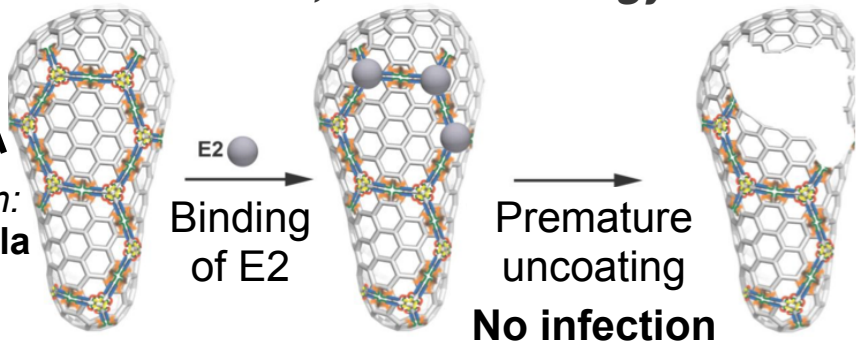


Key person:
Juan Perilla
(UIUC)
Structure
Discovered
on Blue Waters:
Nature **497** (2013)

Blue Waters Reveals Structure of HIV Capsid



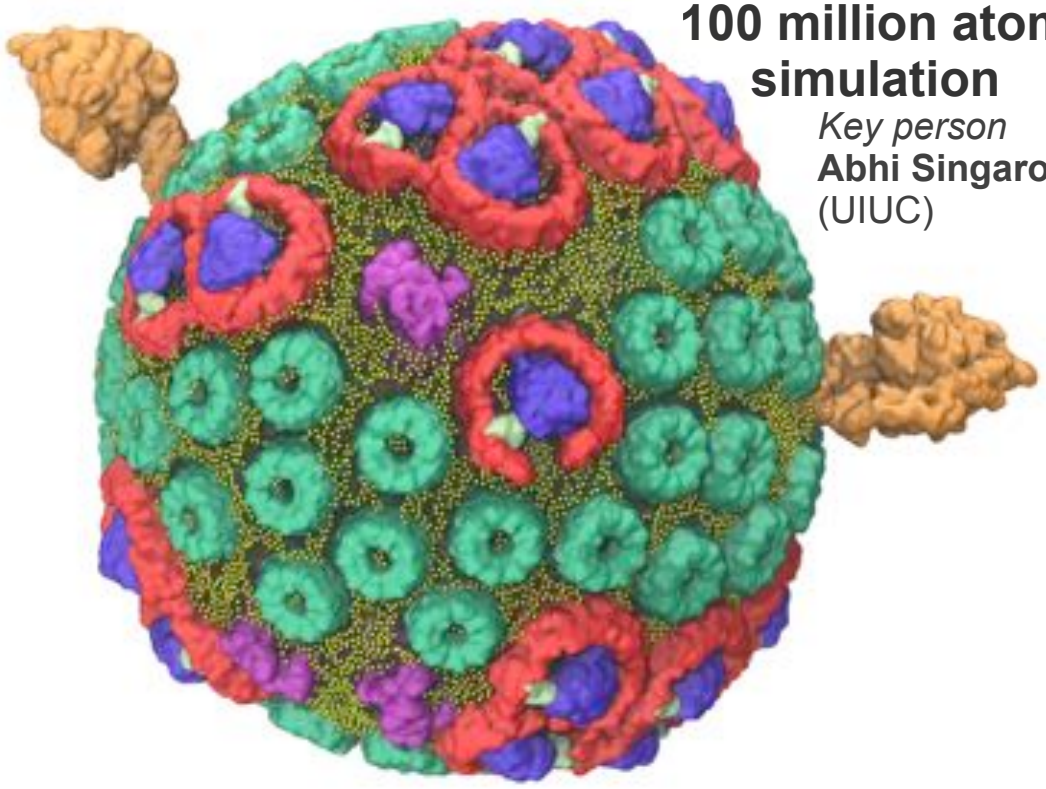
Structure shows: capsid tricks human cell and infects it; counterstrategy seen



