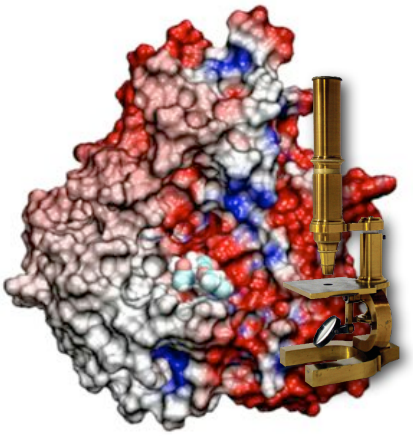
Discoveries Through the Computational Microscope

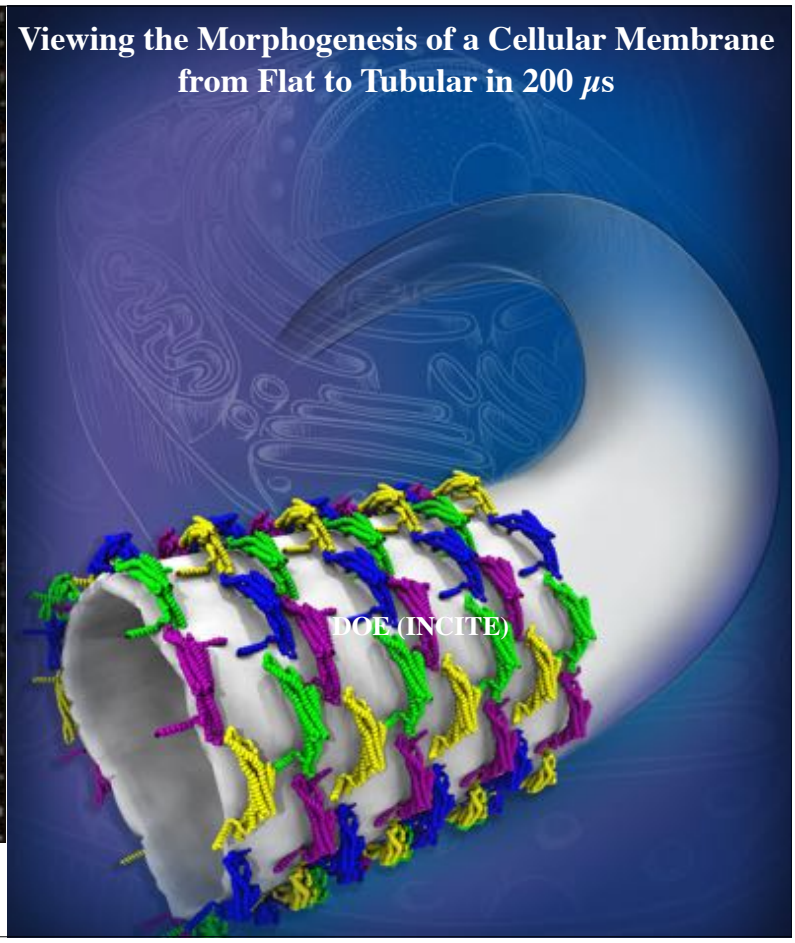
Accuracy • Speed-up • Unprecedented Scale



