Enhanced Charm++ Replica Facility
For The Computational Microscope

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http://www.ks.uiuc.edu/Research/namd/

NCSA/UIUC Enhanced Intellectual Services for Petascale Performance (NEIS-P²) Program 2013 Blue Waters Symposium
NAMD: Scalable Molecular Dynamics

2002 Gordon Bell Award

58,000 Users, 2900 Citations

ATP synthase

PSC Lemieux

Computational Biophysics Summer School

Blue Waters Target Application

GPU Acceleration

Illinois Petascale Computing Facility

NVIDIA Tesla

NCSA Lincoln

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Computational Microscopy

Ribosome: synthesizes proteins from genetic information

Silicon nanopore: bionanodevice for sequencing DNA
Molecular Mechanics Force Field

\[ U(\vec{R}) = \sum_{\text{bonds}} k_i^\text{bond} (r_i - r_0)^2 + \sum_{\text{angles}} k_i^\text{angle} (\theta_i - \theta_0)^2 + \]

\[ U_\text{bond} + U_\text{angle} + \sum_{\text{dihedrals}} k_i^\text{dihedral} [1 + \cos (n_i \phi_i + \delta_i)] + \]

\[ U_\text{dihedral} + \sum_{i \neq j} \sum_i 4\varepsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\varepsilon r_{ij}} \]

\[ U_\text{nonbond} \]
Classical Molecular Dynamics

Energy function: \[ U(\vec{r}_1, \vec{r}_2, \cdots \vec{r}_N) = U(\vec{R}) \]

used to determine the force on each atom:

\[ m_i \frac{d^2 \vec{r}_i}{dt^2} = \vec{F}_i = -\nabla U(\vec{R}) \]

Newton’s equation represents a set of N second order differential equations which are solved numerically via the Verlet integrator at discrete time steps to determine the trajectory of each atom:

\[ \vec{r}_i(t + \Delta t) = 2\vec{r}_i(t) - \vec{r}_i(t - \Delta t) + \frac{\Delta t^2}{m_i} \vec{F}_i(t) \]

Small terms added to control temperature and pressure.
# Biomolecular Time Scales

<table>
<thead>
<tr>
<th>Motion</th>
<th>Time Scale (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bond stretching</td>
<td>$10^{-14}$ to $10^{-13}$</td>
</tr>
<tr>
<td>Elastic vibrations</td>
<td>$10^{-12}$ to $10^{-11}$</td>
</tr>
<tr>
<td>Rotations of surface sidechains</td>
<td>$10^{-11}$ to $10^{-10}$</td>
</tr>
<tr>
<td>Hinge bending</td>
<td>$10^{-11}$ to $10^{-7}$</td>
</tr>
<tr>
<td>Rotation of buried sidechains</td>
<td>$10^{-4}$ to 1 sec</td>
</tr>
<tr>
<td>Allosteric transitions</td>
<td>$10^{-5}$ to 1 sec</td>
</tr>
<tr>
<td>Local denaturations</td>
<td>$10^{-5}$ to 10 sec</td>
</tr>
</tbody>
</table>

Max Timestep: 1 fs
Parallel Programming Lab
University of Illinois at Urbana-Champaign

http://charm.cs.illinois.edu/

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Beckman Institute, UIUC
Historical perspective

- 1993: First paper with Charm++ as a name for our system appeared in OOPSLA ‘93
  - Prior to that we had a C-based system called Charm
  - So, it has been (gulp) 20 years!
- NAMD development in Charm++ : 94-95
- 1994: Articulated Design Philosophy
Object based over-decomposition

• Let the programmer decompose computation into objects
  – Work units, data-units, composites
• Let an intelligent runtime system assign objects to processors
  – RTS can change this assignment during execution
• This empowers the RTS
  – The research agenda started with the simple precept above, just before NAMD,
  – Continued until now!
Charm++

- Multiple indexed collection of C++ objects
- Programmer expresses communication between objects
Over-decomposition

Message-driven execution
- Perfect prefetch
- Automatic overlap of Communication and Computation

Migratability
- Compositionality

Introspective and adaptive runtime system
- Dynamic load balancing (topology-aware, scalable)
- Temperature/Power/Energy Optimizations

Fault Tolerance
Charm++ is a robust system

- Nightly build system
  - Dozens of machine, OS, Network, compiler combinations
  - 50,000 NAMD users depend on it
- Git repository, in addition to regular releases
- Online manuals, tutorials, ..
- Recent addition of Redmine (publicly accessible) to track bug-reports, bug-fixes, and feature development
Charm++ is scalable & efficient

- Demonstrated on many min-apps of our own
  - Barnes-Hut (scaled to 32k+ cores)
  - LU (HPL)
  - LeanMD
  - Structured Adaptive Mesh Refinement (AMR)
  - FFT
  - Sparse-Triangular solver
  - ....
  - HPC Challenge award in 2011 (shared w Chapel)
Some Charm++ Applications

NAMD

OpenAtom

ChaNGa

Rocstar

Episimdemics

Others:
• BRAMS
• ISAM
• Stochastic Optimization
• ...

