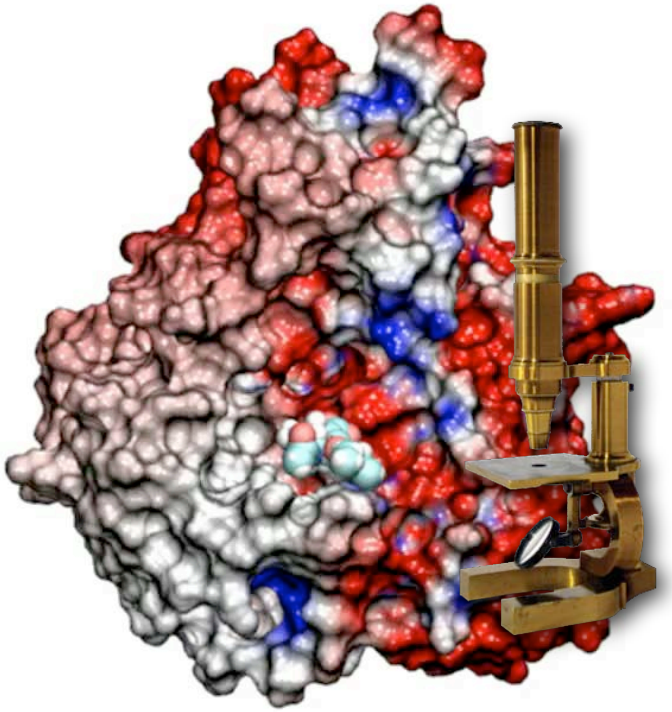
# Discoveries Through the Computational Microscope

Accuracy • Speed-up • Unprecedented Scale



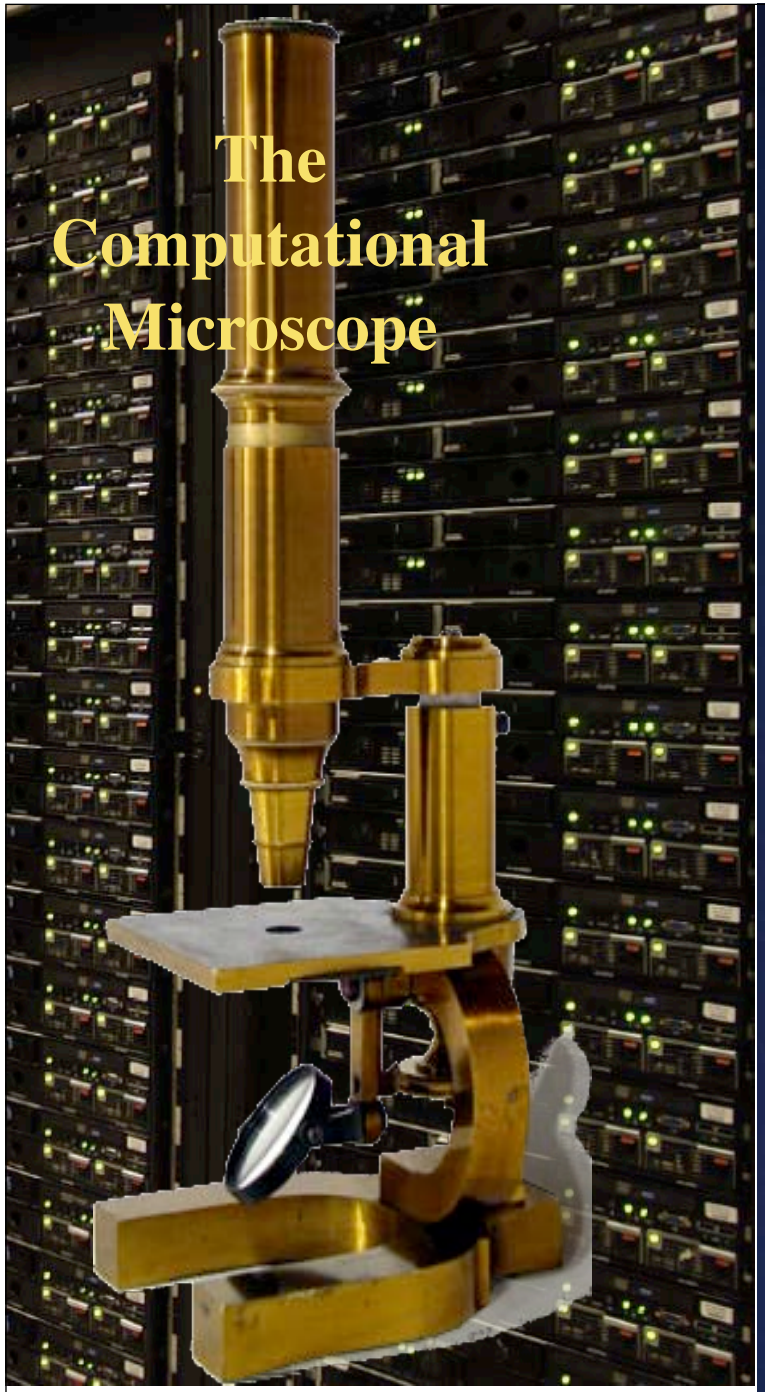

Investigation of drug (Tamiflu) resistance of the "swine" flu virus demanded **fast response!**

Klaus Schulten

Department of Physics and

Theoretical and Computational Biophysics Group

University of Illinois at Urbana-Champaign

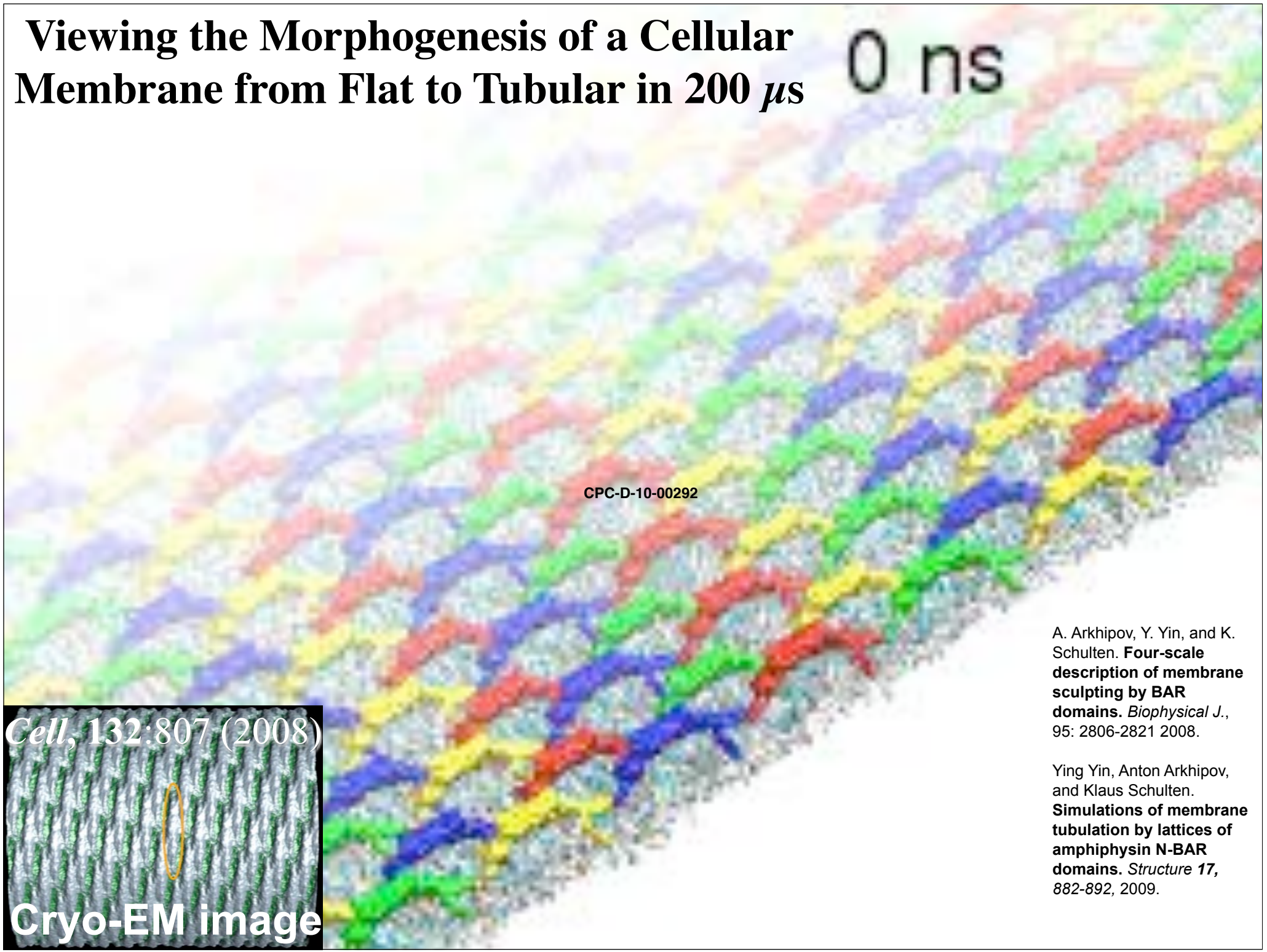



**100 - 1,000,000 processors**

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

DOE (INCITE)

