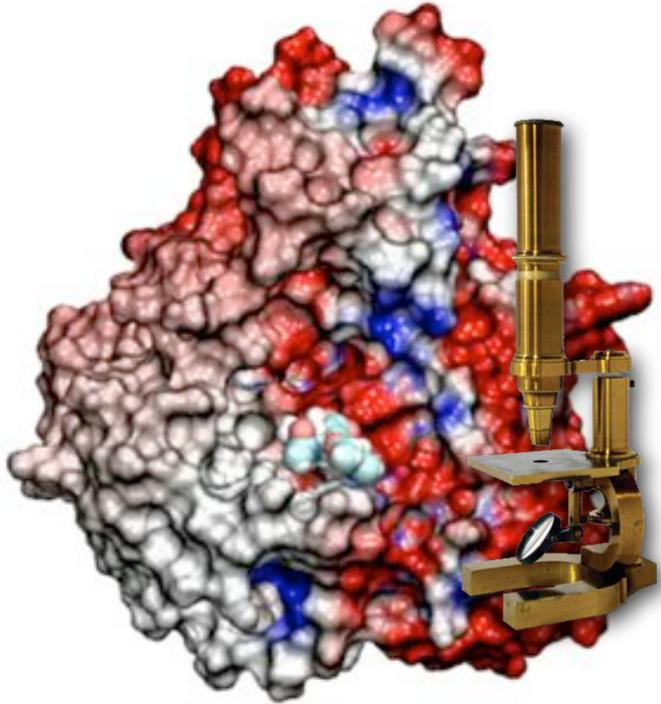


# Discoveries Through the Computational Microscope

Accuracy • Speed-up • Unprecedented Scale



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

Klaus Schulten

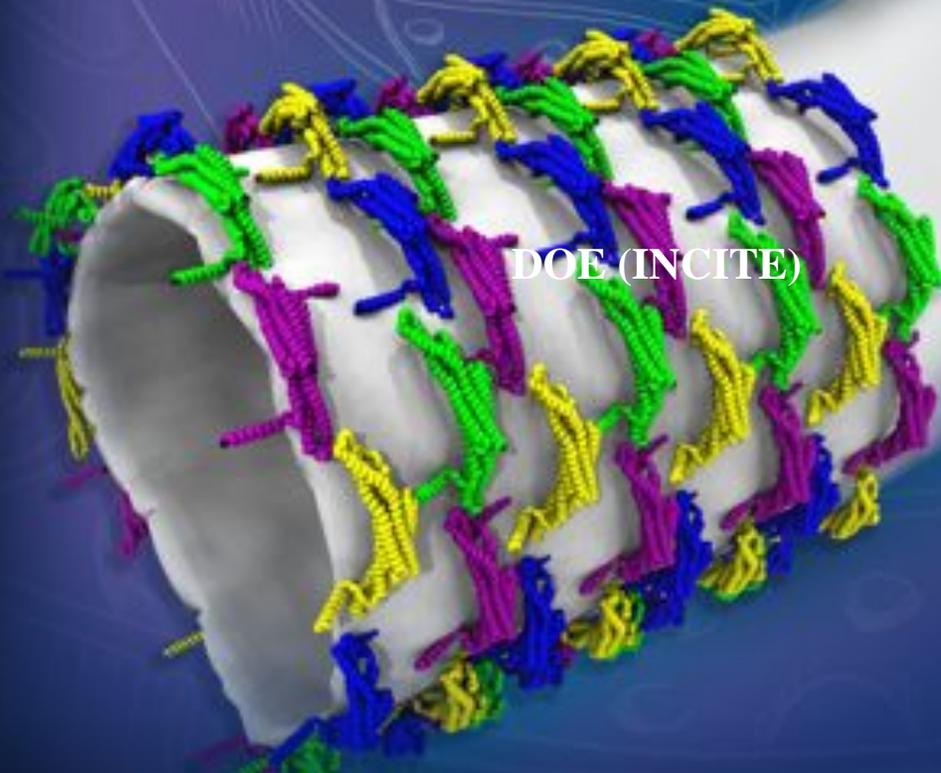
Department of Physics and  
Theoretical and Computational Biophysics Group  
University of Illinois at Urbana-Champaign

**The  
Computational  
Microscope**



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

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



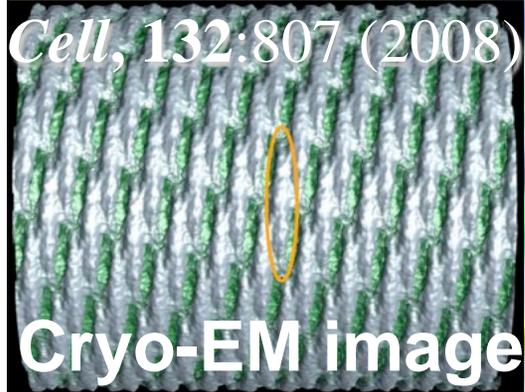
DOE (INCITE)

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

0 ns

CPC-D-10-00292

*Cell*, 132:807 (2008)