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An upcoming book
Surveys seven major applications developed using Charm++
Charm++ Used by NAMD

• Parallel C++ with *data driven* objects.
• Asynchronous method invocation.
• Prioritized scheduling of messages/execution.
• Measurement-based load balancing.
• Portable messaging layer.
NAMD Overlapping Execution

Phillips et al., SC2002.

Objects are assigned to processors and queued as data arrives.
NAMD 2.8 Highly Scalable Implicit Solvent Model

NAMD Implicit Solvent is 4x more scalable than Traditional Implicit Solvent for all system sizes, implemented by one GRA in 6 months.

100M Atoms on Titan vs Jaguar

Published at SC12

5x5x4 STMV grid
PME every 4 steps

New Optimizations
- Charm++ uGNI port
- Node-aware optimizations
- Priority messages in critical path
- Persistent FFT messages for PME
- Shared-memory parallelism for PME
Larger machines enable larger simulations
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1990-2017
Physics of in vivo Molecular Systems

Biomolecular interactions span many orders of magnitude in space and time. Center software provides multi-scale computational modeling.

Biomolecular interactions span many orders of magnitude in space and time. Center software provides multi-scale computational modeling.

- femtoseconds
- Ångstrom
- hours
- microns

**MD**
- Potential-based
  - all atom
- Atomic interactions
- Configuration sampling

**BD**
- Potential-based
  - coarse grained
- Nonspecific interactions
- Nonspecific binding

**RDME**
- Probability-based
- Reaction probabilities
- Diffusion probabilities

**Center Software**
- NAMD: Scalable Molecular Dynamics
- MDFF: Molecular Dynamics Flexible Fitting
- HMMM: Highly Mobile Membrane Mimetic
- VMD: Visual Molecular Dynamics
- BrownianMover: Brownian Dynamics
- LatticeMicrobes: Whole Cell Simulations

**Molecular Systems**
- BD: Brownian Dynamics
- RDME: Reaction-diffusion master equation
Collaborative Driving Projects

1. Ribosome
   R. Beckmann (U. Munich)
   J. Frank (Columbia U.)
   T. Ha (UIUC)
   K. Fredrick (Ohio state U.)
   R. Gonzalez (Columbia U.)

2. Blood Coagulation Factors
   J. Morrissey (UIUC)
   S. Sligar (UIUC)
   C. Rienstra (UIUC)
   G. Gilbert (Harvard)

3. Whole Cell Behavior
   W. Baumeister (MPI Biochem.)
   J. Xiao (Johns Hopkins U.)
   C.N. Hunter (U. Sheffield)
   N. Price (U. Washington)

4. Biosensors
   R. Bashir (UIUC)
   J. Gundlach (U. Washington)
   G. Timp (U. Notre Dame)
   M. Wanunu (Northeastern U.)
   L. Liu (UIUC)

5. Viral Infection Process
   J. Hogle (Harvard U.)
   P. Ortoleva (Indiana U.)
   A. Gronenborn (U. Pittsburgh)

6. Integrin
   T. Ha (UIUC)
   T. Springer (Harvard U.)

7. Membrane Transporters
   H. Mchaourab (Vanderbilt U.)
   R. Nakamoto (U. Virginia)
   D.-N. Wang (New York U.)
   H. Weinstein (Cornell U.)
Viral Infection Driving Projects

**Poliovirus**

Poliovirus is a model system for understanding how non-enveloped viruses bind to and enter a host cell.

**Human Immunodeficiency Virus 1**

Knowledge of HIV capsid atomic structure may reveal disassembly mechanism and guide novel therapies.

Ribosome Driving Project

Target of over 50% of antibiotics

Many related diseases. e.g. Alzheimer’s disease due to dysfunctional ribosome (J. Neuroscience 2005, 25:9171-9175)

Localization failure of nascent chain lead to neurodegenerative disease (Mol. Bio. of the Cell 2005, 16:279-291)
NAMD 2.6 Replica Exchange (2006)

- Implemented entirely in Tcl:
  - Rapid development
  - User-modifiable
  - Portable

- Master Tcl interpreter:
  - Splits allocated nodes and launches NAMD slaves
  - Communicates with slaves via Unix network sockets
  - Issues commands to slave Tcl interpreters

- Slave Tcl interpreter in NAMD slaves:
  - Listen to master socket
  - Run commands
  - Return results

- Supports parallel tempering

Not portable
NAMD 2.9 MPI-Based Replica Exchange

- Small patch for Charm++ MPI machine layer startup code:
  - Call MPI_Comm_split() to create “row” and “column” communicators
  - Charm++ uses “row” communicators instead of MPI_COMM_WORLD
  - Tcl interface to MPI_Send(), MPI_Recv(), MPI_Sendrecv() on “columns”