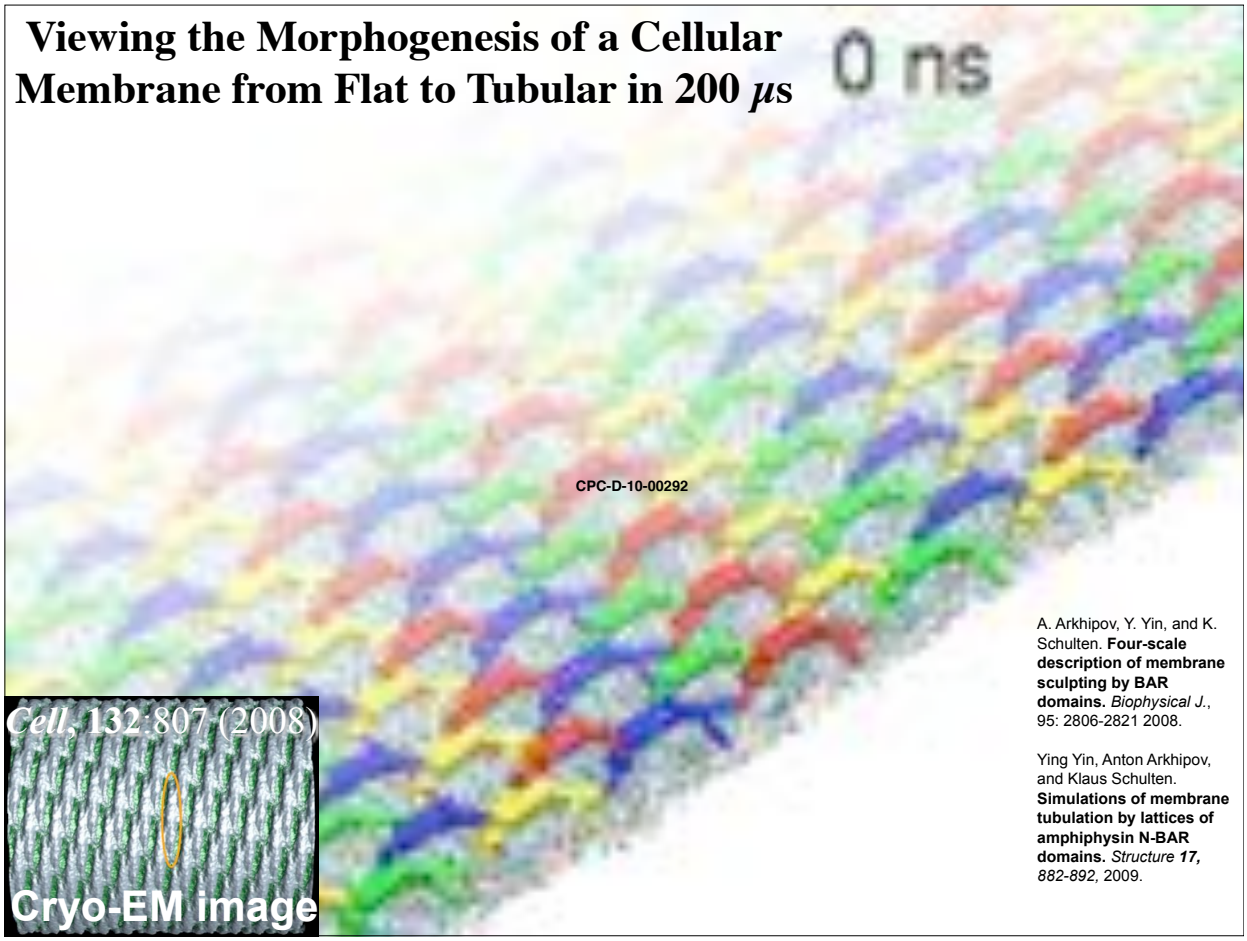
Investigation of drug (Tamiflu) resistance of the "swine" flu virus demanded **fast response!**

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 μs

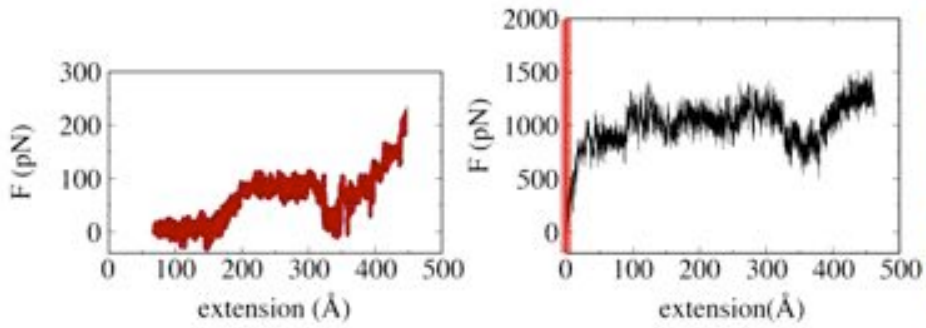


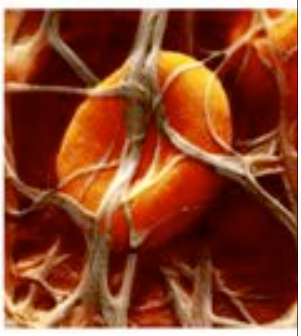
A. Arkhipov, Y. Yin, and K. Schulten. **Four-scale description of membrane sculpting by BAR domains.** *Biophysical J.*, 95: 2806-2821 2008.

