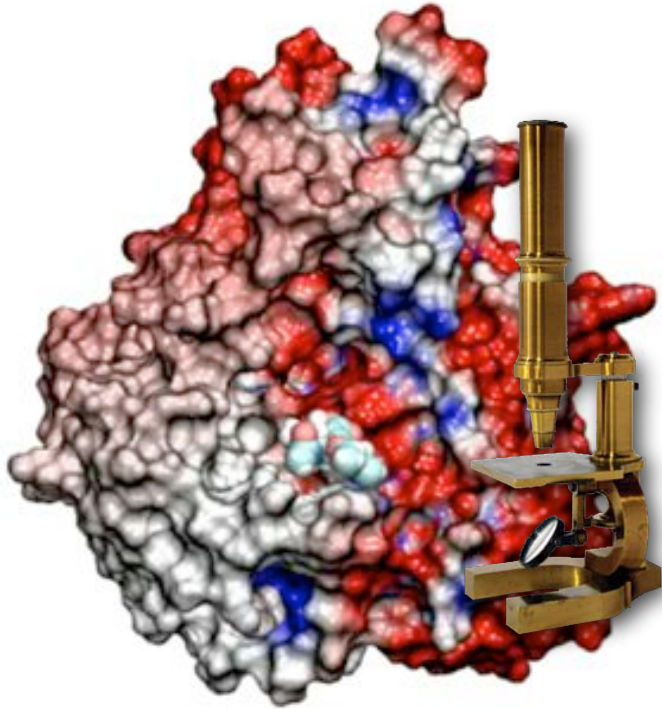


Discoveries Through the Computational Microscope

Accuracy • Speed-up • Unprecedented Scale



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

Klaus Schulten

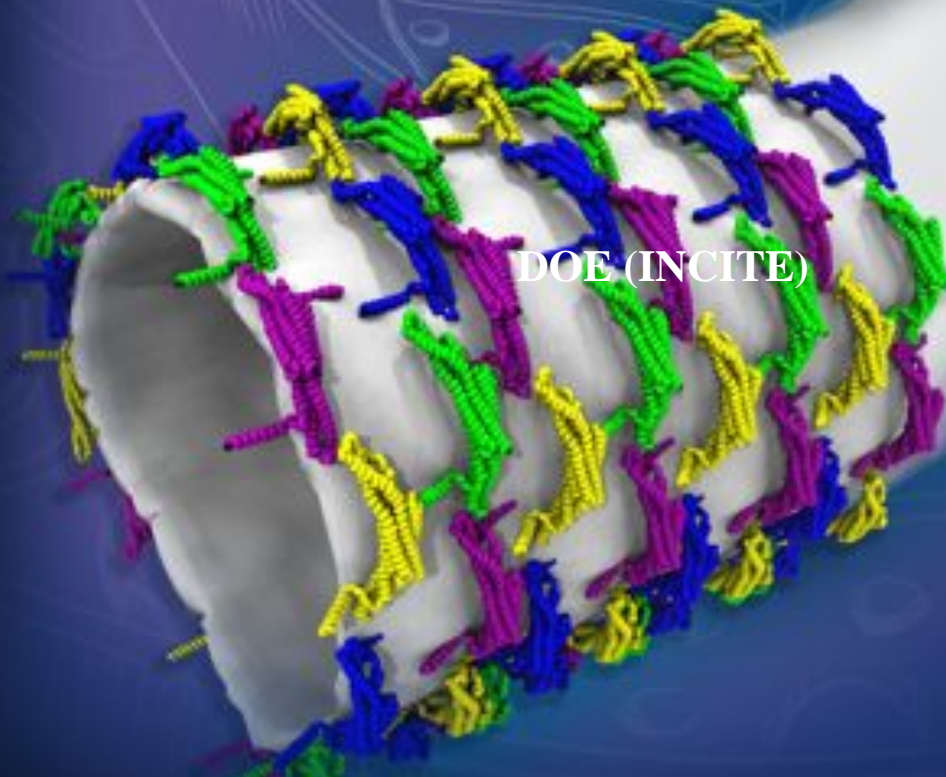
Department of Physics and
Theoretical and Computational Biophysics Group
University of Illinois at Urbana-Champaign