- Easier to use and more efficient:
  - Eliminates complex, machine-specific launch scripts
  - Scalable pair-wise communication between replicas
  - Fast communication via high-speed network

- Basis for many enhanced sampling methods:
  - Parallel tempering (temperature exchange)
  - Umbrella sampling for free-energy calculations
  - Hamiltonian exchange (alchemical or conformational)

- Great power and flexibility:
  - Enables petascale simulations of modestly sized systems
  - Leverages features of Collective Variables module
  - Tcl scripts can be highly customized and extended

Released in NAMD 2.9
NEIS-P² Project: Bypass MPI

- Modify Charm++ “LRTS” generic machine layer
- Enable fine-grained inter-replica communications
- Optimize replica partitions for machine topology

LRTS Gemini doubles usable XE nodes for strong scaling and is essential for use of multiple GPU-accelerated nodes per replica.
NAMD 2.10 Scalable Replica Exchange

• More general Charm++ integration:
  – NAMD 2.9 used MPI communicator splitting
  – NAMD 2.10 splits replicas in Charm++ low-level runtime (LRTS)
  – LRTS underlies MPI, Cray (uGNI), and BlueGene/Q (PAMI) implementations

• Basis for many enhanced sampling methods:
  – Parallel tempering (temperature exchange)
  – Umbrella sampling for free-energy calculations
  – Hamiltonian exchange (alchemical or conformational)
  – Finite Temperature String method
  – Nudged elastic band

• Better scaling for individual replicas:
  – Cray uGNI layer essential for multi-node GPU replicas
  – IBM BlueGene/Q will benefit similarly from PAMI layer
  – Porting native InfiniBand (ibverbs) layer to LRTS
NEIS-P² Collateral Benefits

• Adds a new dimension of parallelism to Charm++
  – Existing code runs unmodified within a partition
  – Enables evolution from petascale to exascale
• Supports partitions of different sizes
  – Single-node master partition
  – Small output-buffering partition
  – Varying performance requirements
• Enables pruning of undesirable nodes from job
  – Extract compact set of nodes from allocation
  – Eliminate Gemini shared with other jobs
• Enables replication-based soft fault tolerance
Free Energy Landscapes of GlpT Transporter Obtained from Bias-Exchange (Umbrella Sampling) Simulations

Mahmoud Moradi
Tajkhorshid Lab, May 2013
Inward-Facing ⇔ Outward-Facing (IF-OF) Transition of GlpT Transporter

Only the substrate-free (apo) IF structure is available.


The proposed mechanism.
Molecular Dynamics Simulation Protocols

1. Equilibrating GlpT in explicit solvent/membrane in the apo IF state (~120,000 atoms).
2. Finding/optimizing a biasing protocol capable of inducing the IF→OF transition in a reliable way through advanced colvar (collective variables) techniques.
3. Free energy calculations using bias-exchange umbrella sampling simulations based on the optimized biasing protocol.
4. Repeating the simulations for a substrate-bound GlpT and comparing the results to those of the apo GlpT.
IF ↔ OF transition induced by imposing rotational change on helices TM1 and TM7 (using orientation quaternions)

Number of water molecules along the pore (per Å) (verifying the transition from IF to OF)

10 ns IF equilibrium
20 ns nonequilibrium (IF → OF)
10 ns OF equilibrium
Free Energy Calculations Using Bias-Exchange Umbrella Sampling

- *Colvars*: orientation quaternions associated with helices 1 and 7 (two quaternion-based colvars).
- Initial conformations: 12 conformations selected from the optimized transition pathway (nonequilibrium simulations).
- Colvar centers and force constants associated with different replicas: Optimized (empirically) to get similar exchange rates for all neighboring replicas (28-35%).

Only 12 replicas (each running for 40 ns) are enough for a good sampling.
Following the trajectory of one of the 12 shows that it visits most of the windows in 40 ns.
GlpT Free Energy Maps

Free Helices - Involved in the cytoplasmic opening/closing

Steered Helices - Involved in the periplasmic opening/closing
GlpT Free Energy Minima

No sample
≥12
11
10
9
8
7
6
5
4
3
2
1
0

kcal/mol

TM1^TM7

TM1^TM7

OF

IF

apo state

P_i-bound state

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GlpT Least Free Energy Path

Method of Ensing et al., JPCB 109 6676 (2005).

No sample

≥12

11

10

9

8

7

6

5

4

3

2

1

0

kcal/mol

TM1^TM7

 apo state

 TM5^TM11

 TM1^TM7

 P_i-bound state

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It turns out the $P_i$ substrate lowers the barrier and shifts the global minimum from the IF to the OF state.
Thanks to: NIH, NSF, DOE, 
**Nikhil Jain, Yanhua Sun, Gengbin Zheng, Eric Bohm, Mahmoud Moradi**

James Phillips  
Beckman Institute, University of Illinois  
http://www.ks.uiuc.edu/Research/namd/