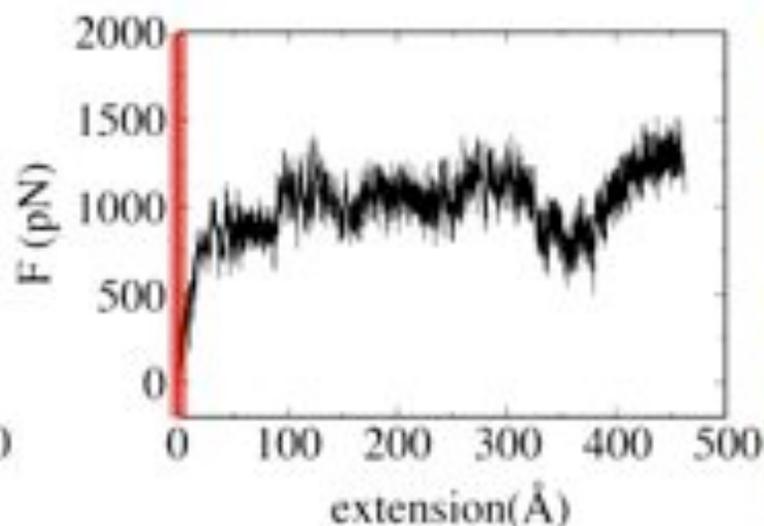
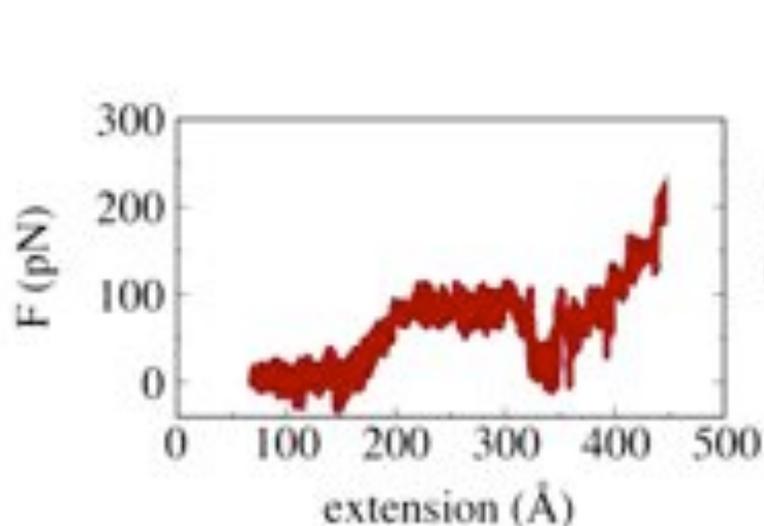
Cryo-EM image

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)



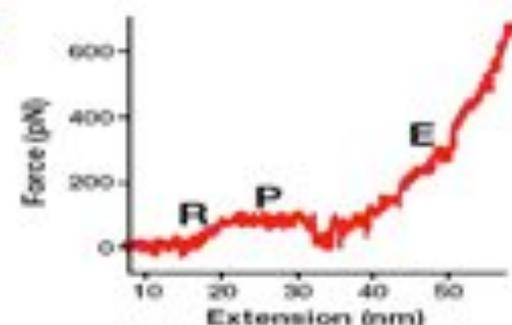
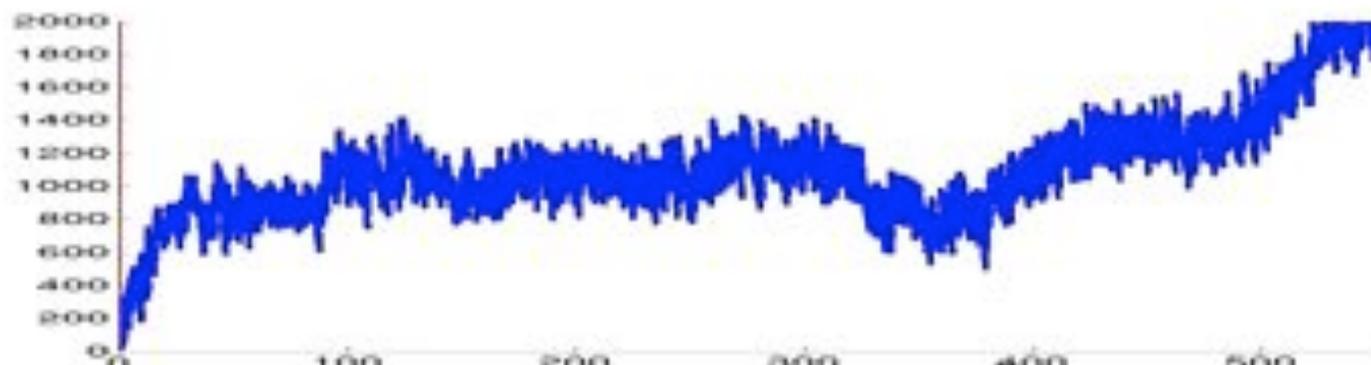
**20ns SMD Simulation of fibrinogen, 1.06 million atoms, 1.2 ns/day with pencil decomposition, 15 days on PSC XT3 Cray (1024 processors)**

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.