The Computational Microscope

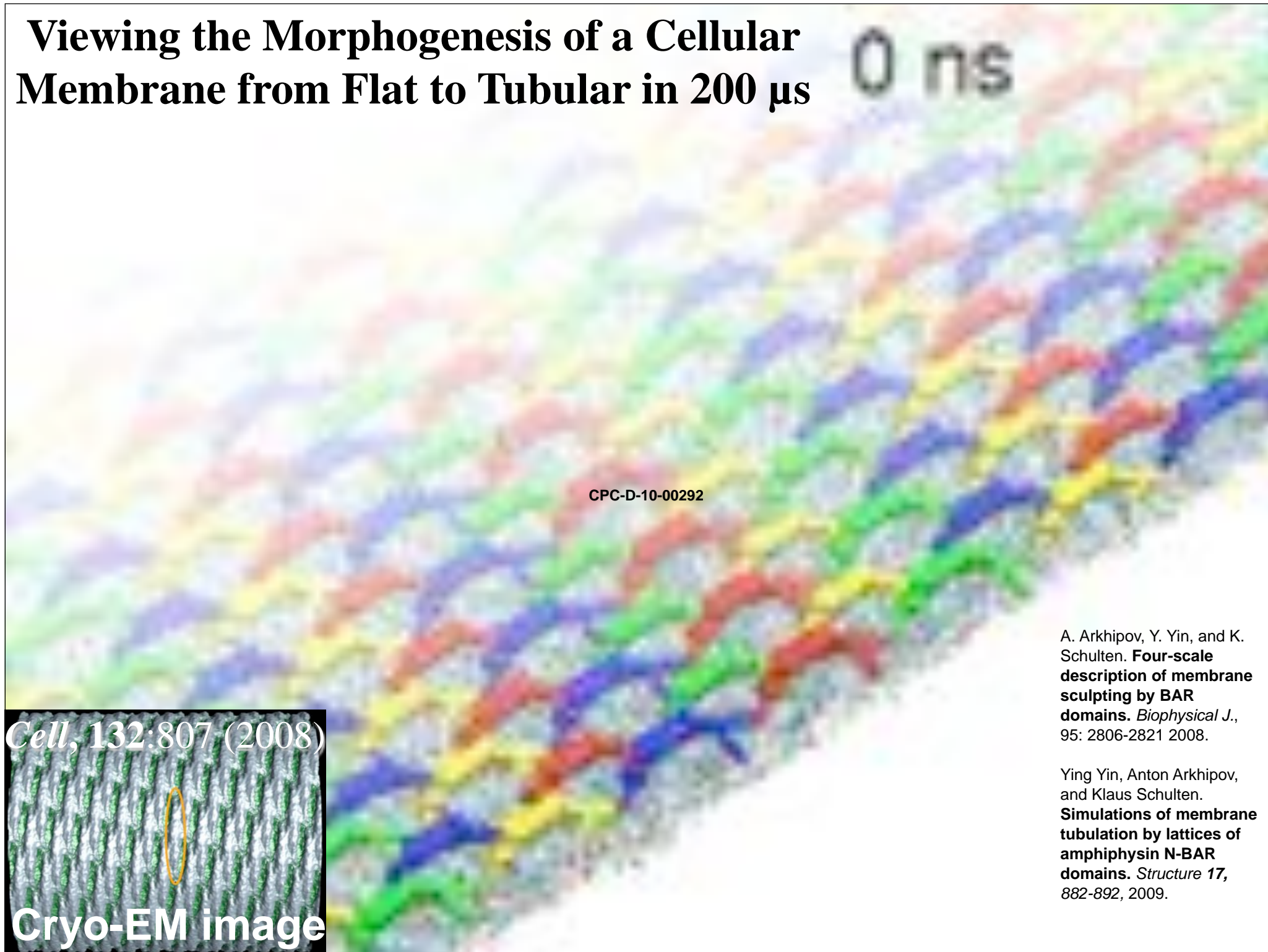


**100 - 1,000,000
processors**

**Viewing the Morphogenesis of a Cellular Membrane
from Flat to Tubular in 200 μ s**

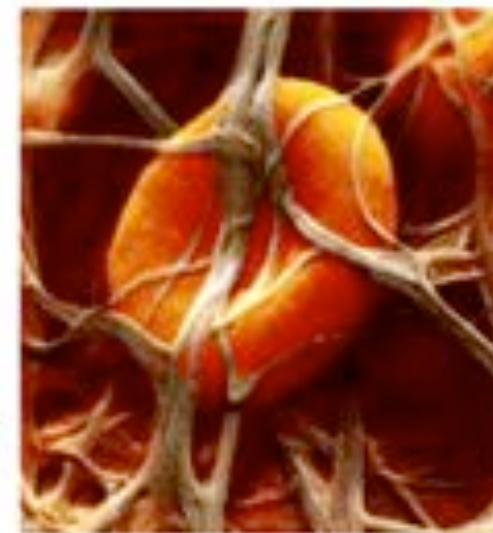
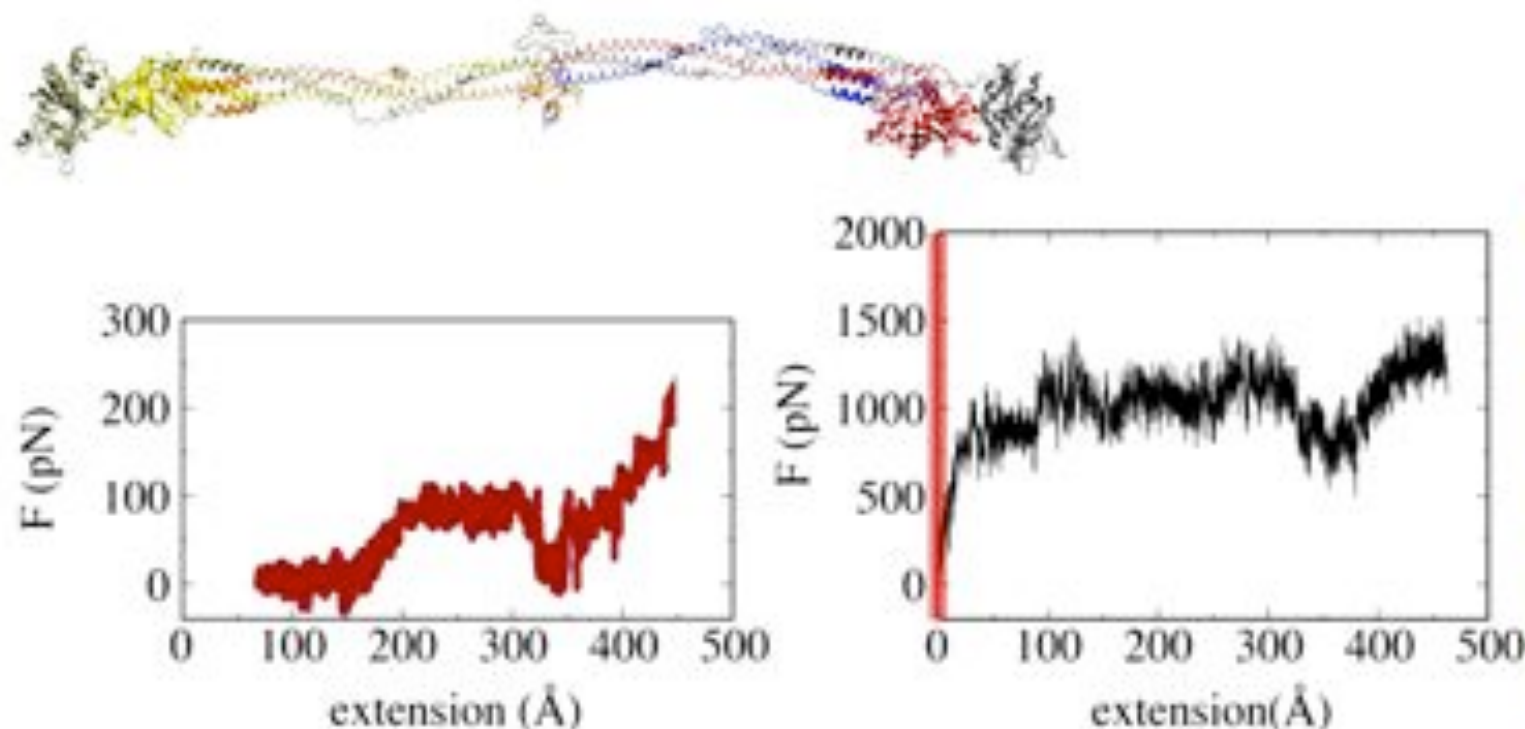