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





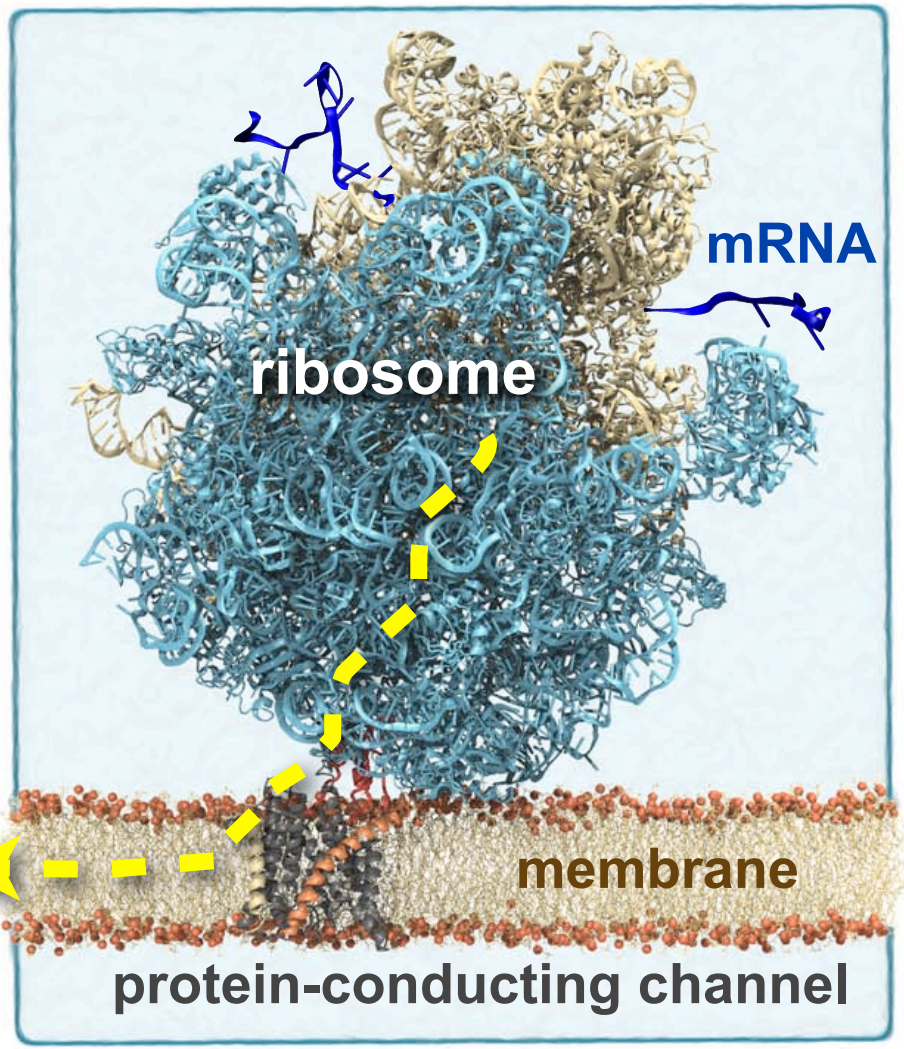


A. Arkhipov, Y. Yin, and K. Schulten. **Four-scale description of membrane sculpting by BAR domains.** *Biophysical J.*, 95: 2806-2821 2008.

Ying Yin, Anton Arkhipov, and Klaus Schulten. **Simulations of membrane tubulation by lattices of amphiphysin N-BAR domains.** *Structure* ***17,*** *882-892,* 2009.

# 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!**



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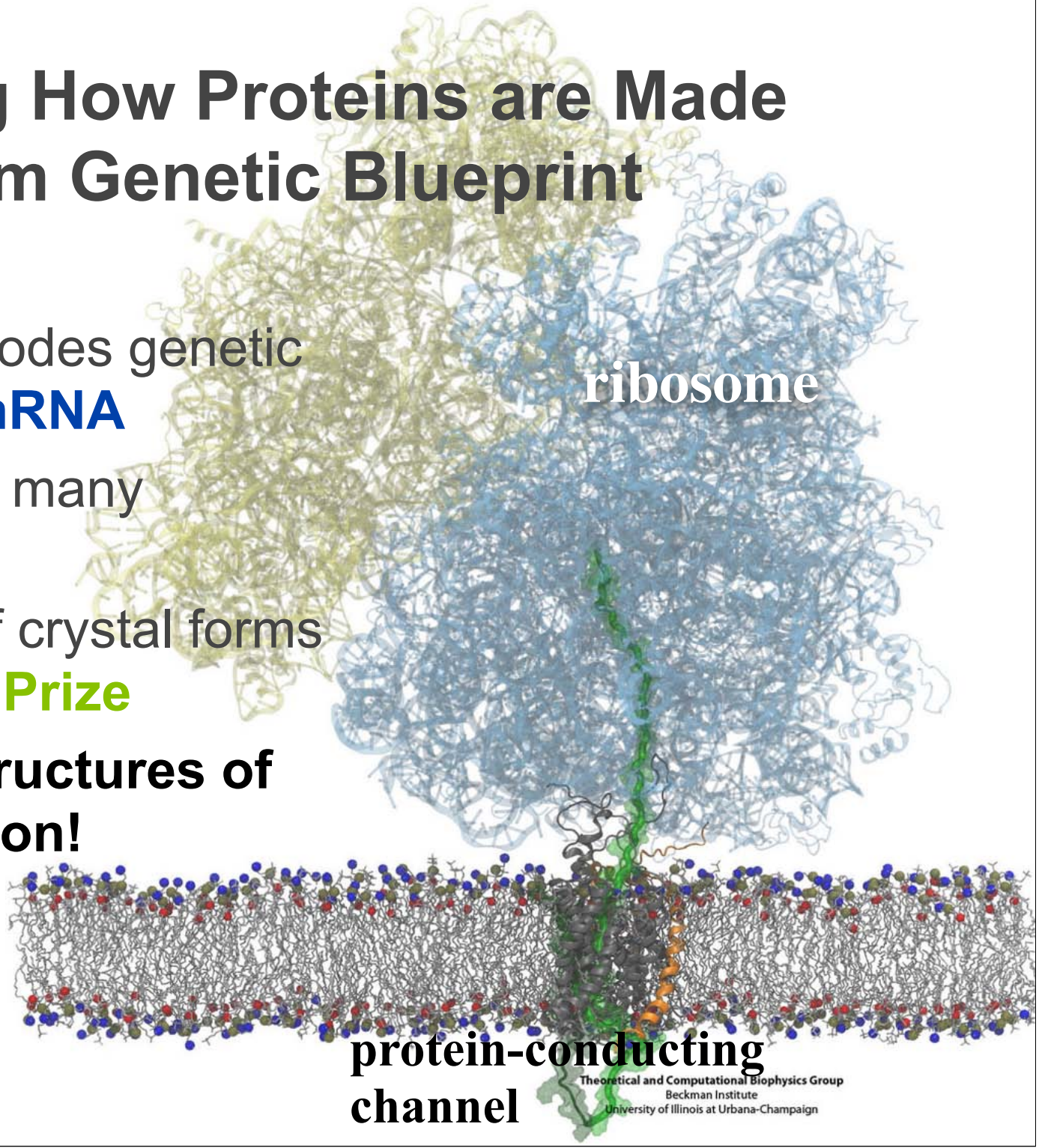
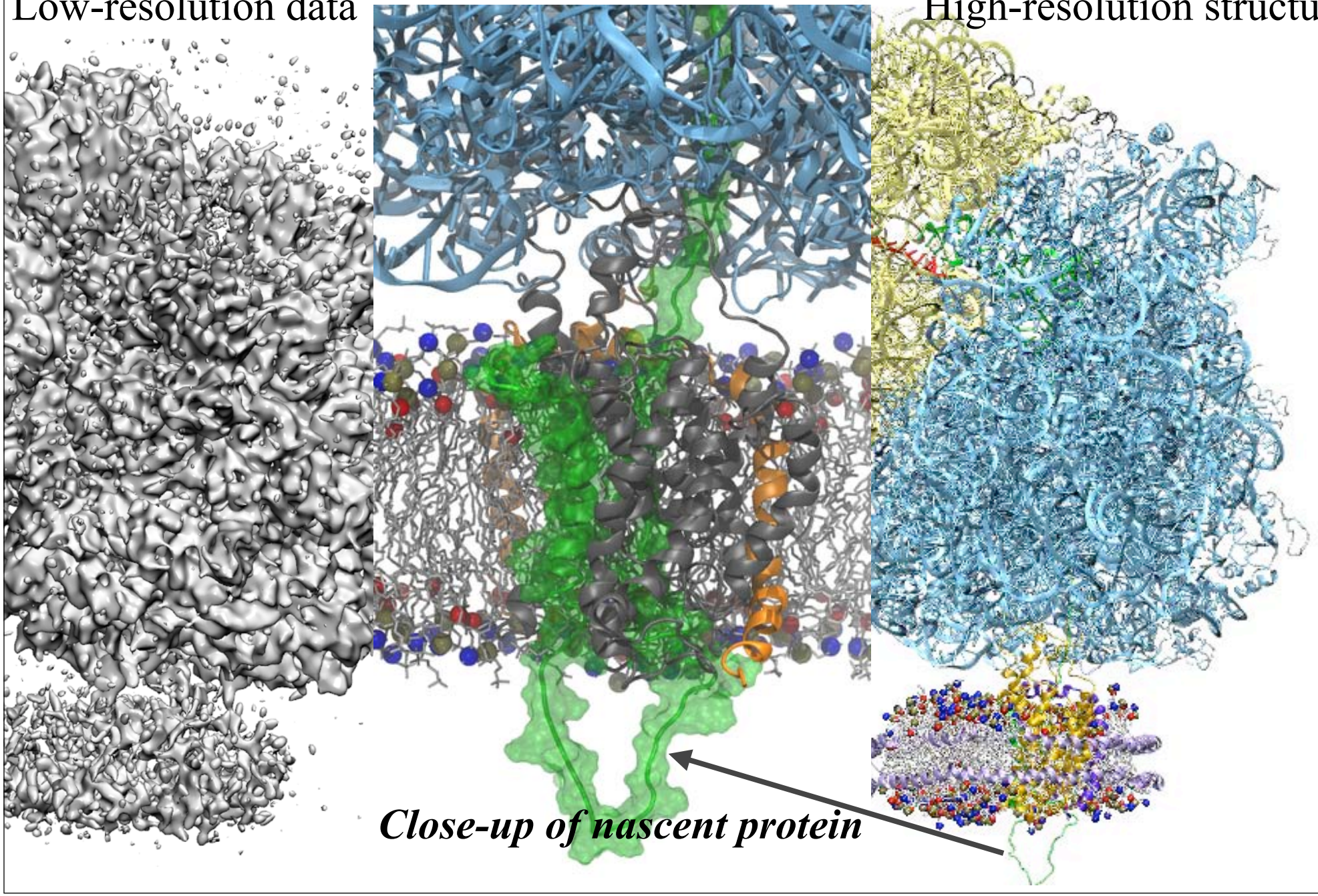