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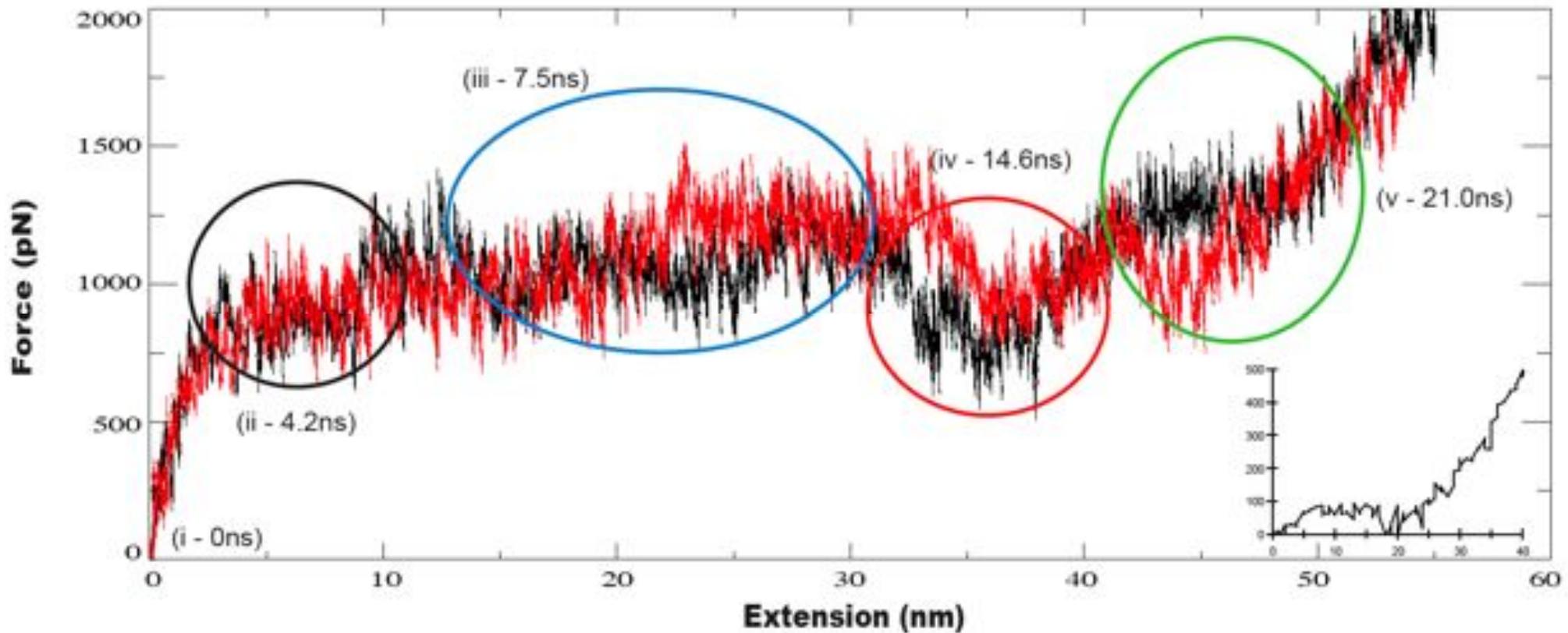
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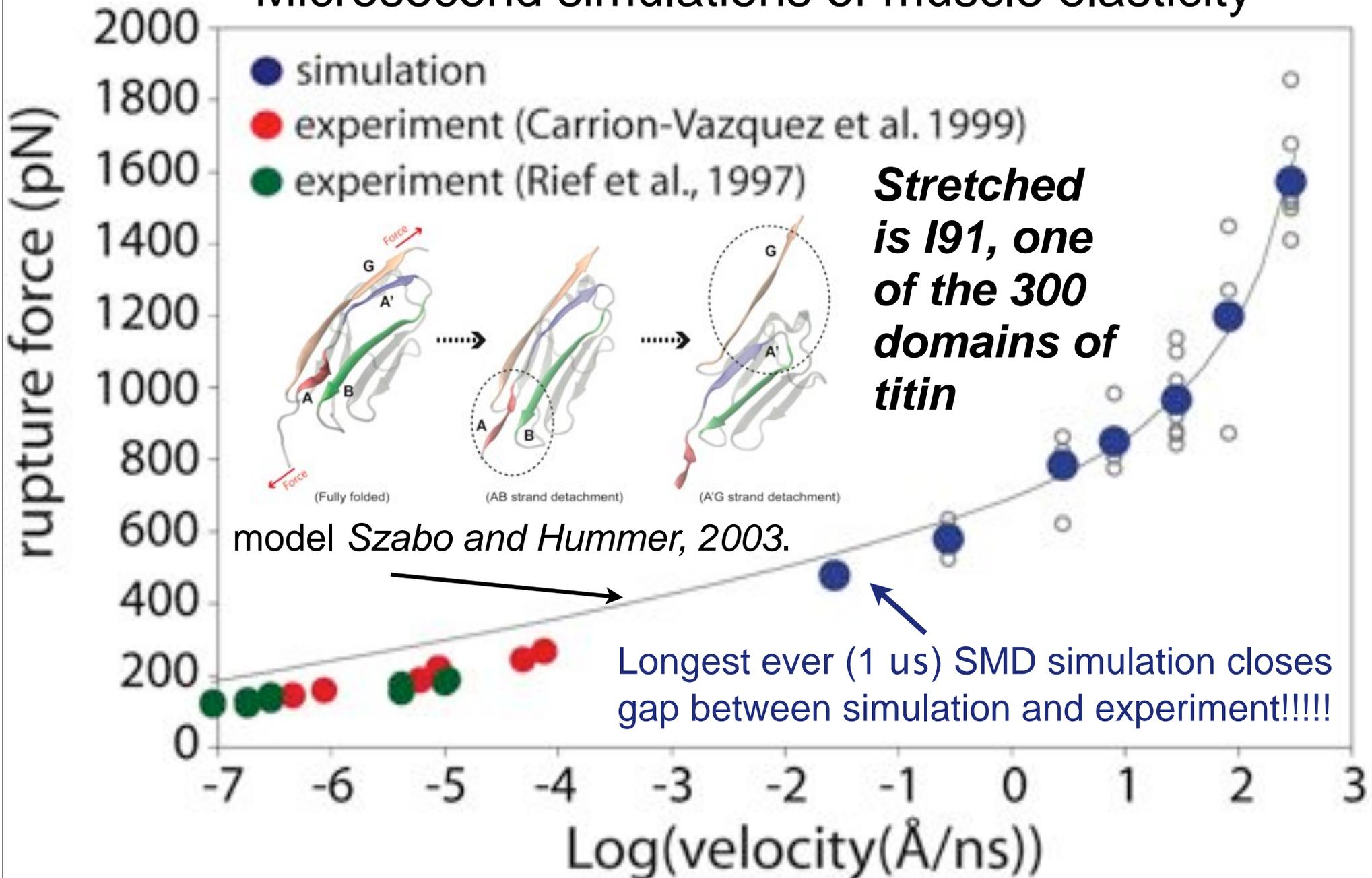
# Petascale simulations will Permit Sampling