Viewing the Morphogenesis of a Cellular Membrane from Flat to Tubular in 200 μ s



Inspecting the mechanical Strength of a blood clot

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



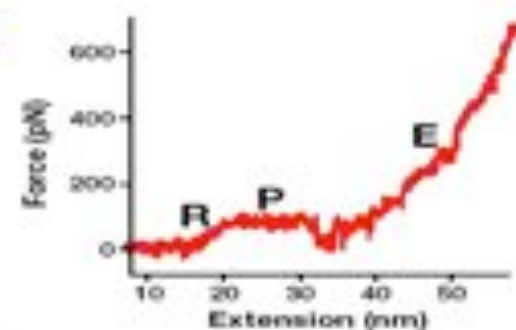
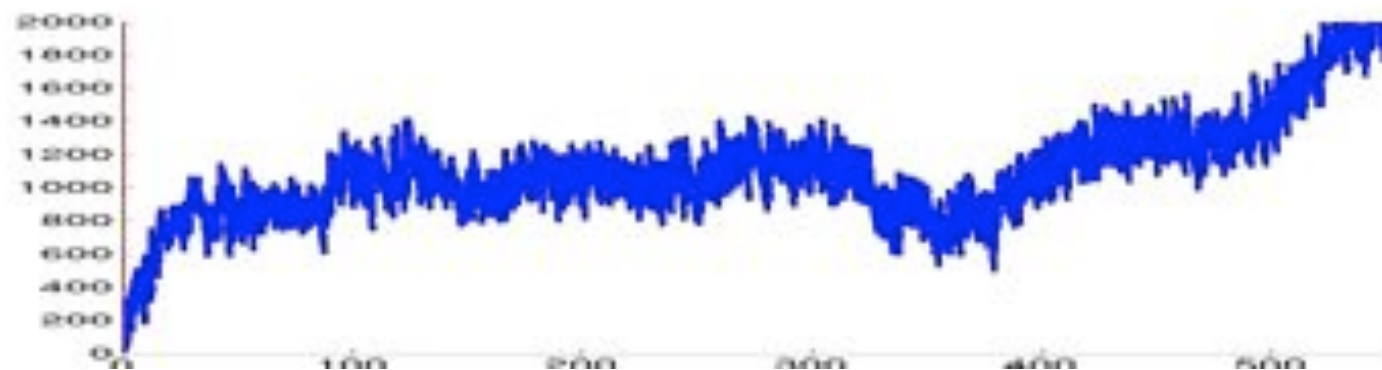
20ns SMD Simulation of fibrinogen, 1.06 million atoms, 1.2 ns/day with pencil decomposition, 15 days on PSC XT3 Cray (1024 processors)

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.

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)

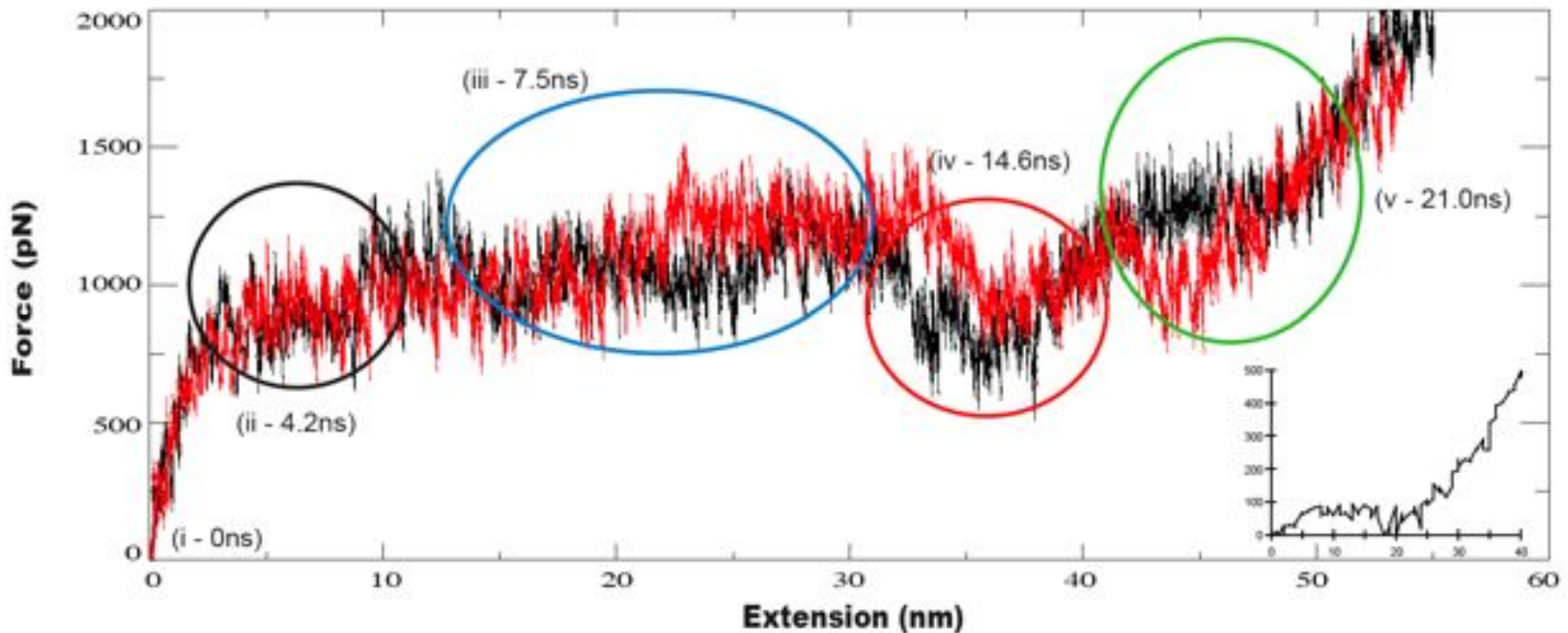
B. Lim, E. Lee, M. Sotomayor, and K. Schulten. **Molecular basis of fibrin clot elasticity.** *Structure*, 16:449-459, 2008.

