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

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
VMD: A Thinking Tool

to visualize and analyze trajectories from small peptides...

video: www.lundbeckfoundation.com
VMD: A Thinking Tool

...to extremely large biological structures

VMD: A Thinking Tool

and provides state-of-the-art rendering

video: www.lundbeckfoundation.com
VMD Plugins
Advanced Tools developed **In-House** and by **External Users**

### Analysis
- APBSRun
- CadCCD
- Contact Map
- GoRGUI
- HeatMapper
- ILSTools
- IRSpecGUI
- MultiSeq
- NAMD Energy
- NAMD Plot
- NetworkView
- NMViz
- ParaFEPE
- PBCTools
- PDEPut
- Propka GUI
- RamaPut
- RMSD Tool
- RMSD Trajectory Tool
- RMSD Visualizer Tool
- Salt Bridges
- Sequence Viewer
- Symmetry Tool
- Timeline
- VMDMap

### Modeling
- Autoionize
- AutoPSF
- Chirality
- Cionize
- Cispeptide
- CGTools
- Dowsor
- Force Field Toolkit
- Inorganic Builder
- MDFF
- Membrane
- Merge Structures
- Molefacture
- Mutator
- Nanotube
- Paratool
- Pfgen
- RESPTool
- RNAView
- Solvate
- SSRestraints
- TopoTools

### Visualization
- Clipping Plane Tool
- Clone Rep
- DemoMaster
- Dipole Watcher
- InterSurf
- Navigate
- NavFly
- MultiMolAnim
- Color Scale Bar
- Virtual DNA Viewer
- VMD Movie Maker

### 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
- InterOw
- SurfOw
- vmdOw

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**Tool to compute force field parameters for small molecules**

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
- GoRGUI
- HeatMappar
- ILSTools
- IRSpecGUI
- MultiSeq
- NAMD Energy
- NAMD Plot
- NetworkView
- NMWiz
- ParseFEP
- PBCTools
- PropKa GUI
- RamaPlot
- RMSE Tool
- RMSE Trajectory Tool
- RMSE Visualizer Tool
- Salt Bridges
- Sequence Viewer
- Symmetry Tool
- Timeline
- VolMap

**Tool for free-energy changes in alchemical transformations**

List of Most Read Articles for 2012

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

**NMWiz**
Normal Mode Wizard for VMD

**ParseFEP**

**PBCTool**

ProDy interface

VMD Plugins

Advanced Tools developed In-House and by External Users

A tool to identify events in molecular dynamics trajectories

Extreme Scaling Workshop, 2013, 43-50.

MD simulations can now fold proteins


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

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

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

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

We agreed with experiment. So what did we discover?

\[ \Phi(\lambda) = F(\lambda) + \frac{1}{2} F'(\lambda)^2 - \frac{1}{3} F''(\lambda)^3 + O(1/\lambda^2) \]

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

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.

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

Crystallography and simulation permit investigation into how the system functions.

\[
\text{Extension} = \sum \langle x_i \exp[fx_i/k_B T]\rangle_{V_i} / \langle \exp[fx_i/k_B T]\rangle_{V_i} = g(f)
\]

We look at six domains.
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

Key person: Rafael Bernardi (UIUC)

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
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*  

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

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

Ankyrin repeats form an extremely soft spring

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

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


ssDNA bases get tilted one way in narrow pore!

Discover How Membrane Protein Functions - Aquaporin

Nobel Prize in 2003 was awarded to Peter Agre

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

water orientation prevents proton passage

protein dipole

water diffuses 10 times slower than in bulk
Aquaporin Conducts Water, But Not Protons

Protein dipole

Water orientation prevents proton passage

Free energy (kcal/mol)

Coordinate along the channel (Å)

18 kcal/mol

Aquaporin Conducts Water, But Not Protons

Proton passage barrier calculated by Quantum Mechanics


All-Atom Molecular Dynamics Today

HIV Capsid
ATP Synthase
Lysozyme
Aquaporin
STMV
Ribosome
Photosynthetic Chromatophore

Number of Atoms

10^8
10^7
10^6
10^5

(2 nm)^3
(100 nm)^3
Blue Waters Fights Antibiotic Drug Resistance - Todays Medical Emergency No. One

The erythromycin drug disturbs bacterial protein synthesis.

Macrolide antibiotics allosterically predispose the ribosome for translation arrest. 

Collaborators: Mankin (UIC), Wilson (LMUM)

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

BlueWaters Opens New Chapter in HIV Treatment

HIV-1 virion

186 hexamers
12 pentamers
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