# Viewing How Proteins Are Made from Genetic Blueprint

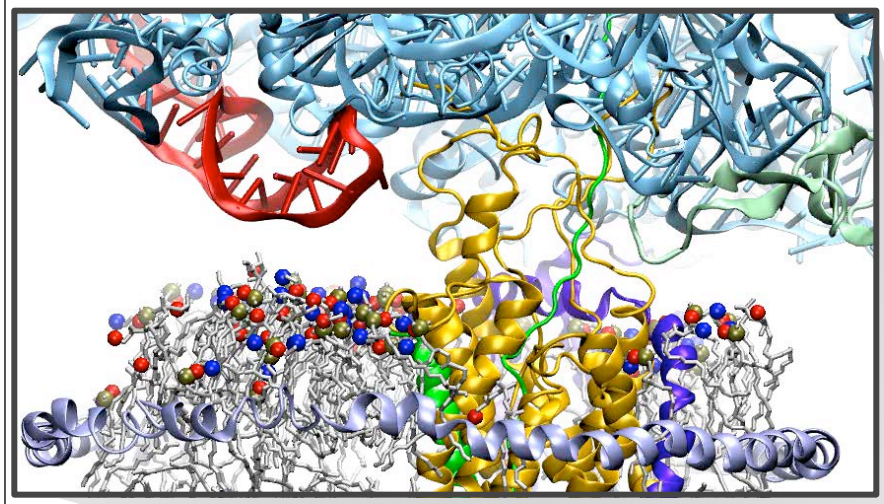
Low-resolution data

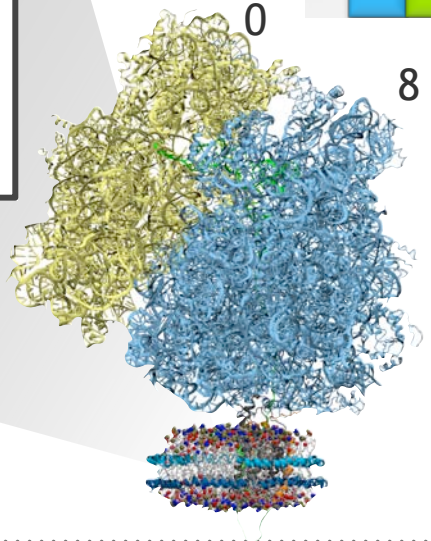
High-resolution structure



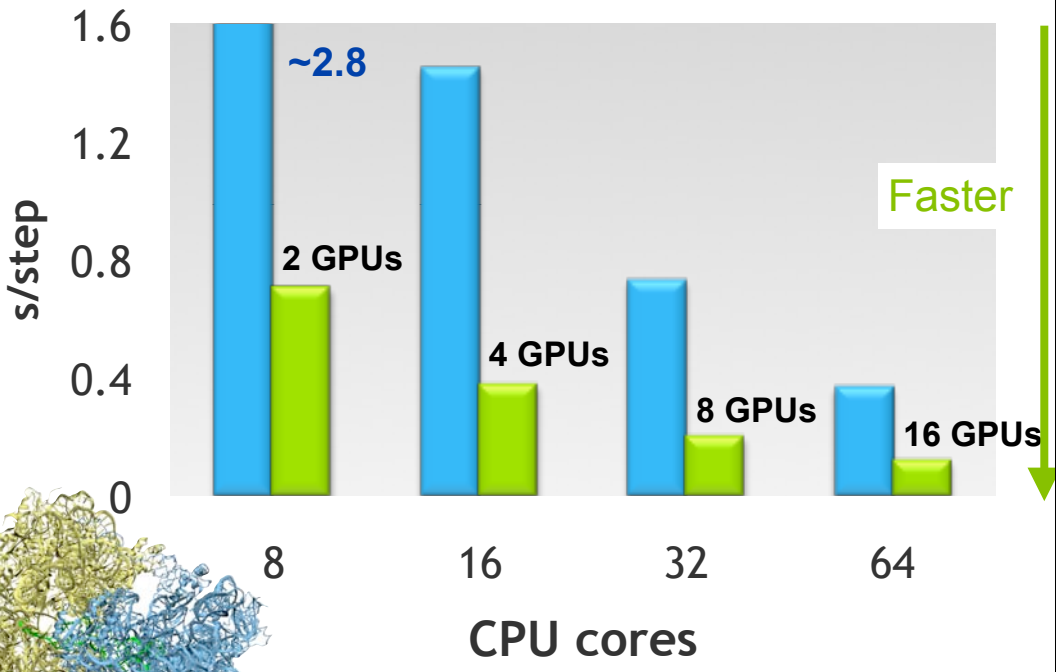
*Close-up of nascent protein*

# GPU Solution 3: Molecular Dynamics Simulations





Molecular dynamics simulation of protein insertion process



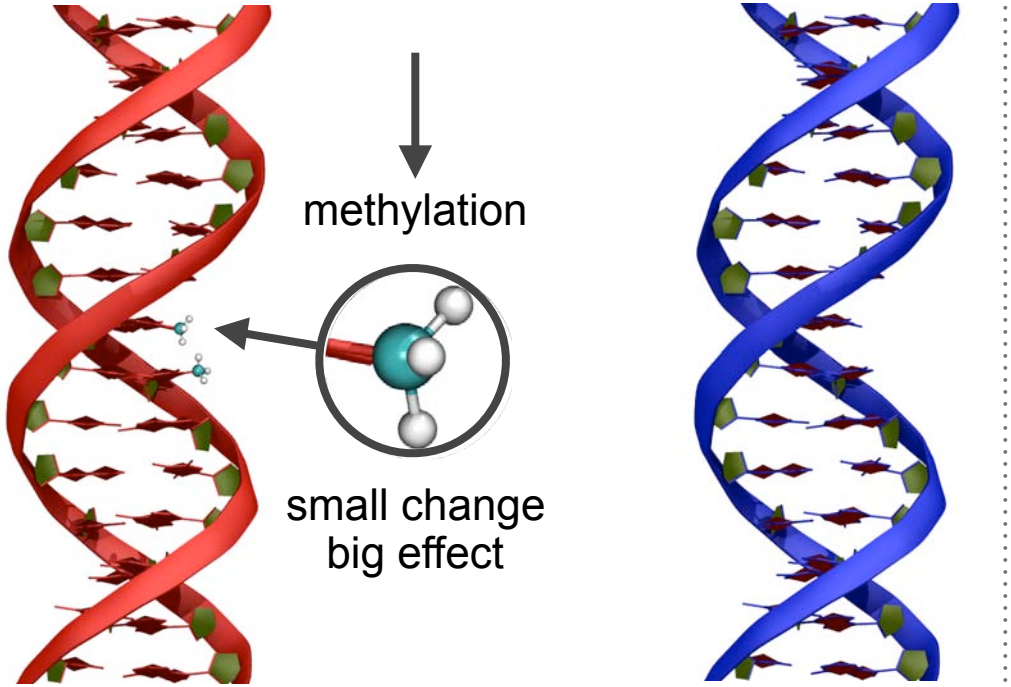

NCSA Lincoln Cluster performance (8 Intel cores and 2 NVIDIA Tesla GPUs per node, 1 million atoms)

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

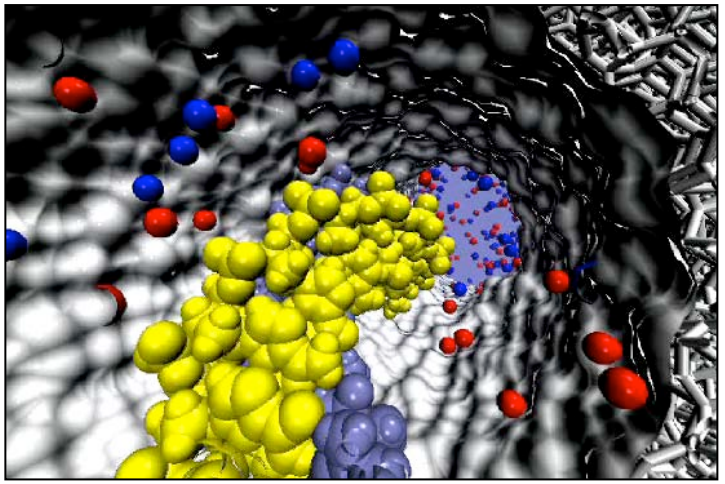
# Viewing Nanopore Sensors

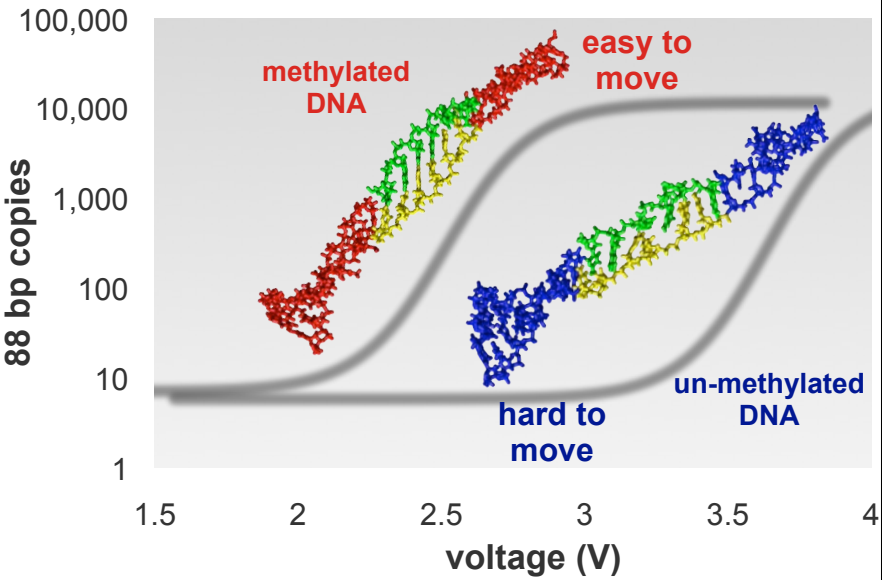
**Genetics: Genes control our bodies and experiences!**
**Epigenetics: Our bodies and experiences control the genes!**

