Discoveries Through the Computational Microscope

Investigation of drug (Tamiflu) resistance of the “swine” flu virus demanded fast response!

Klaus Schulten
Department of Physics and
Theoretical and Computational Biophysics Group
University of Illinois at Urbana-Champaign
The Computational Microscope

Viewing the Morphogenesis of a Cellular Membrane from Flat to Tubular in 200 $\mu$s

100 - 1,000,000 processors

DOE (INCITE)
Viewing the Morphogenesis of a Cellular Membrane from Flat to Tubular in 200 µs


Viewing How Proteins are Made from Genetic Blueprint

- **Ribosome** — Decodes genetic information from mRNA
- Important target of many antibiotics
- Static structures of crystal forms led to 2009 Nobel Prize
- But one needs structures of ribosomes in action!
Viewing How Proteins are Made from Genetic Blueprint

- **Ribosome** — Decodes genetic information from **mRNA**
- Important target of many **antibiotics**
- Static structures of crystal forms led to 2009 **Nobel Prize**
- But one needs structures of ribosomes in action!
Viewing How Proteins Are Made from Genetic Blueprint

Low-resolution data

High-resolution structure

Close-up of nascent protein
GPU Solution 3: Molecular Dynamics Simulations

NCSA Lincoln Cluster performance (8 Intel cores and 2 NVIDIA Tesla GPUs per node, 1 million atoms)

- 2 GPUs: ~2.8 s/step
- 4 GPUs
- 8 GPUs
- 16 GPUs

Molecular dynamics simulation of protein insertion process

GPUs reduced time for simulation from two months to two weeks!
**Viewing Nanopore Sensors**

**Genetics:** Genes control our bodies and experiences!
**Epigenetics:** Our bodies and experiences control the genes!

Epigenetics made possible through DNA methylation

Detect methylation with **nanopores**

Related pathologies: obesity, depression, cancer

- methylated DNA
- un-methylated DNA

**voltage (V)**

- 1.5
- 2
- 2.5
- 3
- 3.5
- 4

- 88 bp copies

- 1
- 10
- 100
- 1,000
- 10,000
- 100,000

- methylated DNA
- easy to move
- un-methylated DNA
- hard to move
Viewing Nanopore Sensors
Create a **Better Nanopore** with Polymeric Materials

New materials, new problems: Nanoprecipitation

Radial distribution functions identify nanoprecipitation

Precipitate
Liquid

nanoprecipitation of ions
GPU Solution 4: Computing Radial Distribution Functions

- 4.7 million atoms
- 4-core Intel X5550 CPU: **15 hours**
- 4 NVIDIA C2050 GPUs: **10 minutes**
- Fermi GPUs ~3x faster than GT200 GPUs: larger on-chip shared memory

![Graph showing Radial Distribution Functions](image)

- **Precipitate**
- **Liquid**

![Bar chart comparing performance](image)

- Intel X5550, 4-cores @ 2.66GHz
- 6x NVIDIA Tesla C1060 (GT200)
- 4x NVIDIA Tesla C2050 (Fermi)

**Faster**
Inspecting the mechanical Strength of a blood clot

Collaborator: Bernard C. Lim (Mayo Clinic College of Medicine)

20ns SMD Simulation of fibrinogen, 1.06 million atoms, 1.2 ns/day with pencil decomposition, 15 days on PSC XT3 Cray (1024 processors)


A Blood Clot
Red blood cells within a network of fibrin fibers, composed of polymerized fibrinogen molecules.
Inspecting the mechanical Strength of a blood clot

Collaborator: Bernard C. Lim (Mayo Clinic College of Medicine)

20ns SMD Simulation of fibrinogen, 1.06 million atoms, 1.2 ns/day with pencil decomposition, 15 days on PSC XT3 Cray (1024 processors)


A Blood Clot
Red blood cells within a network of fibrin fibers, composed of polymerized fibrinogen molecules.
Petascale simulations will Permit Sampling

For Example Carrying out a Second Simulation Required
by a Referee
Reaching for Overlapping Time Scales

Microsecond simulations of muscle elasticity


- simulation
- experiment (Carrion-Vazquez et al. 1999)
- experiment (Rief et al., 1997)

Stretched is I91, one of the 300 domains of titin

Longest ever (1 us) SMD simulation closes gap between simulation and experiment!!!!!!
Design of Tyrosine Kinase Sensor

- Peptides are attached to a gold surface. The end of oligopeptide contains rhodamine.
- Peptides are exposed to ATP and appropriate kinase.
- Electric field is applied; change in conformation depends on phosphorylation state.
- Distance from rhodamine determines magnitude of fluorescence signal.

Initial sequence: \{1 \text{GLU}\} \{2 \text{GLY}\} \{3 \text{ILE}\} \{4 \text{TYR}\} \{5 \text{GLY}\} \{6 \text{VAL}\} \{7 \text{LEU}\} \{8 \text{PHE}\} \{9 \text{LYS}\} \{10 \text{LYS}\} \{11 \text{LYS}\} \{12 \text{CYS}\}

Peptides are immobilized on the gold covered surface of nanocones. The nanostructures trap incident light within the surface, so they look darker than smooth surface. A thin layer of 5 nm titanium 5 square array pattern are created by a SEPERISE method (see text). A thin layer of 80 nm gold is deposited on top of the nanocone structures to activate the sensor.
MD Simulations Revealed Problems in Design

Initial sequence did not work due to surface adhesion and rhodamine aggregation

• Improved sequence. Avoid residues that strongly bind to gold surface.

• Rhodamines molecules tend to aggregate. Aggregation affects peptide bending.

• MD systems include gold surface, water, ions and 5x5 peptide grid, ~ 100,000 atoms.
• Different sequences tested under positive and negative volt biases.

initial sequence: {1 GLU} {2 GLY} {3 ILE} {4 TYR} {5 GLY} {6 VAL} {7 LEU} {8 PHE} {9 LYS} {10 LYS} {11 LYS} {12 CYS}
Current Design Improved

New sequence: rhodamine removed and measurement replaced by Raman spectroscopy

Rhodamine removed, fluorescence signal discarded

MD Simulations show that phosphorylated tyrosine bends the peptide depending on voltage polarity

Experiments show that peptide bends towards the surface at positive voltages, increasing the intensity of Raman shifts.

Peptide bending is now measured with Raman Spectroscopy. The detection relies on careful comparison of peak points.
Figure 4: Peptide phosphorylation revealed by molecular dynamics simulations. Panels (a) and (b) show the distance from the tyrosine residue to the gold surface for different voltage polarities. Error bars represent ± standard deviation. (a) Non-phosphorylated peptide sensor under +60 V (blue), -60 V (red) and 0 voltage biases. (b) Phosphorylated peptide sensor under +60 V (blue), -60 V (red) and 0 voltage biases. Panels (i) and (ii) show snapshots of two peptides after 5 ns for +60 V (i) and -60 V (ii) voltage biases. The peptides are represented as gray tubes. Rhodamine and tyrosine residues are shown in blue and red colors, respectively.
A new sequence is proposed from molecular dynamics simulations. There are no rhodamine caps, avoiding aggregation. Unnecessary lysine residues are changed to alanine residues. The resulting non-phosphorylated peptide sensor is still insensitive to an electric field, while the phosphorylated one is responsive to an external electric field; therefore the sensor should produce distinctive Raman signatures for opposite voltage polarities. Error bars represent standard deviation. Colors blue, red, and green represent +60 V, -60 V and 0 voltage biases.