Key person:
Juan Perilla
(UIUC)

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

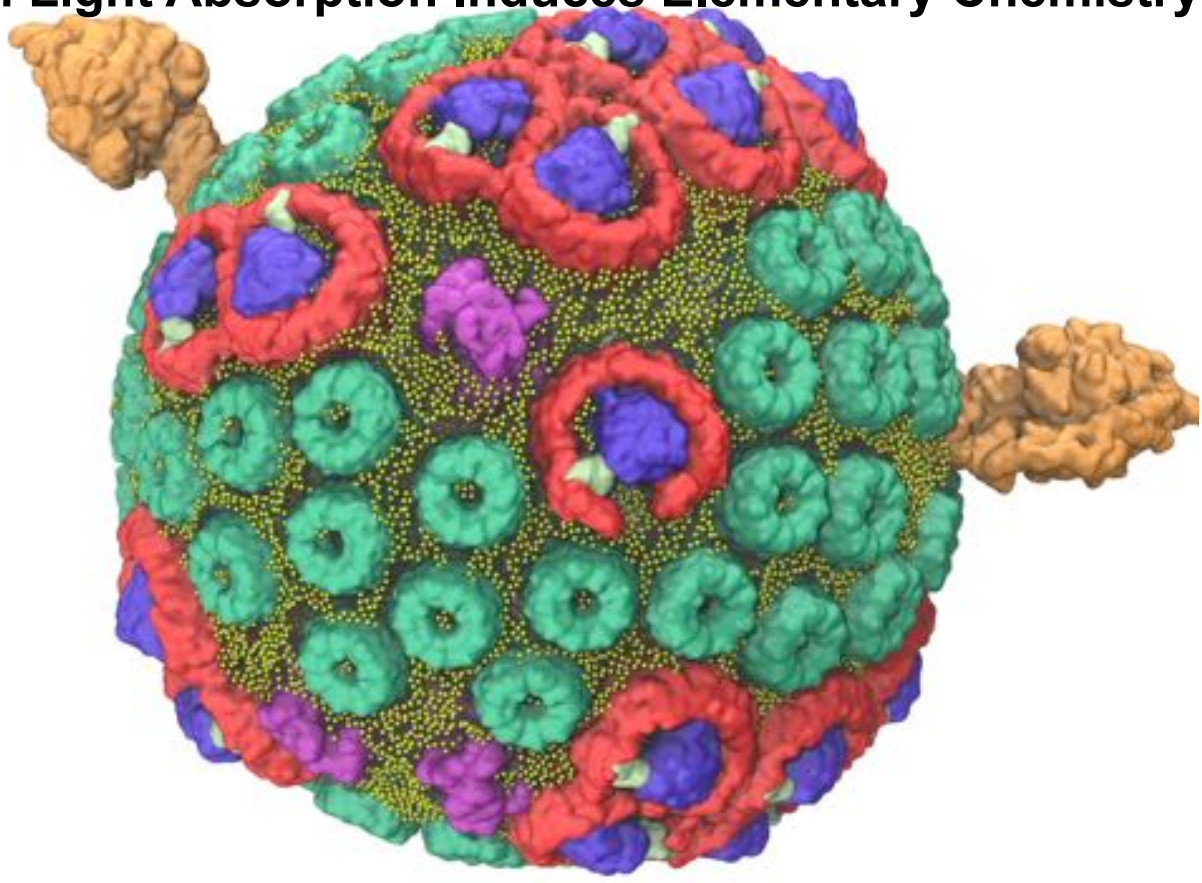
Blue Waters Uncovers Photosynthesis



100 million atom simulation

Key person
Abhi Singaroy
(UIUC)

Sun Light Absorption Induces Elementary Chemistry



Finally Sun Light Produces Biological Fuel ATP