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



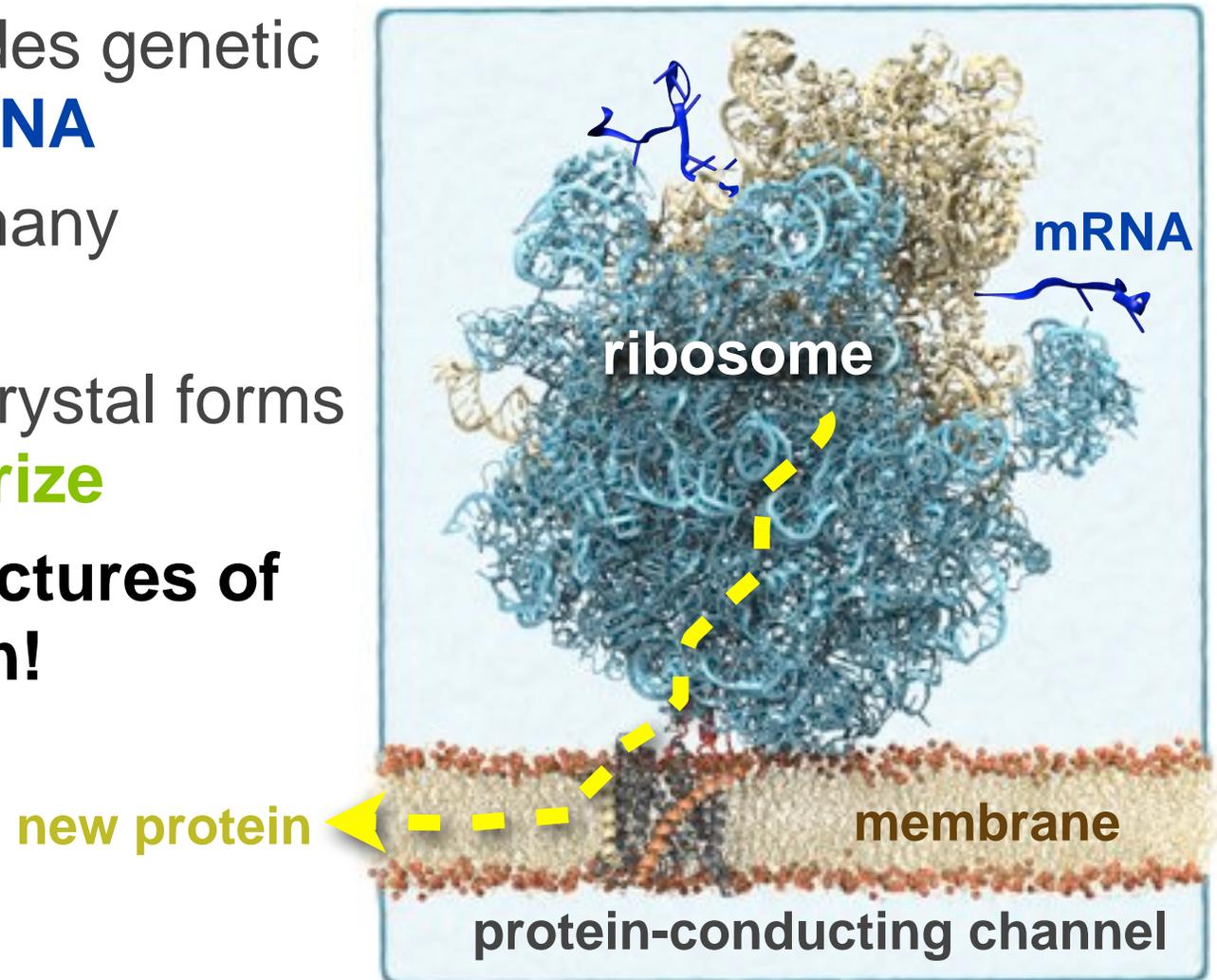
# Reaching for Overlapping Time Scales