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

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)*

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

A Blood Clot
Red blood cells within a network of fibrin fibers, composed of polymerized fibrinogen molecules.

NIH Center for Research Resources

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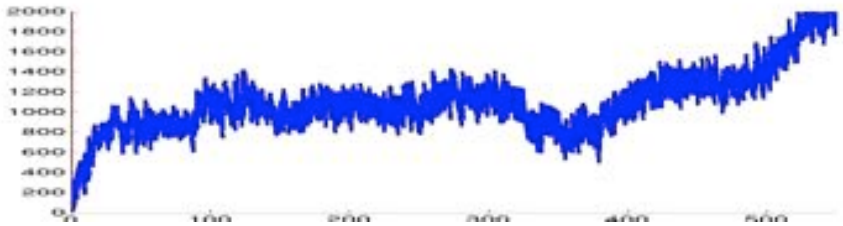

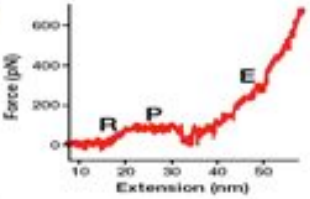

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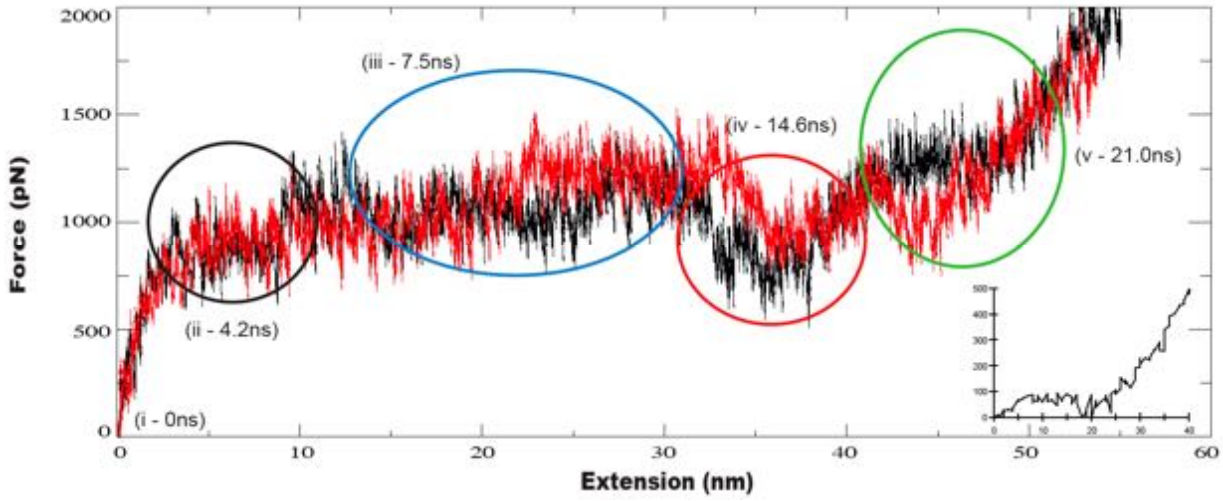
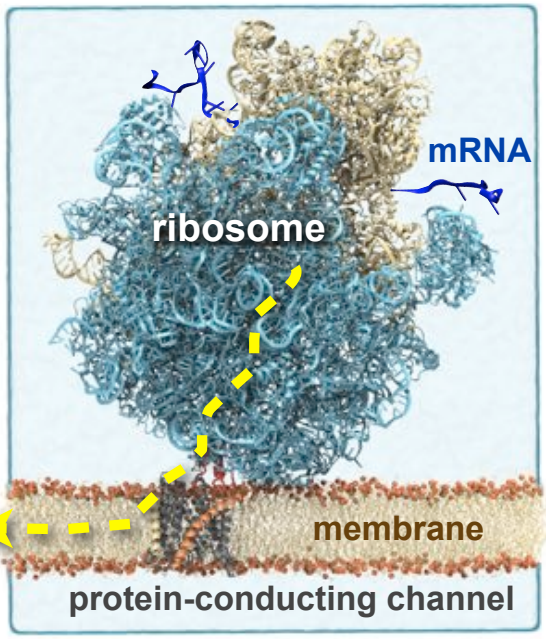
Petascale simulations will Permit Sampling

