**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**

- HIV (2013)
- Cadherin (2005)
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

used by 100,000 scientists worldwide

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

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- IRSpecGUI
- MultiSeq
- NAMD Energy
- NAMD Plot
- NetworkView
- NMWiz
- ParseFEP
- PMEpot
- Propka GUI
- RamaPlot
- RMSD Tool
- RMSD Trajectory Tool
- RMSD Visualizer Tool
- Salt Bridges
- Sequence Viewer
- Symmetry Tool
- Timeline
- VoltMap

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
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- Symmetry Tool
- Timeline
- VoltMap

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

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

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

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

Key Folding Intermediates

Key person
Peter Freddolino
(now U. Michigan)
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

AFM tip exerting force on Ig domain
Forced Unfolding of Titin Ig Domain

We agreed with experiment. So what did we discover?

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-lg elasticity

*Key person*

Jen Hsin (now Google)

**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 permit investigation into how the system functions.

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

*Key person:* Rafael Bernardi (UIUC)

Cohesin

Dockerin

Carbohydrate Binding Module

Challenging environments guided nature in the development of ultrastable protein complexes
Strongest Measured Adhesion Bond

Adhesion becomes stronger when force is applied.

Collaboration with Hermann Gaub (Munich)

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

**AFM MEASUREMENTS**
*Spring constant* ~ 2.4 mN/m

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.
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

PREDICTIONS FROM SIMULATIONS
Unfolding force doubles adding calcium

AFM MEASUREMENTS
Unfolding force doubles adding calcium

Calcium Controlled Elasticity
Calcium prevents unfolding of Cadherin domains

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


Key person: Aleksei Aksimentiev (UIUC)

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

Amit: Yes, yes! But why? But why?
Simulations Assist in the Design of Nanopore Devices for DNA Sensing

Graphene Nanopore Sensing Device

MD simulations combined with quantum mechanics calculations

Counting nucleobases


ssDNA bases get tilted one way in narrow pore!

All-Atom Molecular Dynamics Today

Number of Atoms

HIV Capsid

ATP Synthase

Lysozyme

Aquaporin

STMV

Ribosome

Photosynthetic Chromatophore

(100 nm)$^3$

(2 nm)$^3$


The erythromycin drug disturbs bacterial protein synthesis.


**Collaborators:** Mankin (UIC), Wilson (LMUM)

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