Microsecond simulations of muscle elasticity



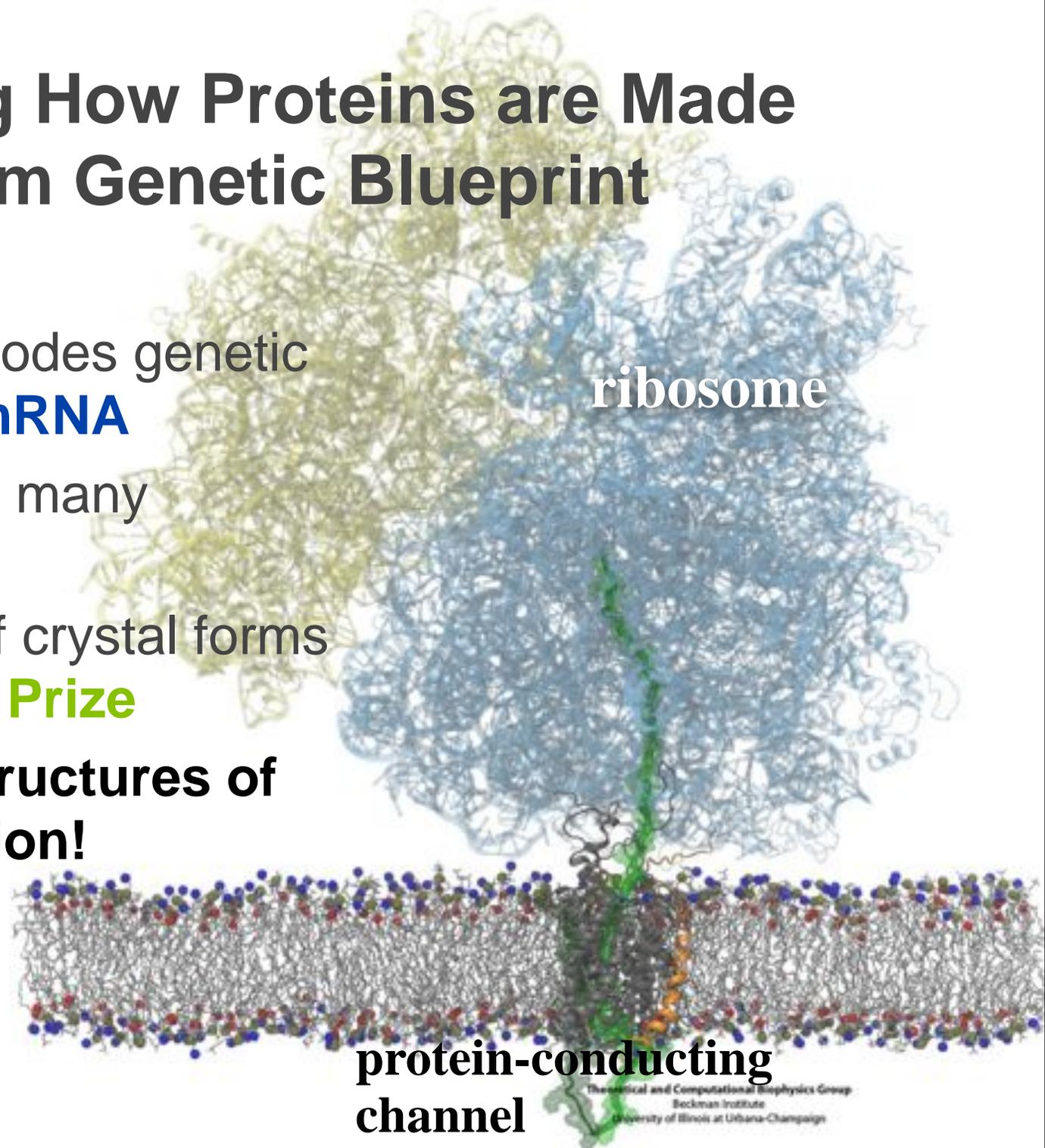
# Viewing How Proteins are Made from Genetic Blueprint