For Example Carrying out a Second Simulation Required by a Referee



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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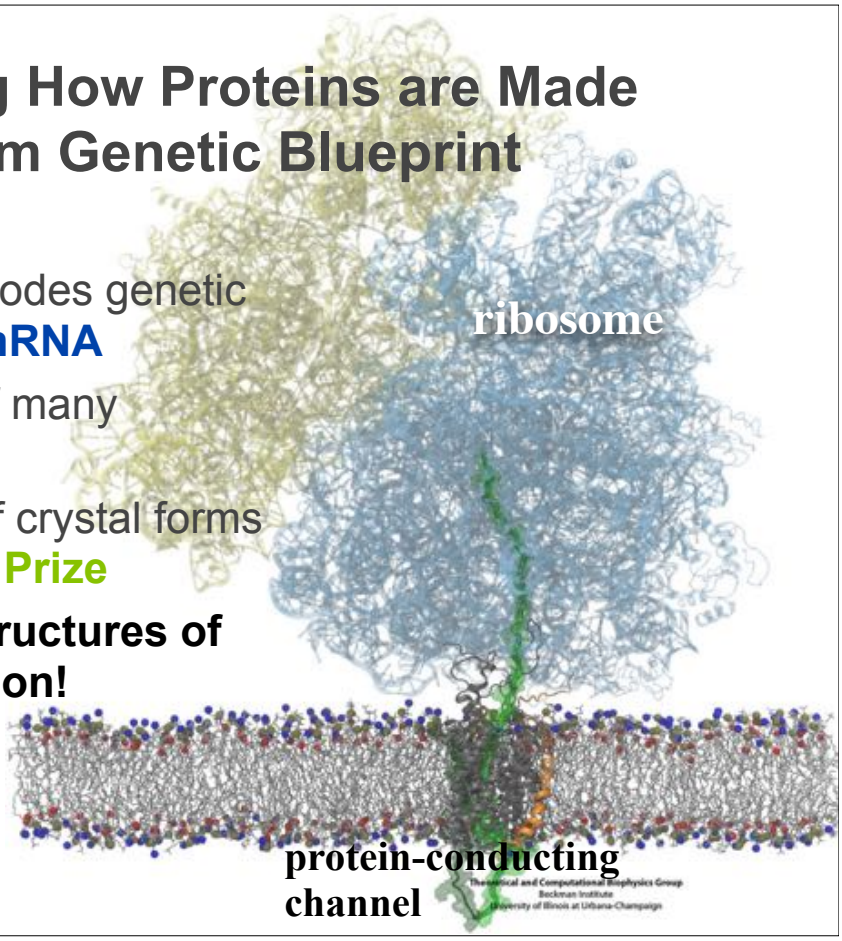
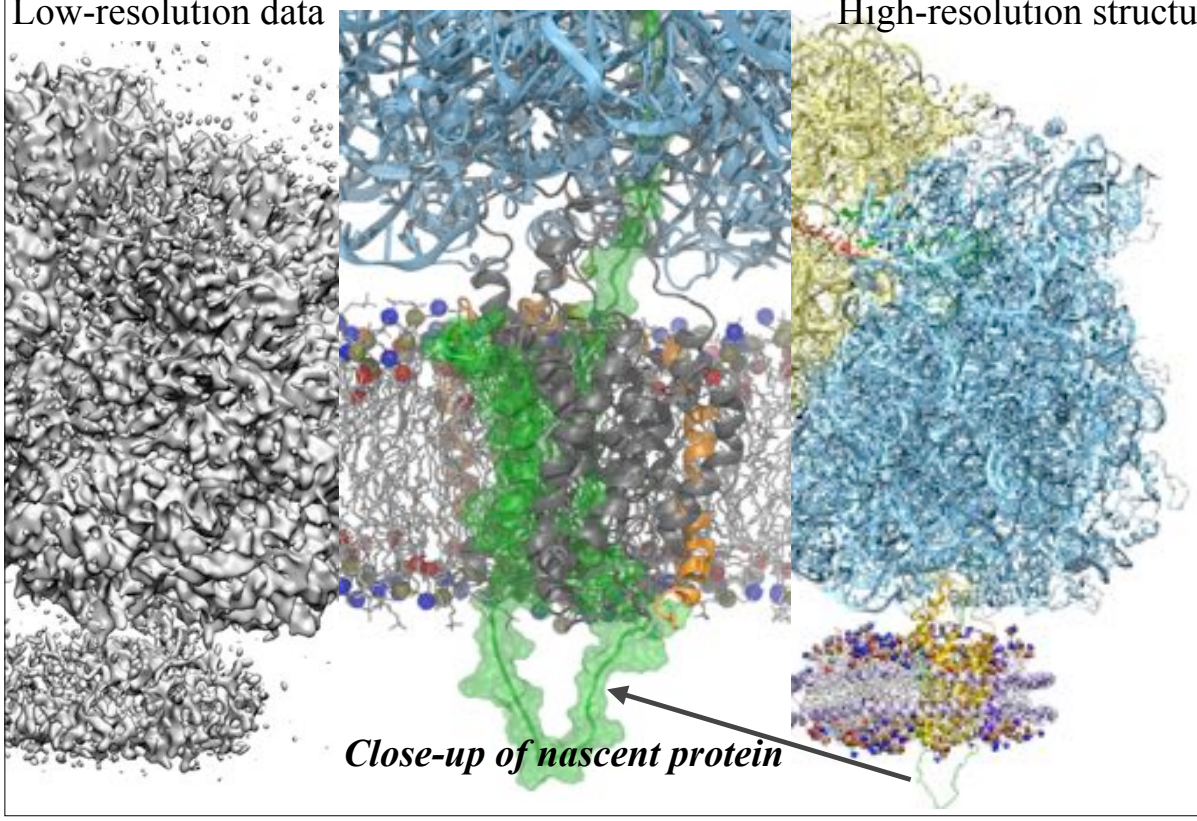