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



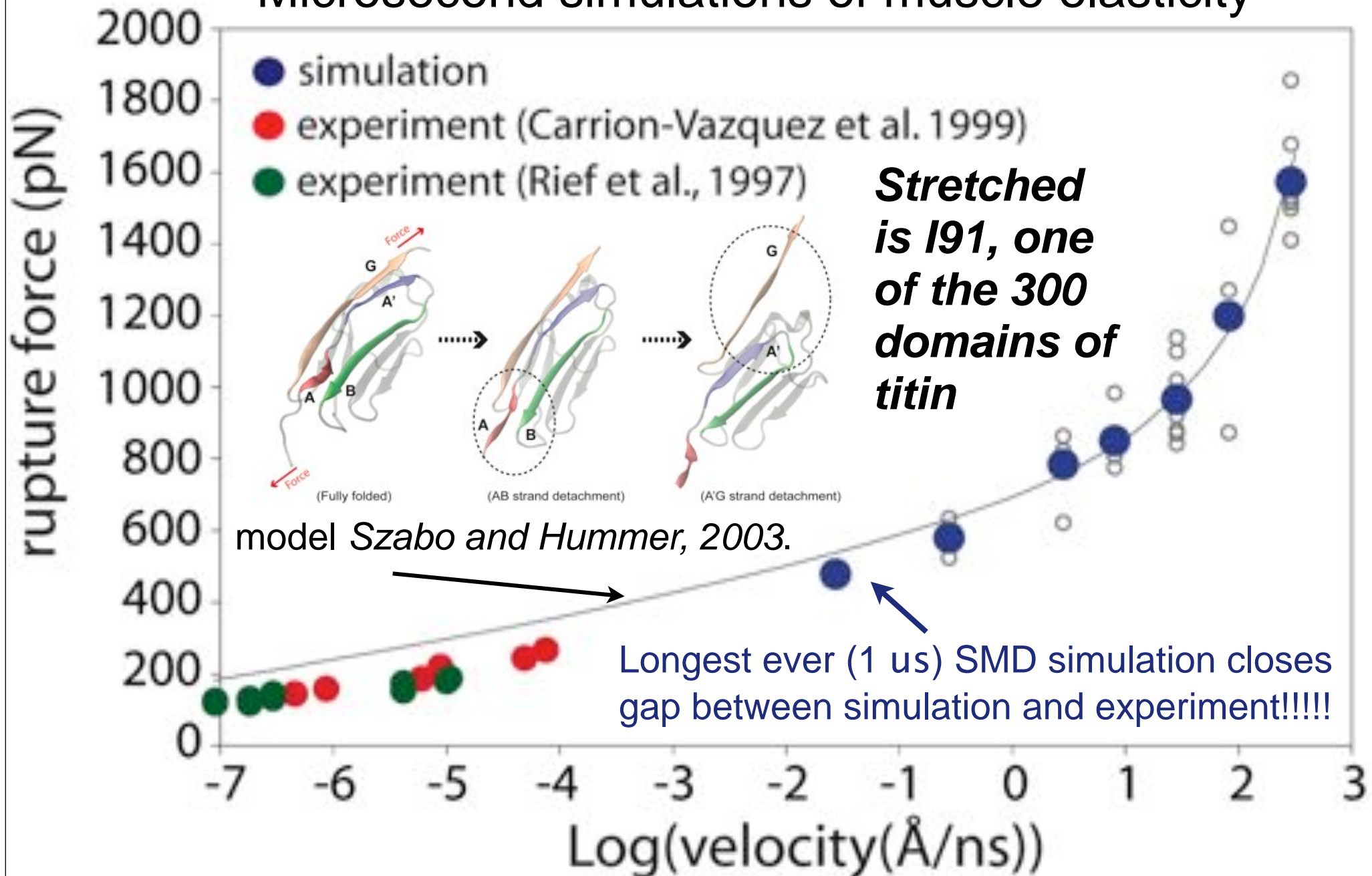
Petascale simulations will Permit Sampling