Epigenetics made possible through DNA methylation




Detect methylation with **nanopores**



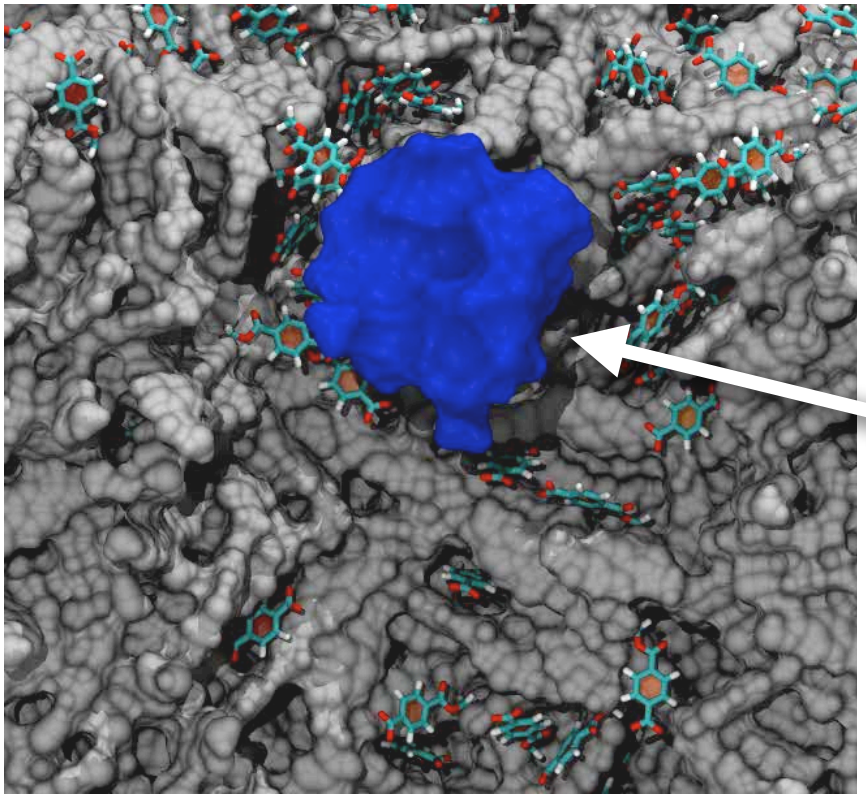



**Related pathologies: obesity, depression, cancer**

# Viewing Nanopore Sensors

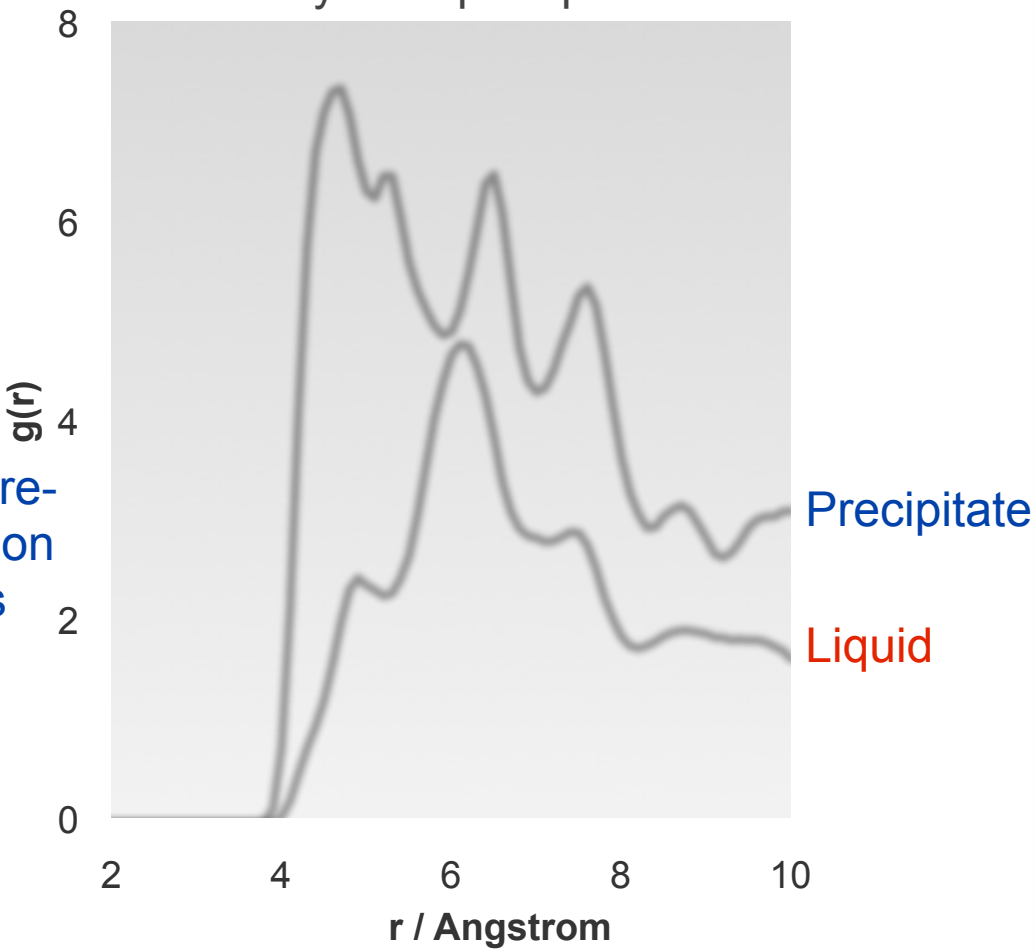
## Create a **Better Nanopore** with Polymeric Materials