- **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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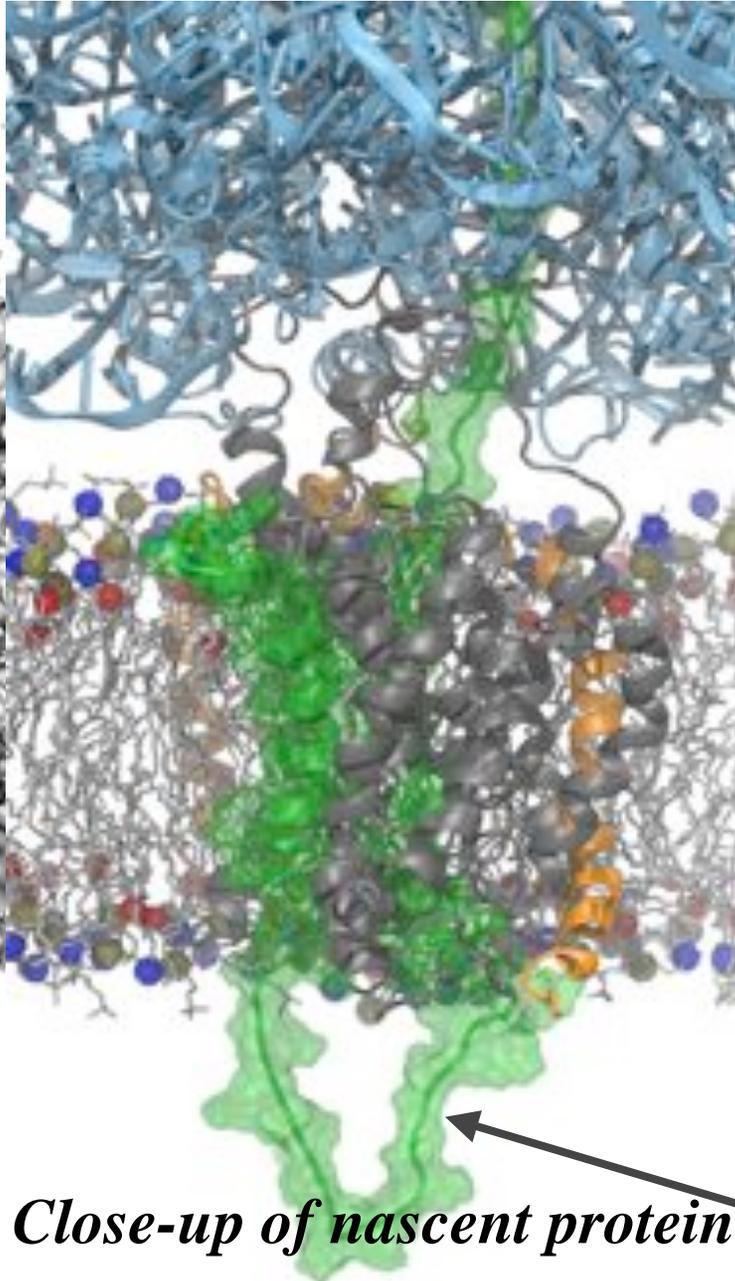
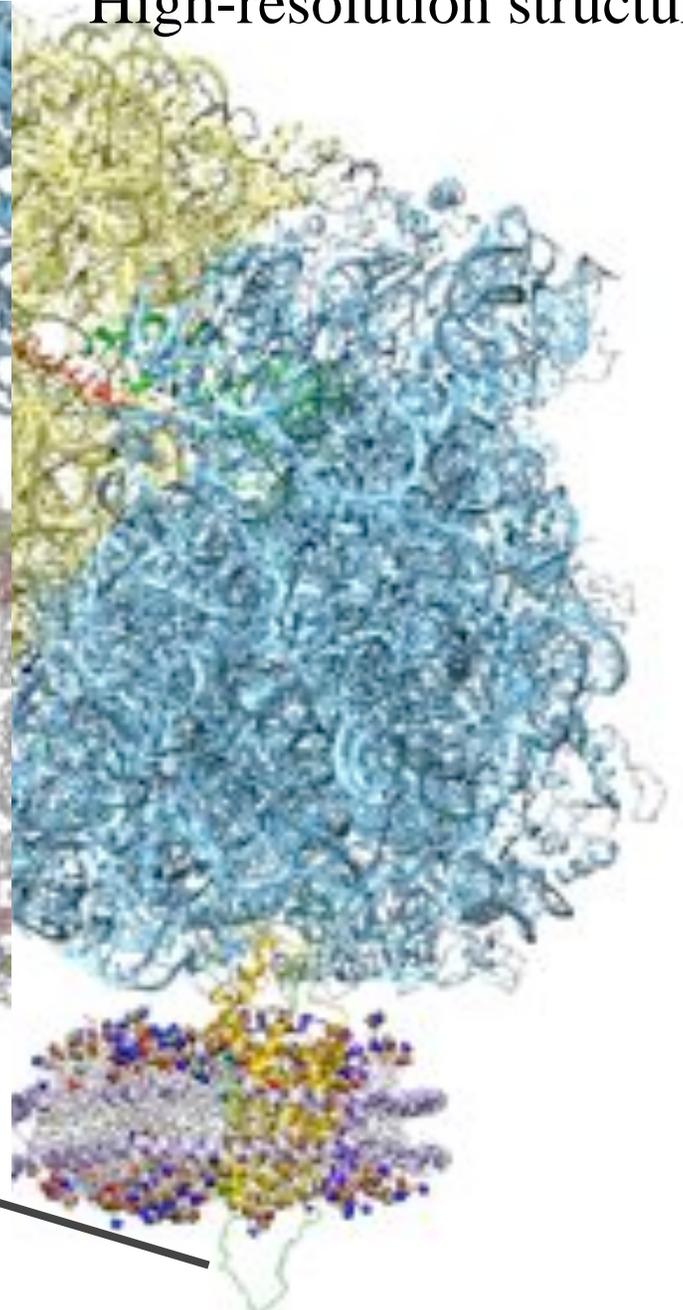