For Example Carrying out a Second Simulation Required by a Referee



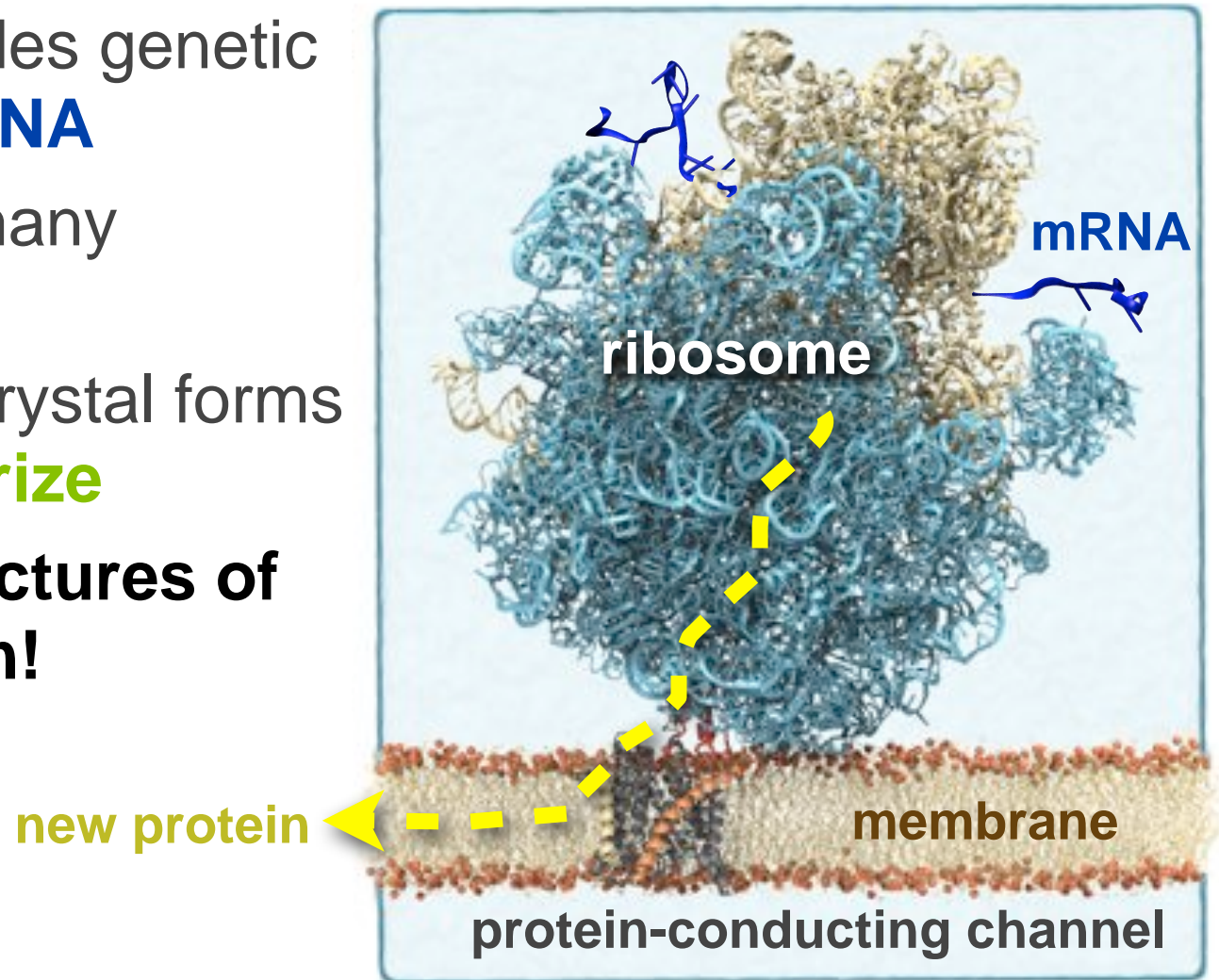
Reaching for Overlapping Time Scales

Microsecond simulations of muscle elasticity



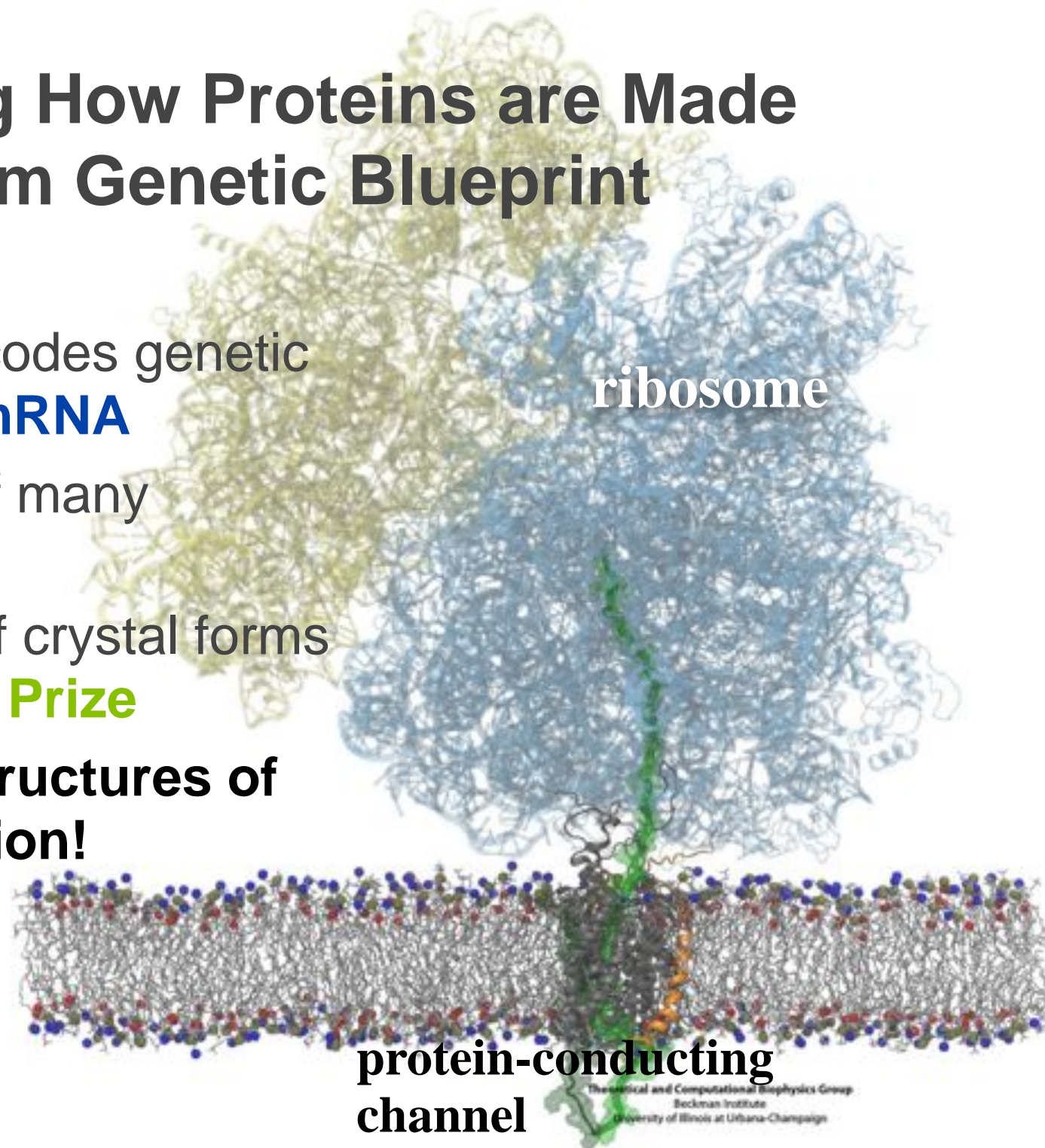
Viewing How Proteins are Made from Genetic Blueprint