**New materials, new problems:**
**Nanoprecipitation**



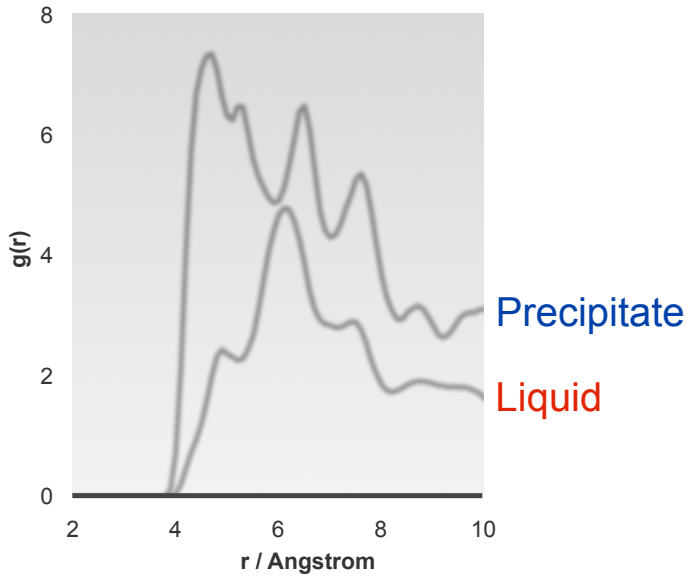
nanopre-
cipitation
of ions

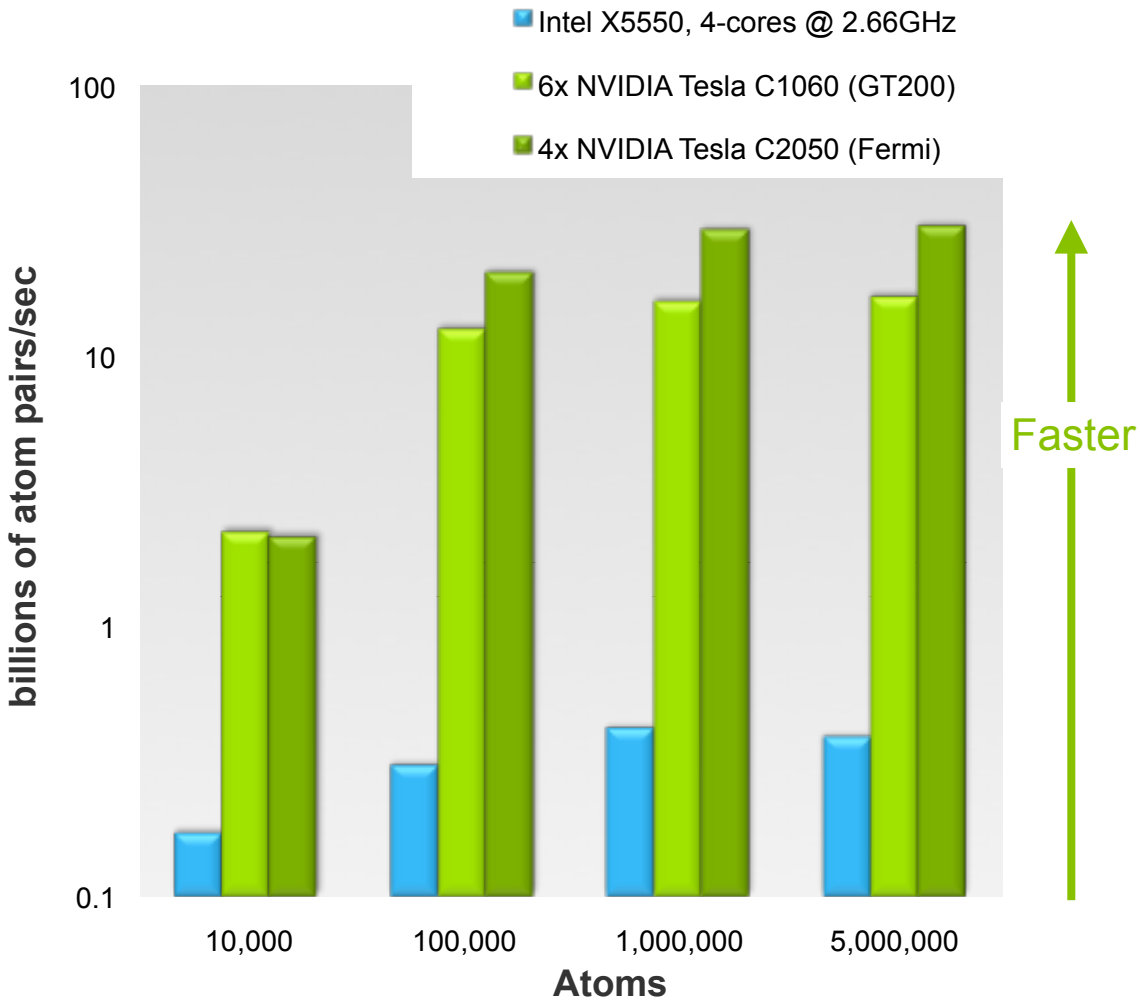
**Radial distribution functions**
identify nanoprecipitation



# GPU Solution 4: Computing Radial Distribution Functions

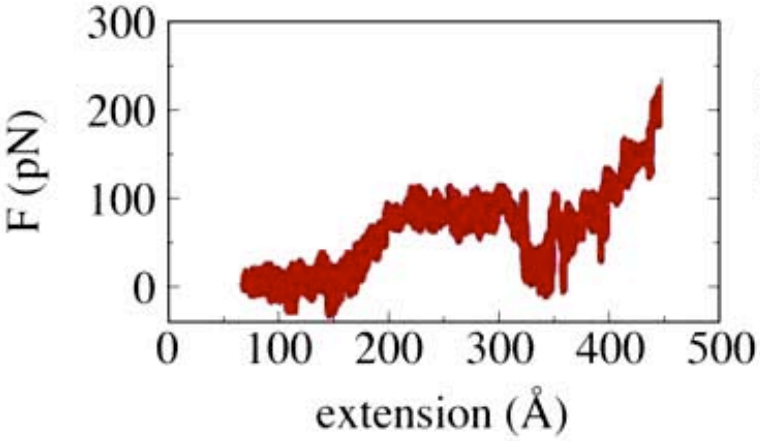
- 4.7 million atoms
- 4-core Intel X5550 CPU: **15 hours**
- 4 NVIDIA C2050 GPUs: **10 minutes**
- Fermi GPUs ~3x faster than GT200 GPUs: larger on-chip shared memory

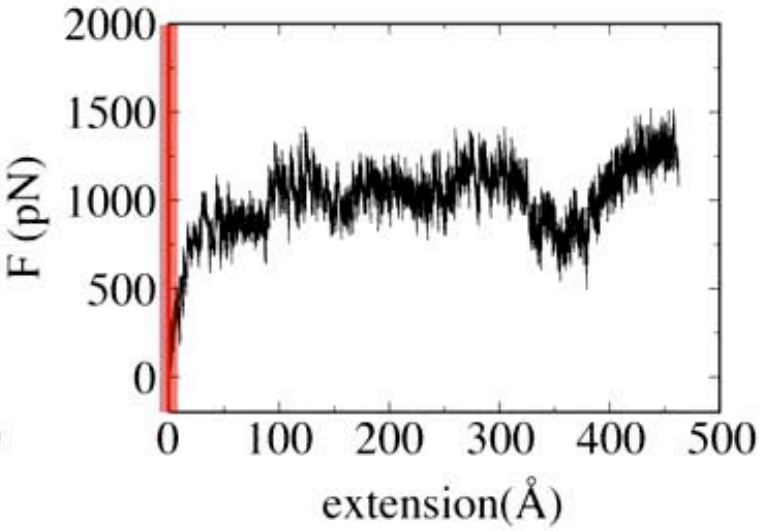


# Inspecting the mechanical Strength of a blood clot

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




**A Blood Clot**

**Red blood cells within a network of fibrin fibers, composed of polymerized fibrinogen molecules.**

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


B. Lim, E. Lee, M. Sotomayor, and K. Schulten. **Molecular basis of fibrin clot elasticity.** *Structure*, 16:449-459, 2008.



NIH Center for Research Resources

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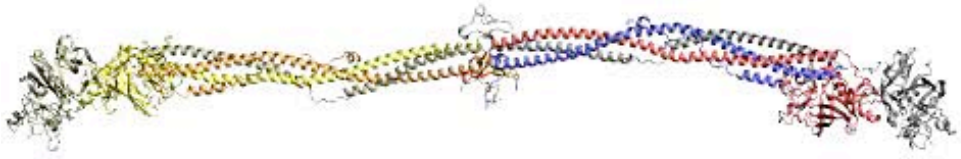