# Viewing How Proteins Are Made from Genetic Blueprint

Low-resolution data



High-resolution structure

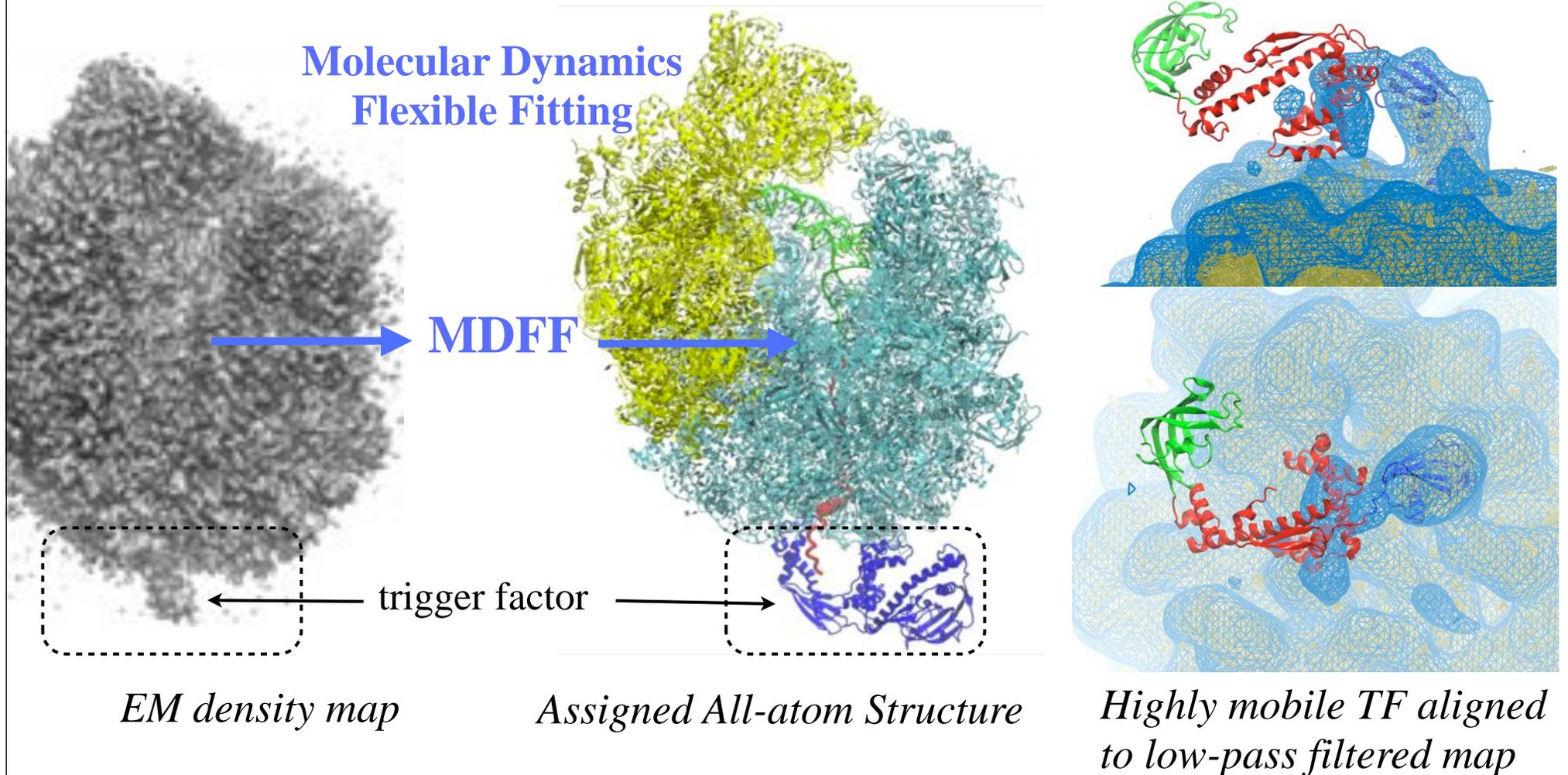


*Close-up of nascent protein*

# 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

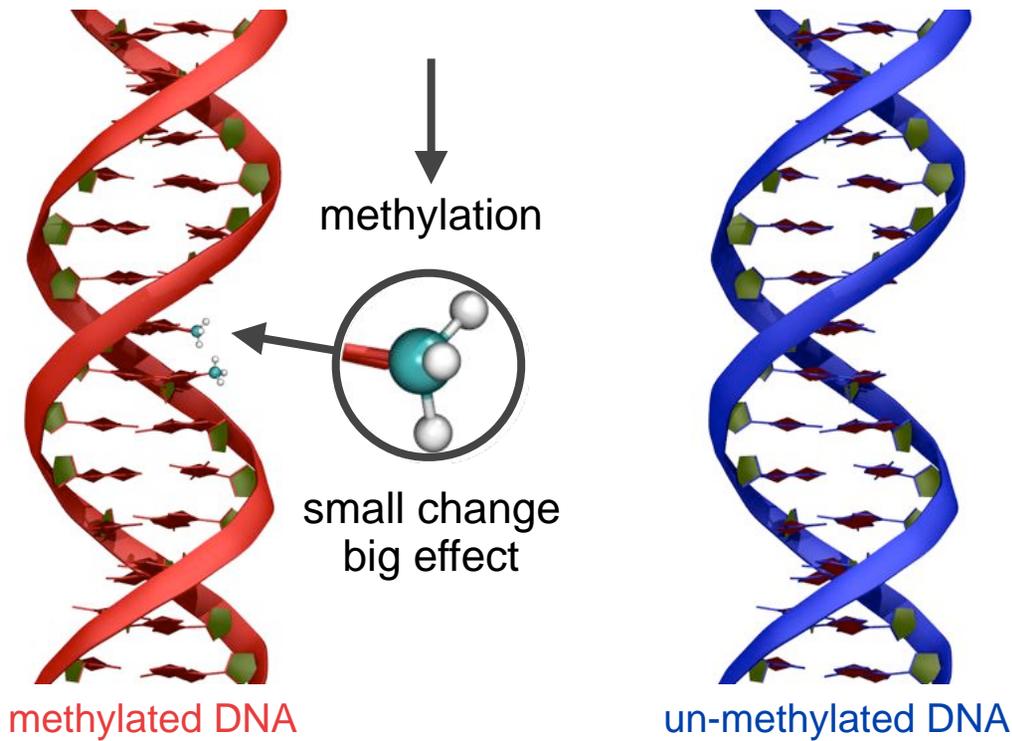


New DBP1-Ribosome effort with collaborator R. Beckmann, U. Munich

# Viewing Nanopore Sensors

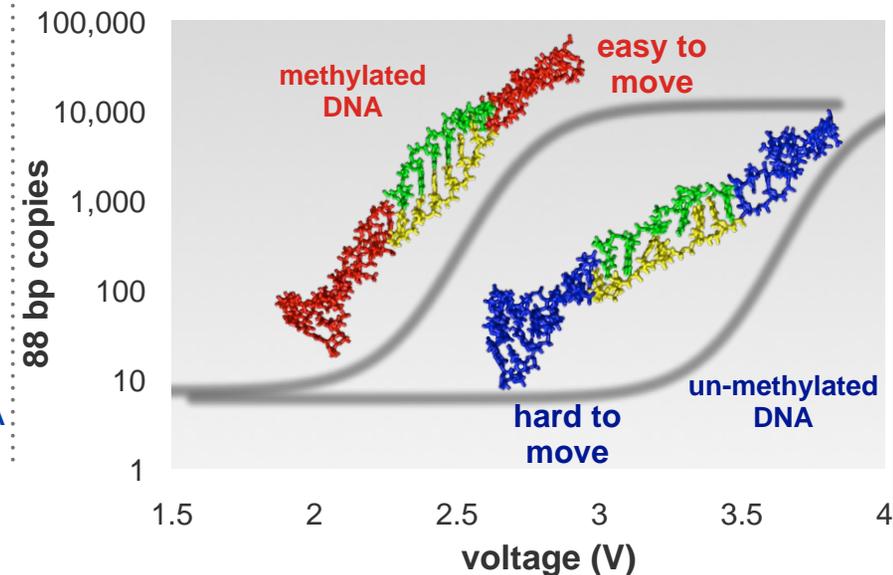
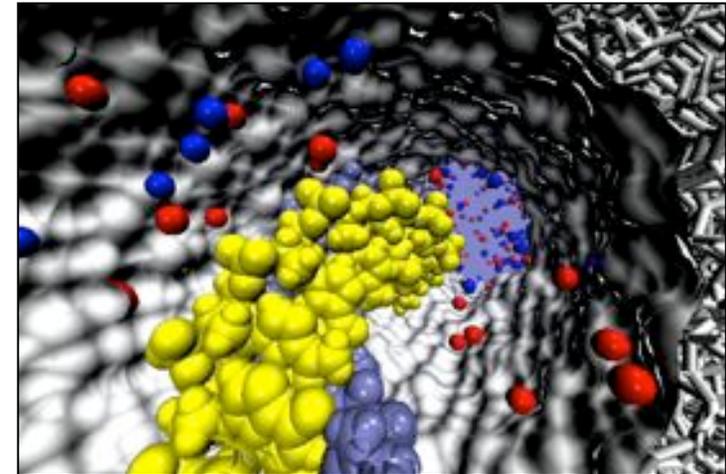
**Genetics: Genes control our bodies and experiences!**  
**Epigenetics: Our bodies and experiences control the genes!**

Epigenetics made possible through DNA methylation



Related pathologies: obesity, depression,  
cancer

Detect methylation with nanopores



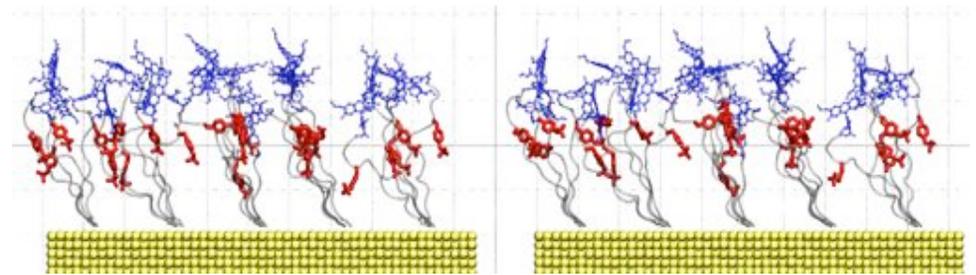
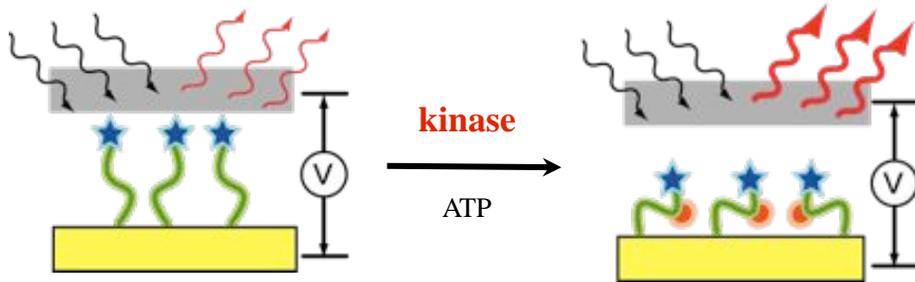