- **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!**



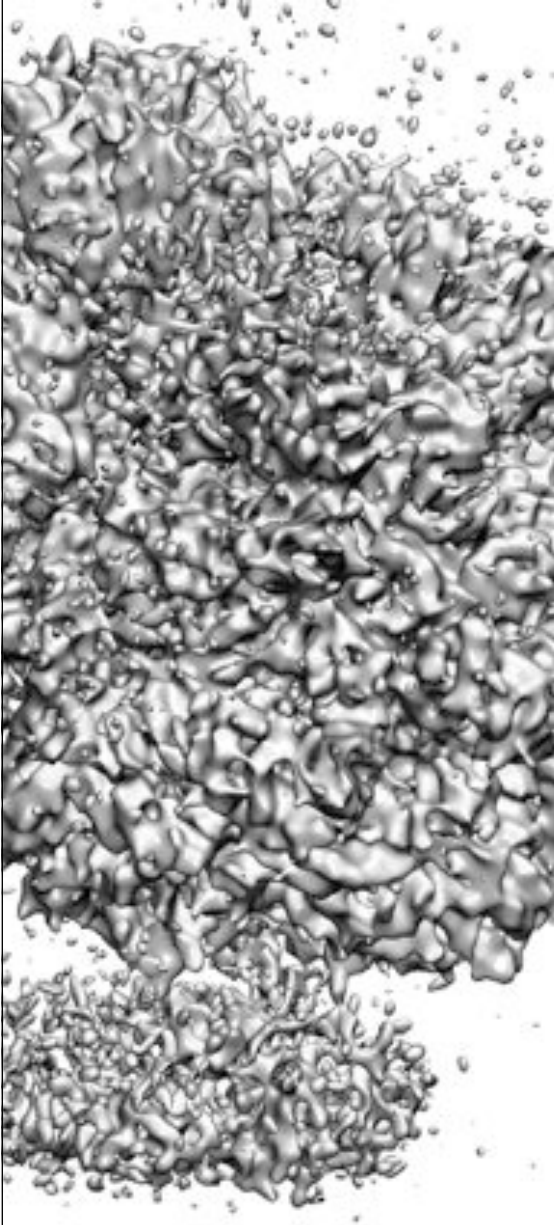
Viewing How Proteins are Made from Genetic Blueprint

- **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!**

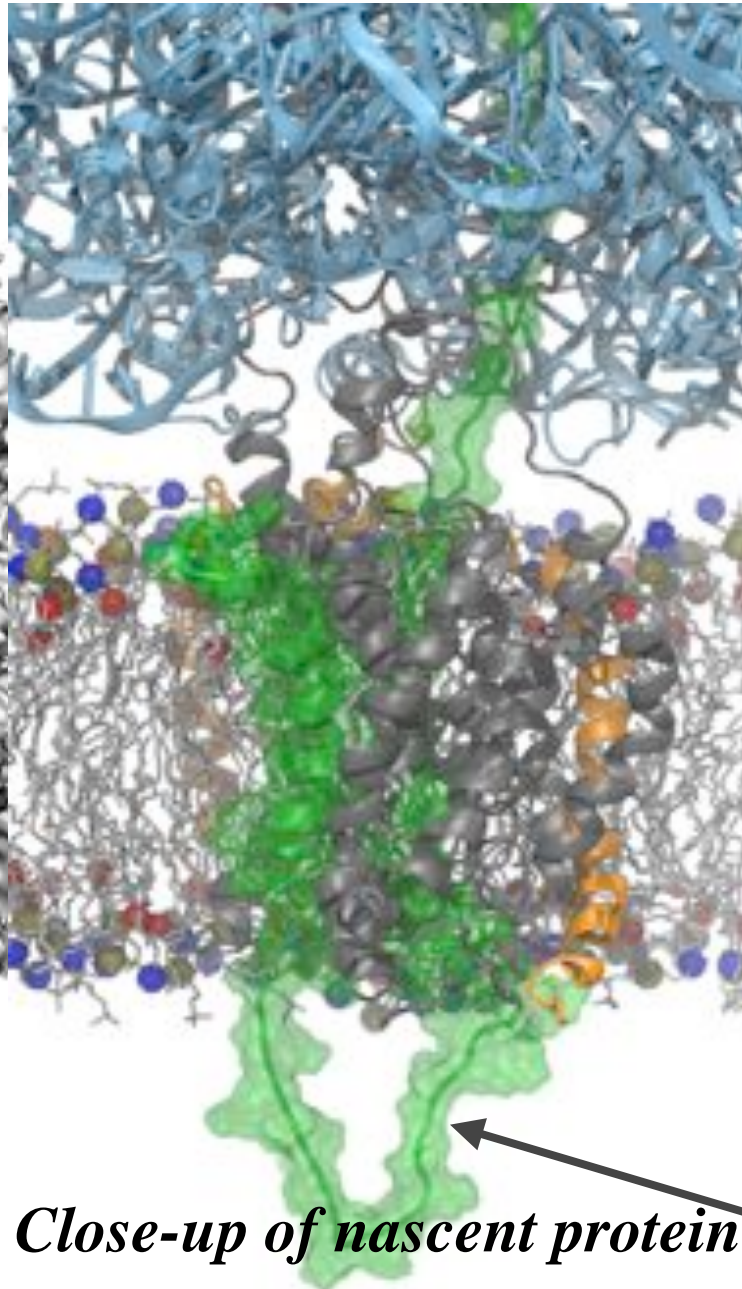
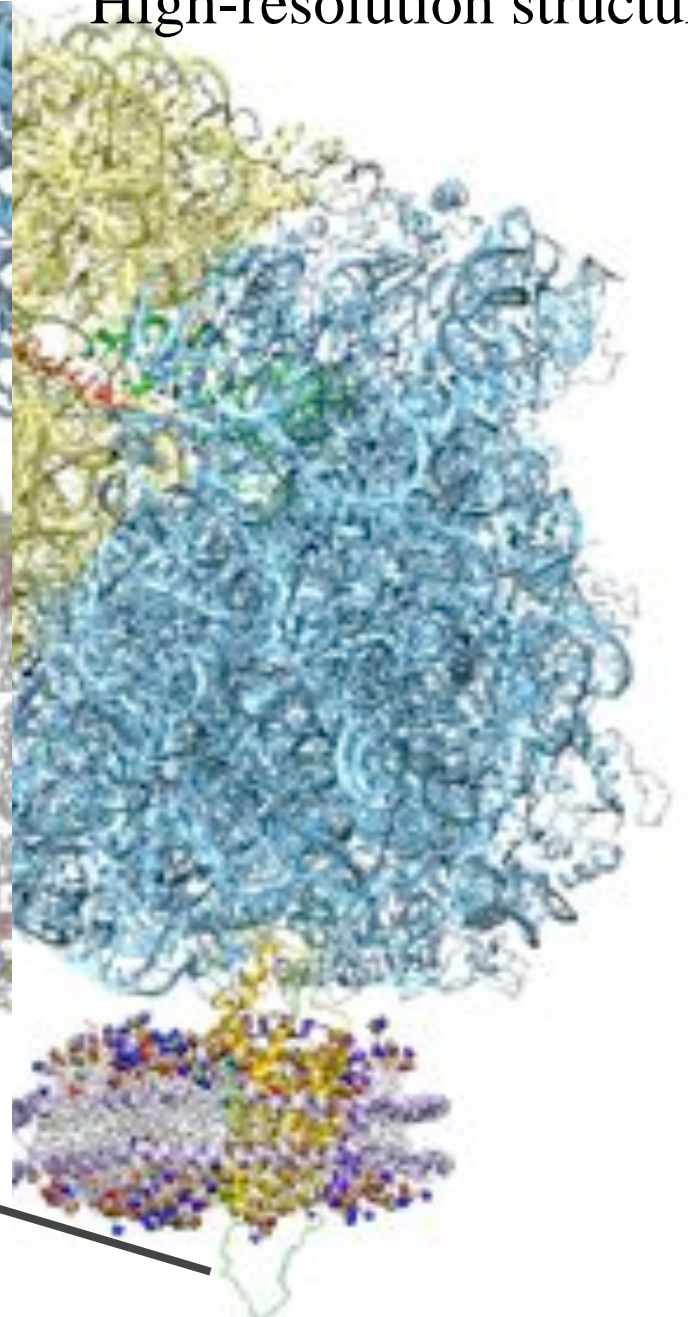