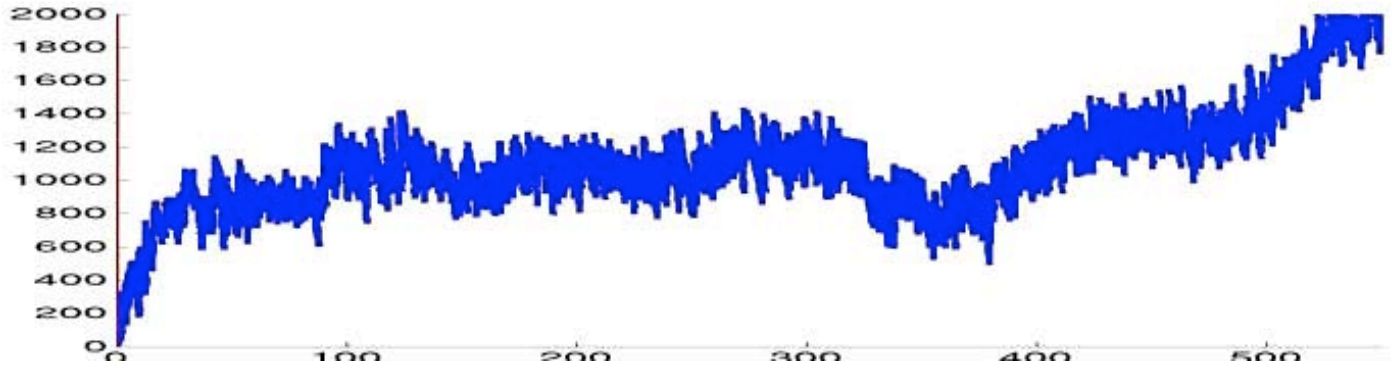


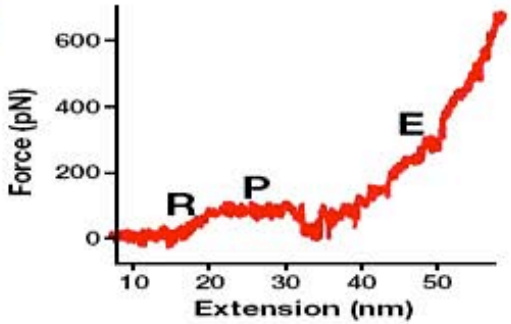


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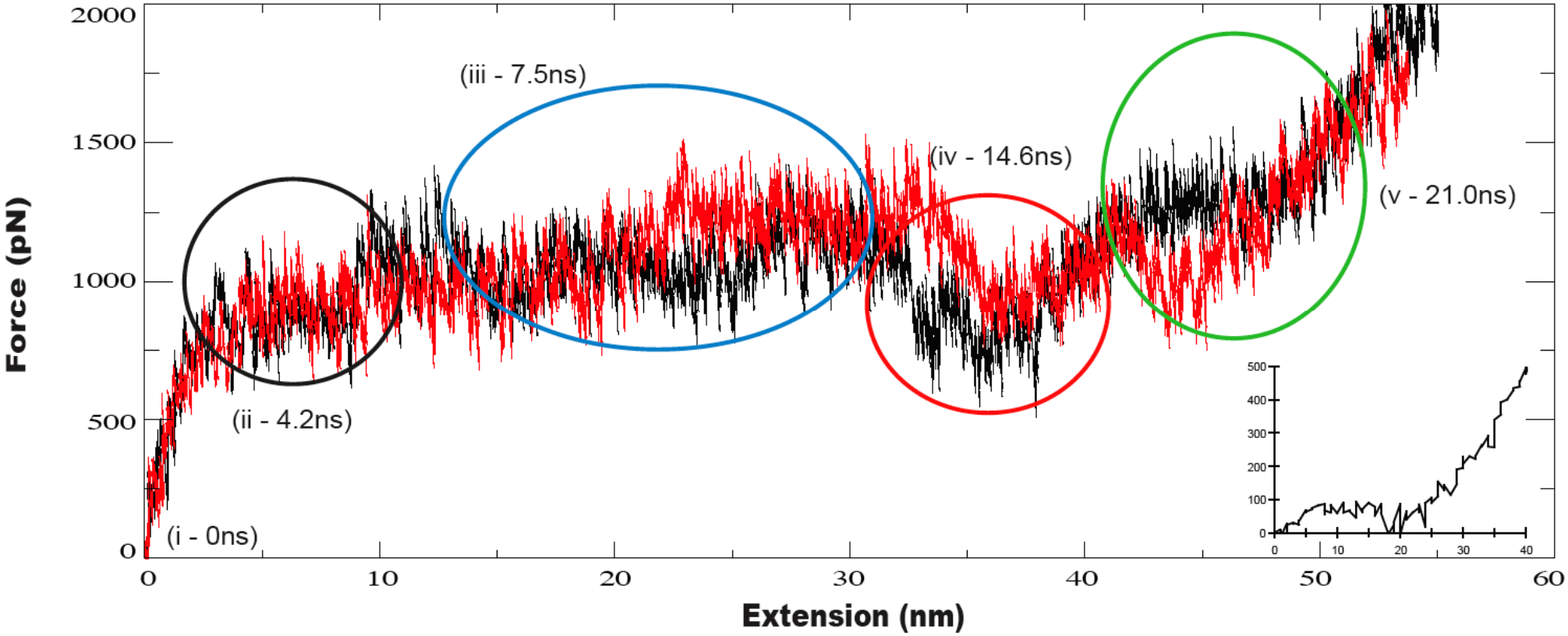
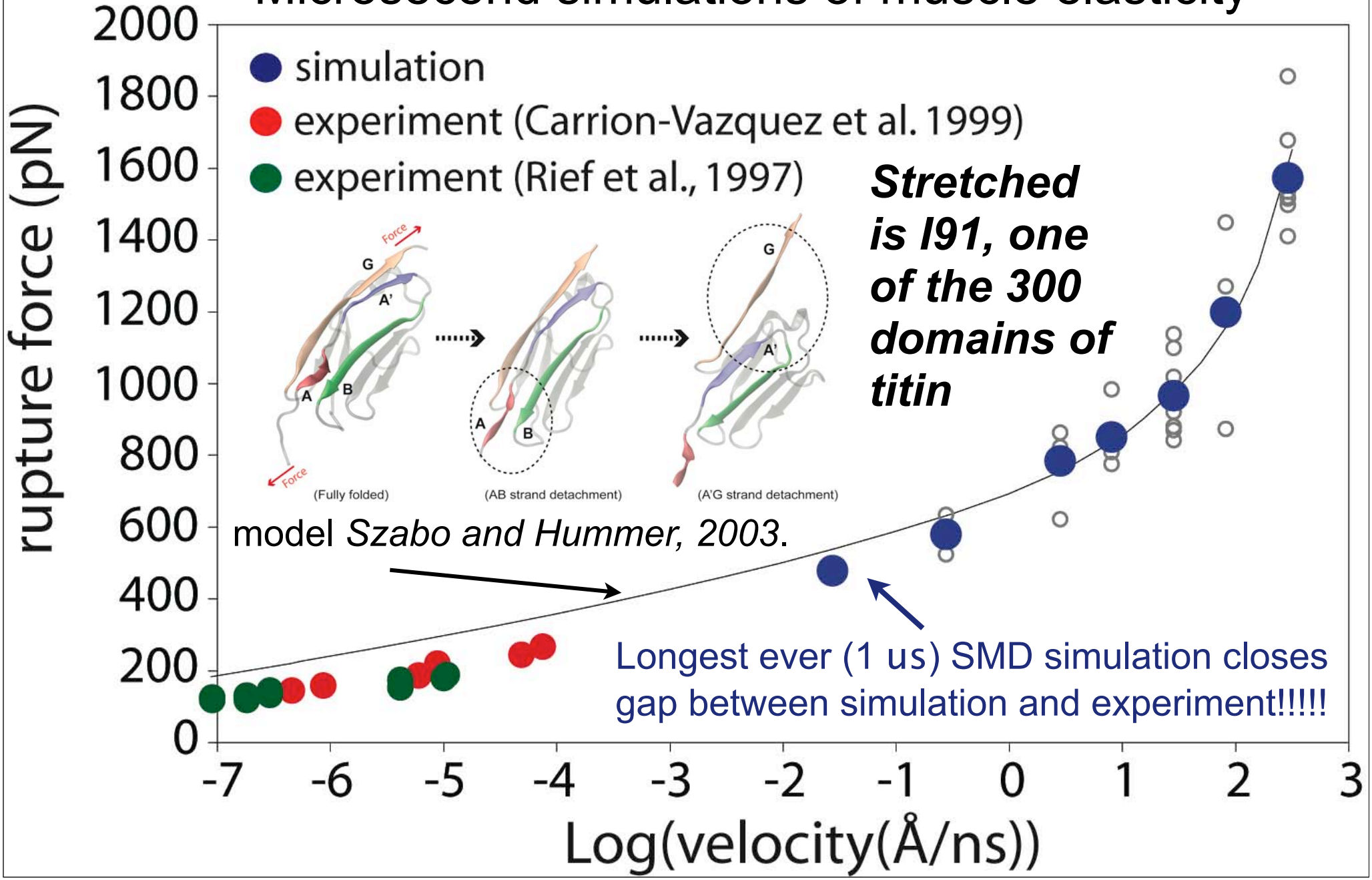
# Petascale simulations will Permit Sampling

*For Example Carrying out a Second Simulation Required by a Referee*

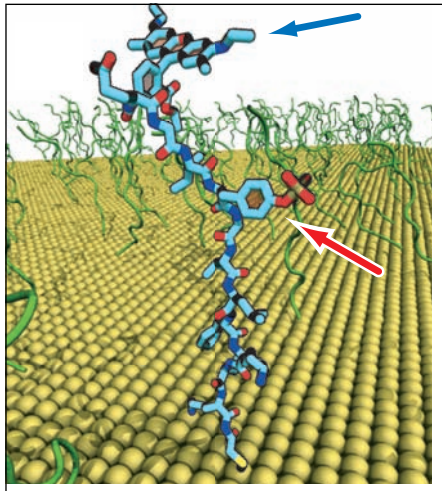


# Reaching for Overlapping Time Scales

## Microsecond simulations of muscle elasticity



# Design of Tyrosine Kinase Sensor

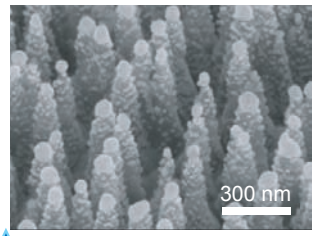


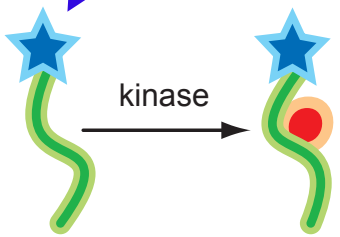
- Peptides are attached to a gold surface. The end of oligopeptide contains rhodamine.
- Peptides are exposed to ATP and appropriate kinase.
- Electric field is applied; change in conformation depends on phosphorylation state.
- Distance from rhodamine determines magnitude of fluorescence signal.

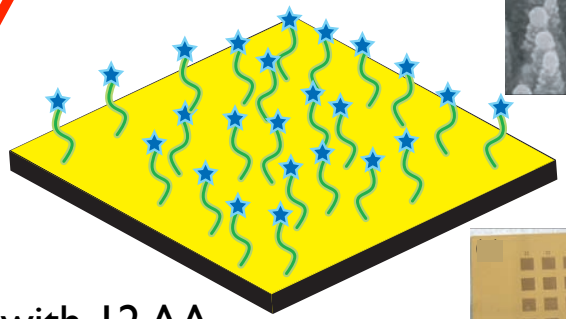
initial sequence: {1 GLU} {2 GLY} {3 ILE} {4 TYR} {5 GLY} {6 VAL} {7 LEU} {8 PHE} {9 LYS} {10 LYS} {11 LYS} {12 CYS}

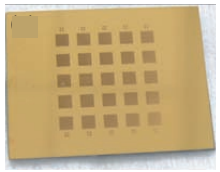
Rhodamine (R6g)