# Recent progress

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

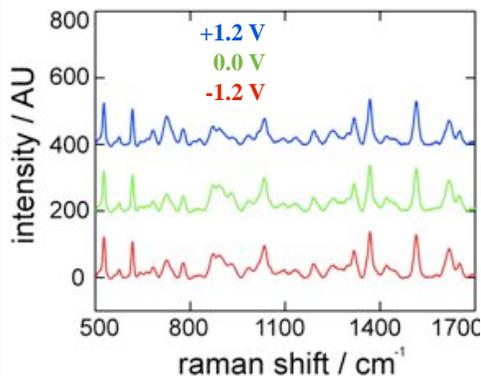
- ❑ Protein kinases are known to regulate the majority of biochemical pathways in the cell
- ❑ Disruption of kinase signaling pathways are frequent causes for diseases, such as cancer and diabetes
- ❑ New nanodevice to detect **kinase** activity

### Key points for creating a functional device:

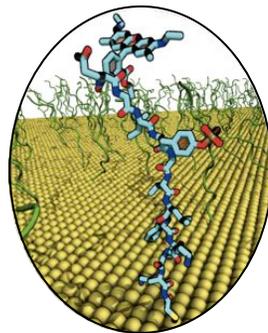
- ❑ Phosphorylated peptides must change conformation under different voltage polarities
- ❑ Peptide conformation must be sensitive to spectroscopic detection



Sequence insensitive to voltage polarity

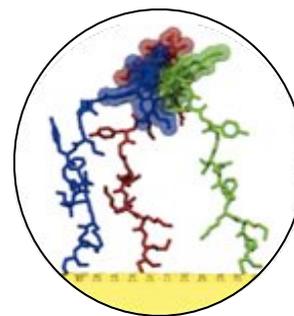


All-atom model



Sequence optimization through MD

MD reveals undesired effects



Optimized sequence responds to voltage polarity