Viewing How Proteins Are Made from Genetic Blueprint

Low-resolution data



High-resolution structure

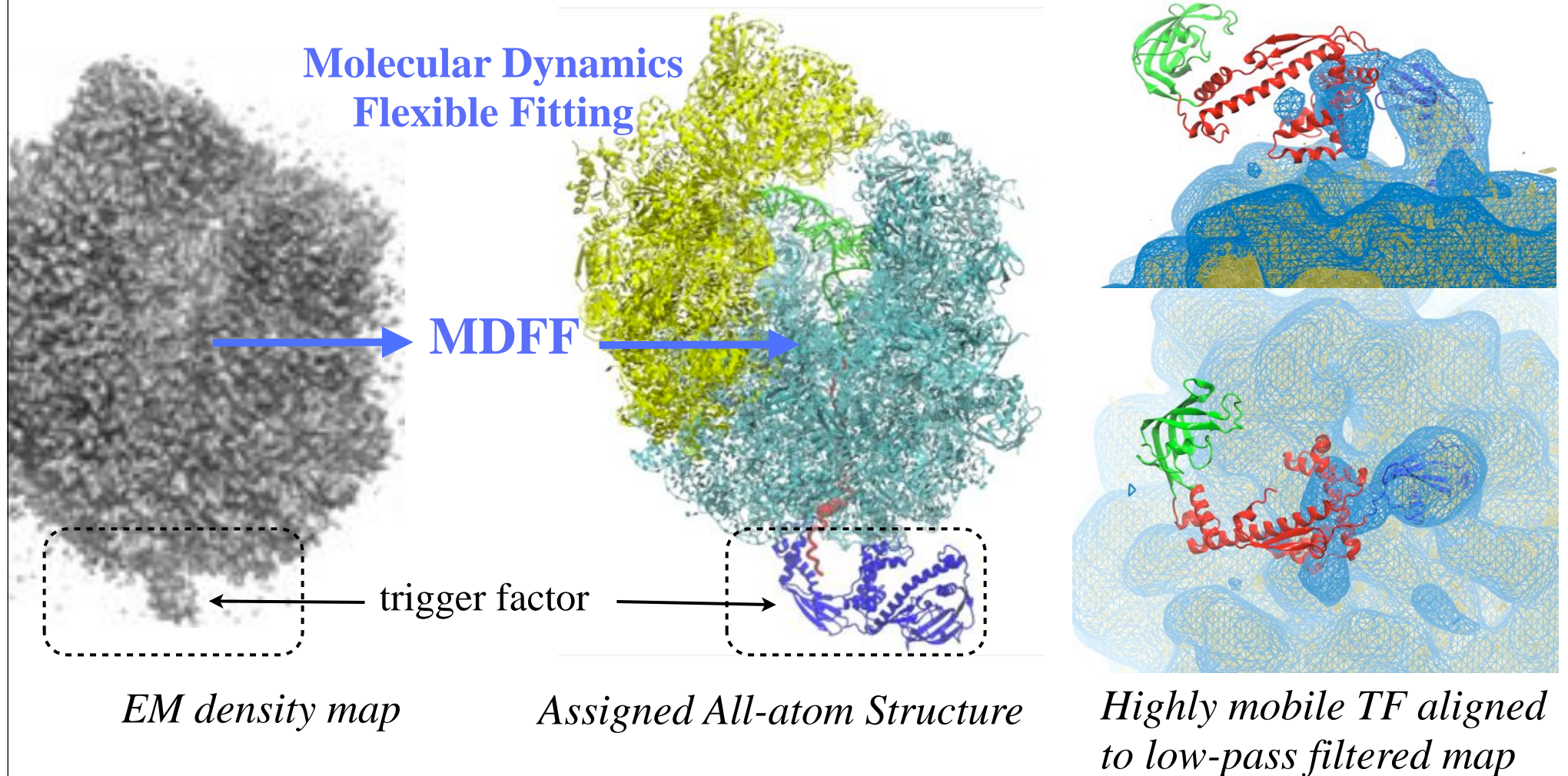


Close-up of nascent protein

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

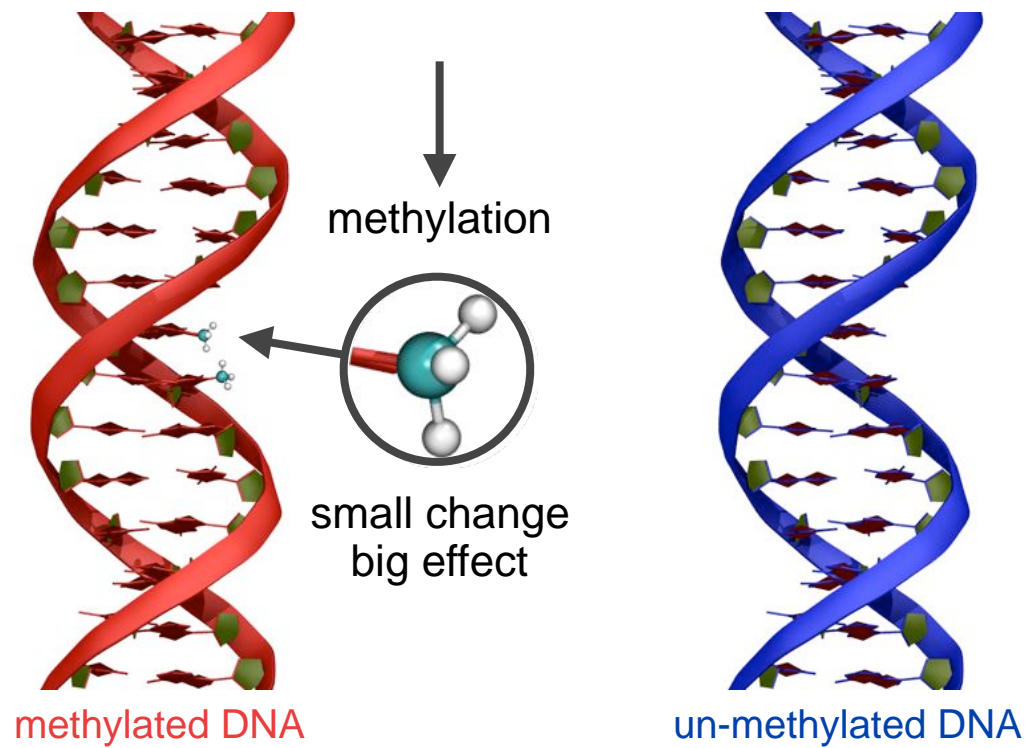


New DBP1-Ribosome effort with collaborator R. Beckmann, U. Munich