Tyrosine residue interacts with kinases by phosphorylation

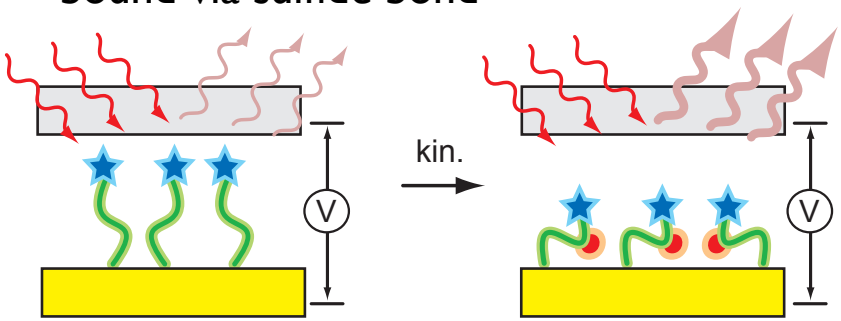


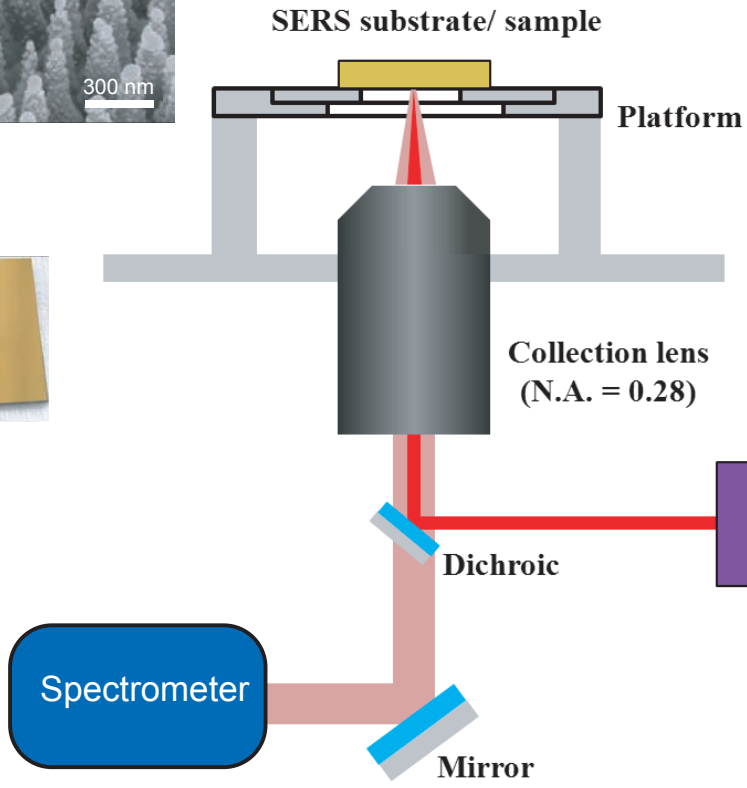





Au surface, oligopeptide with 12 AA, bound via sulfide bond

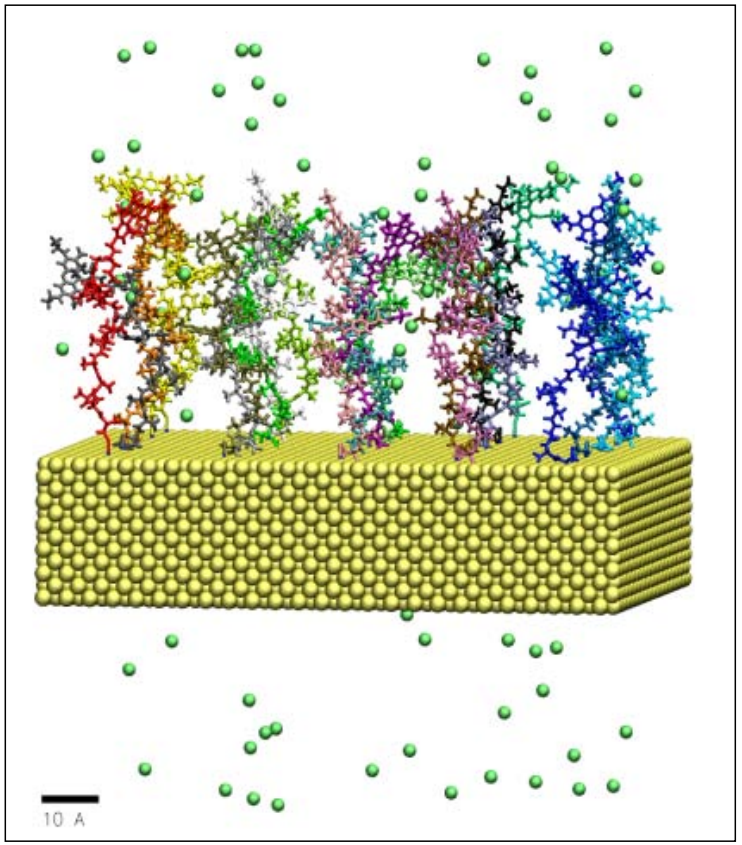


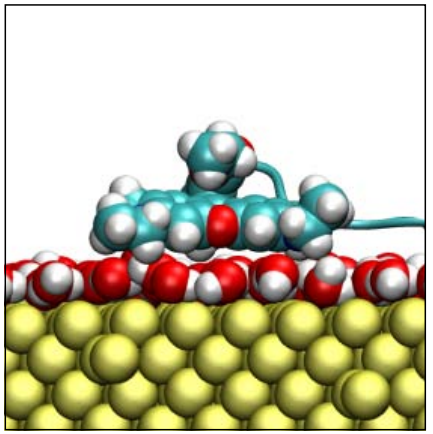
# MD Simulations Revealed Problems in Design

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}

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



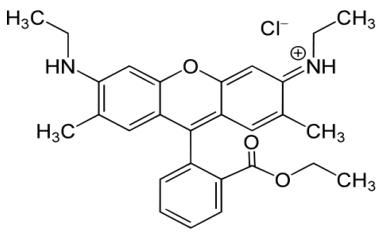

- MD systems include gold surface, water, ions and 5x5 peptide grid, ~ 100,000 atoms.
- Different sequences tested under positive and negative volt biases.

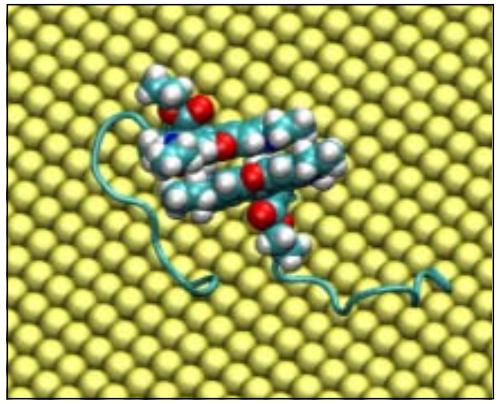


- **Improved sequence**. Avoid residues that strongly bind to gold surface.

- **Rhodamines molecules tend to aggregate**.

Aggregation affects peptide bending.

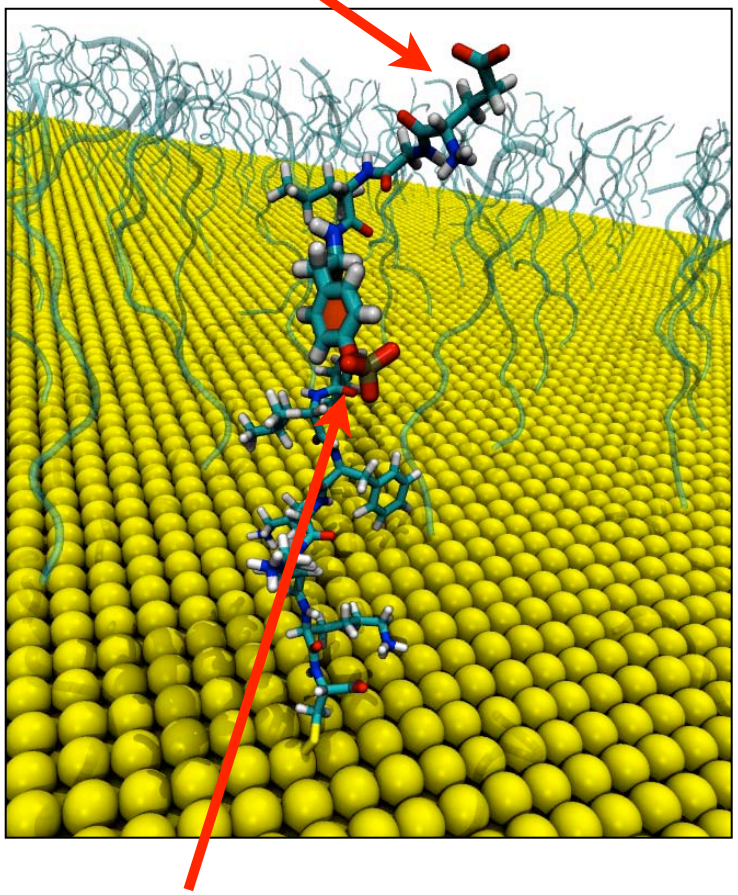


# Current Design Improved

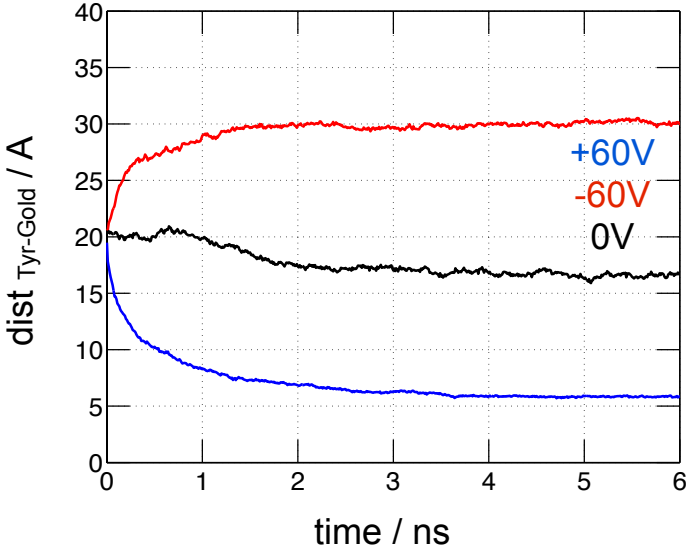
New sequence: rhodamin removed and measurement replaced by Raman spectroscopy