Viewing How Proteins Are Made from Genetic Blueprint

Low-resolution data

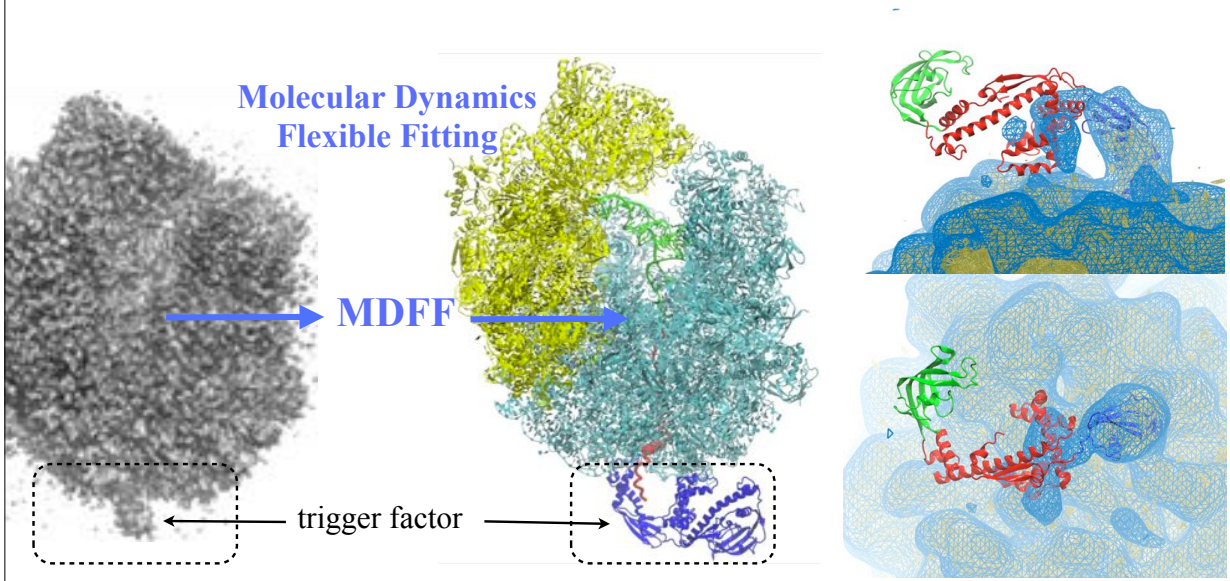
High-resolution structure



Viewing how Proteins are Made from Genetic Blueprint

Trigger Factor Bound to Translating Ribosome

Trigger factor (TF): ribosome-associated chaperon preventing misfolding of nascent chain



EM density map

Assigned All-atom Structure

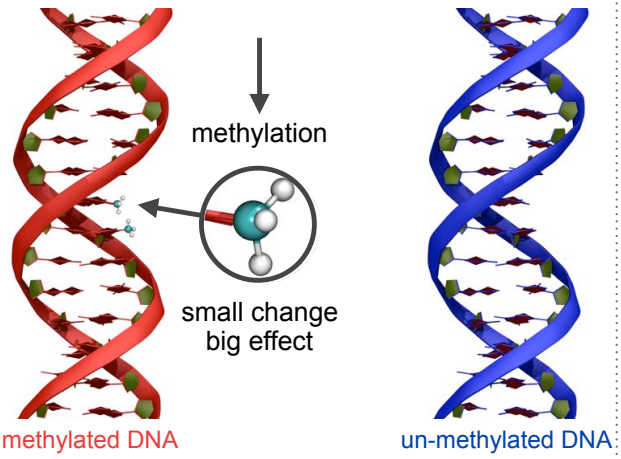
Highly mobile TF aligned to low-pass filtered map

New DBP1-Ribosome effort with collaborator R. Beckmann, U. Munich

Viewing Nanopore Sensors

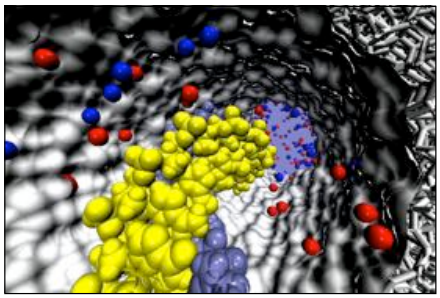
Genetics: Genes control our bodies and experiences!
Epigenetics: Our bodies and experiences control the genes!

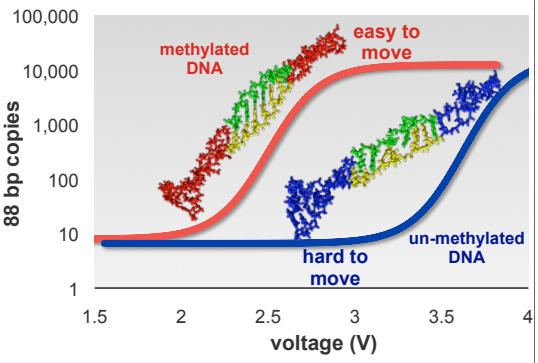
Epigenetics made possible through DNA methylation