Rhodamine removed,
Fluorescence signal discarded

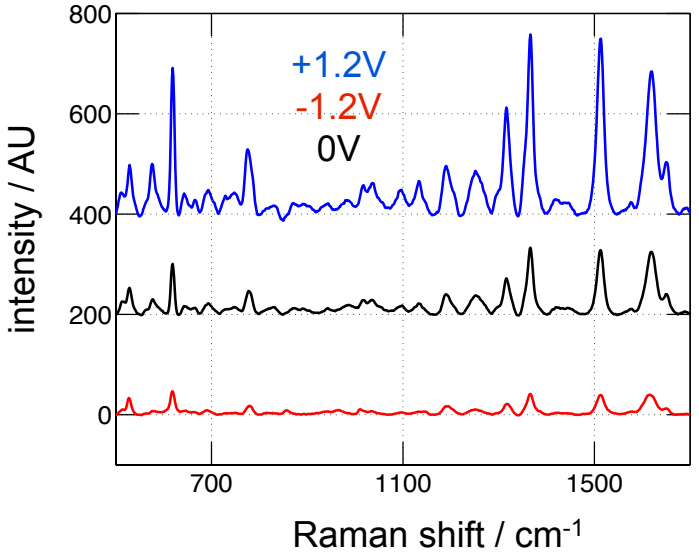


Phosphorylated tyrosine

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



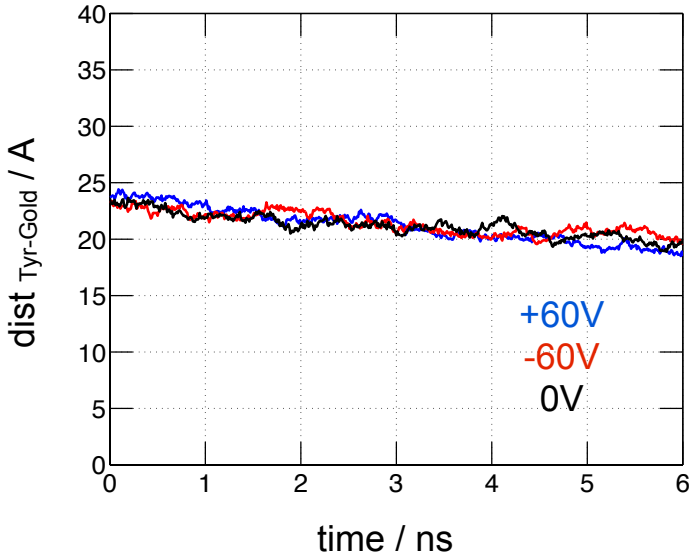

**Experiments** show that peptide bends towards the surface at positive voltages, increasing the intensity of Raman shifts.

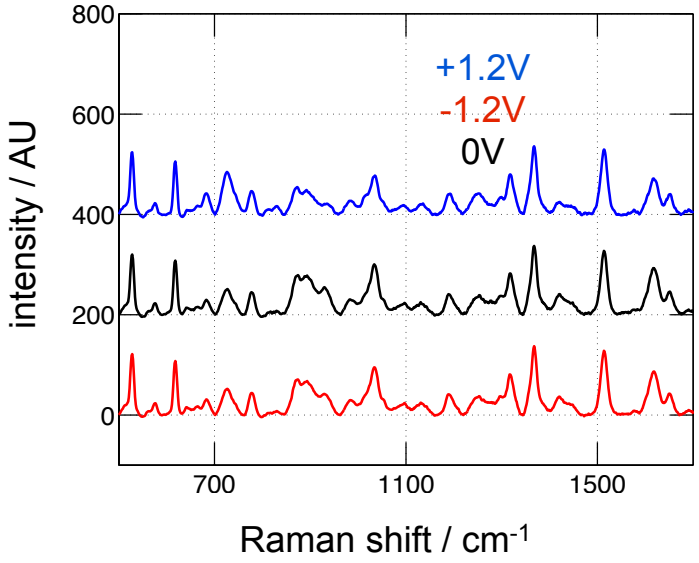



Peptide bending is now measured with Raman Spectroscopy.
The detection relies on careful comparison of peak points

# Unphosphorylated

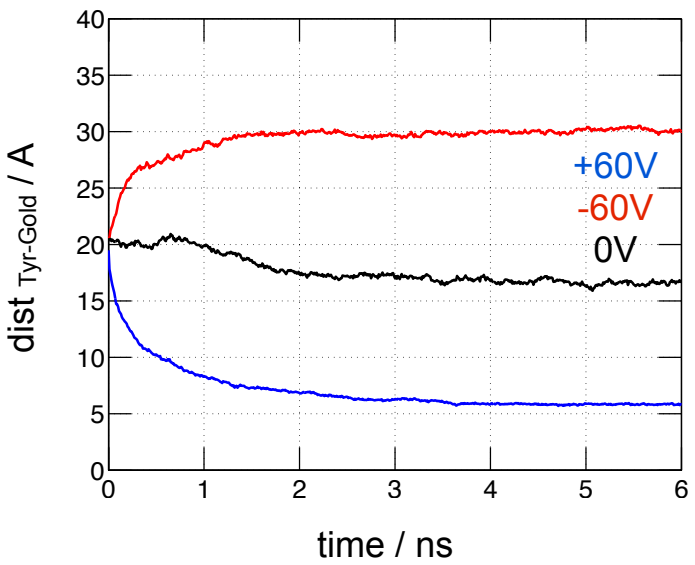
EGI**Y**GVLFKKKC-*AU*

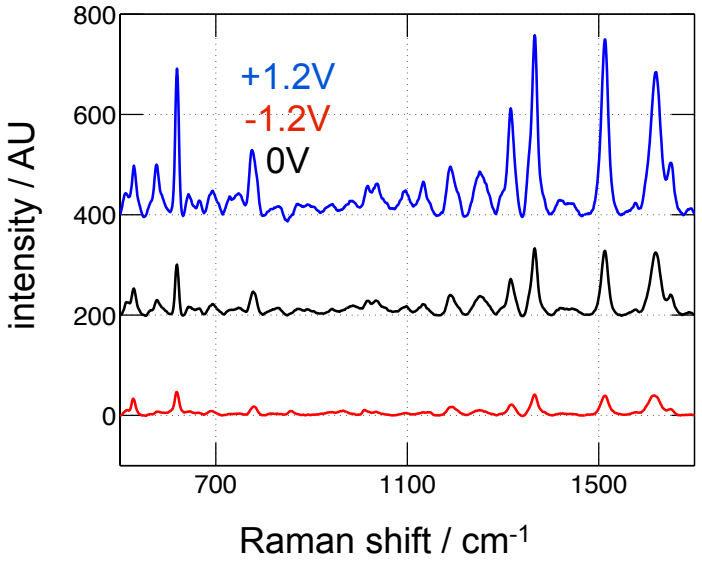


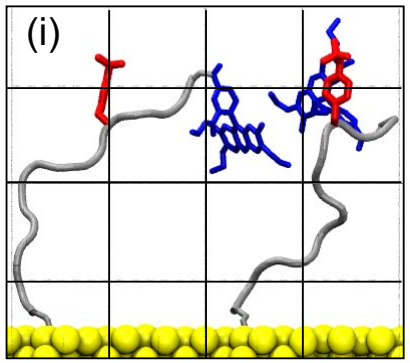



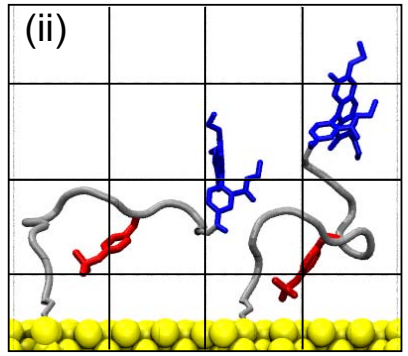

# Phosphorylated

EGI(**pY**)GVLFKKKC-*AU*

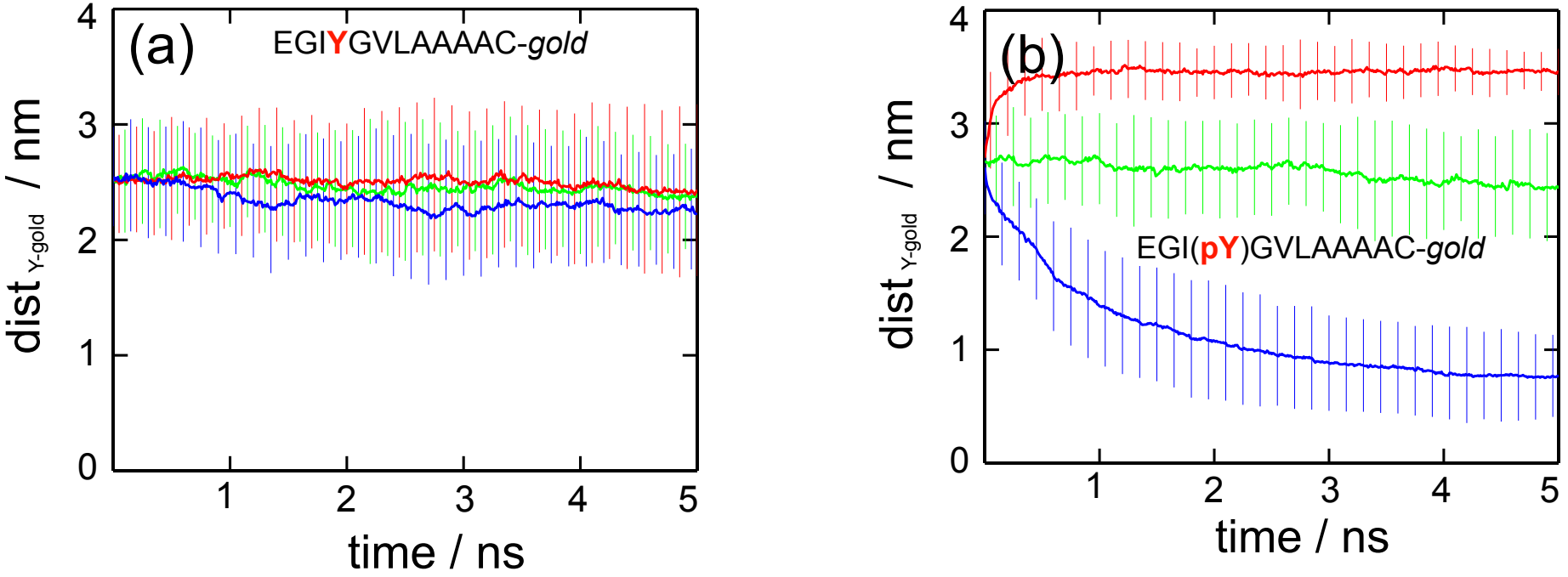


# Simulation-Optimized Sequence




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.