Related pathologies: obesity, depression, cancer

Detect methylation with **nanopores**



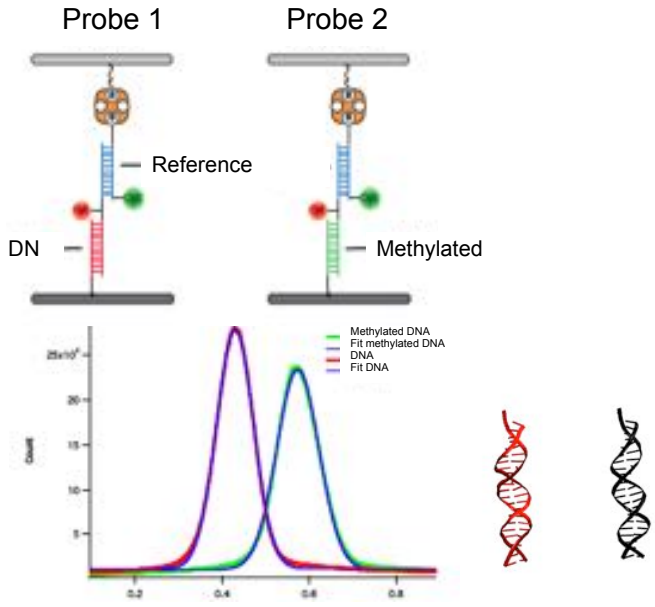


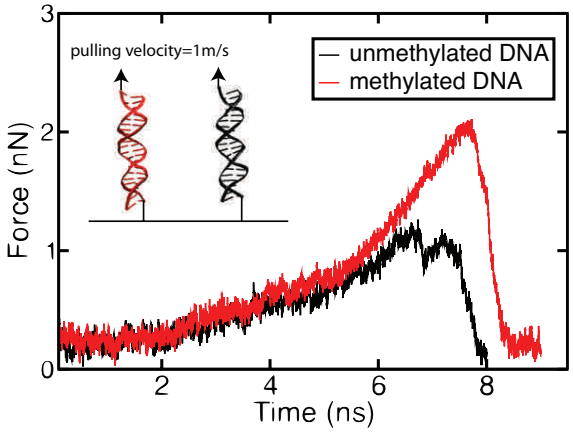
Utkur M. Mirsaidov, Winston Timp, Xueqing Zou, Valentin Dimitrov, Klaus Schulten, Andrew P. Feinberg, and Greg Timp. **Nanoelectromechanics of methylated DNA in a synthetic nanopore.** *Biophysical Journal*, **96**:L32-L34, 2009.

Impact of methylation on mechanic stability of DNA

Experiments: Greg Timp, ECE and Beckman
Hermann Gaub, NanoCenter, U. Munich

Simulations:
Xueqing Zou and Klaus Schulten





DNA
x0 = 0.42957 ± 7.8e-05
width = 0.060307 ± 0.000118

Methylated DNA
x0 = 0.57399 ± 0.000113
width = 0.068616 ± 0.000171

Methylation increases the binding energy of two strands, which makes methylated DNA more stable than unmethylated DNA.

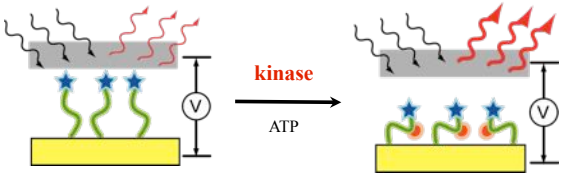
Recent progress

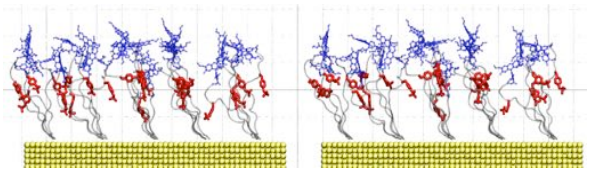
Building a nanodevice for kinase detection (*Collaborator: Logan Liu; UIUC*)

- ❑ Protein kinases are known to regulate the majority of biochemical pathways in the cell
- ❑ Disruption of kinase signaling pathways are frequent causes for diseases, such as cancer and diabetes
- ❑ New nanodevice to detect **kinase** activity

Key points for creating a functional device:

- ❑ Phosphorylated peptides must change conformation under different voltage polarities
- ❑ Peptide conformation must be sensitive to spectroscopic detection





Sequence insensitive to voltage polarity

All-atom model

MD reveals undesired effects

Optimized sequence responds to voltage polarity