Viewing Nanopore Sensors

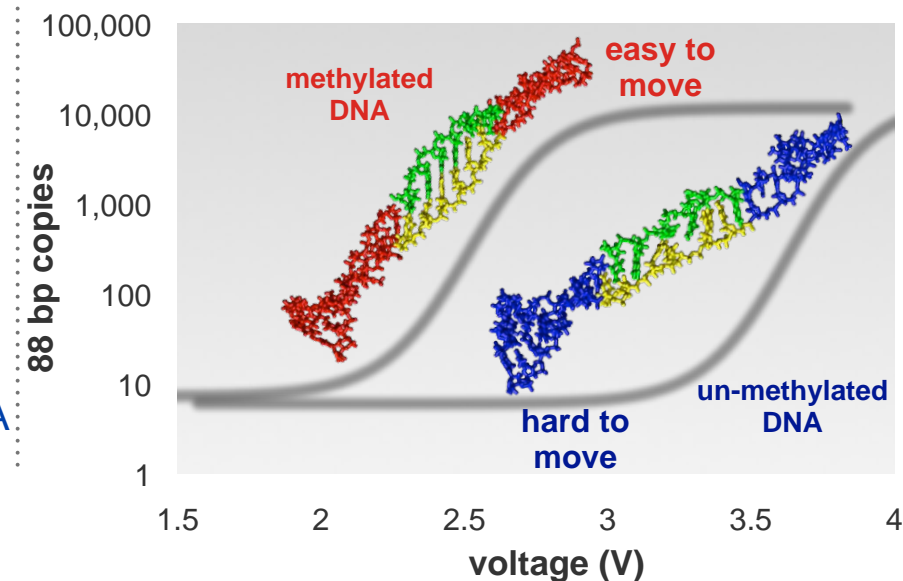
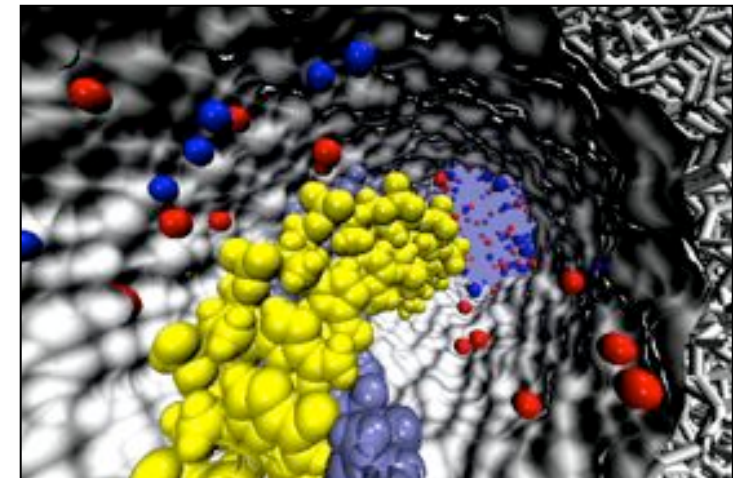
Genetics: Genes control our bodies and experiences!
Epigenetics: Our bodies and experiences control the genes!

Epigenetics made possible through DNA methylation



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

Detect methylation with nanopores



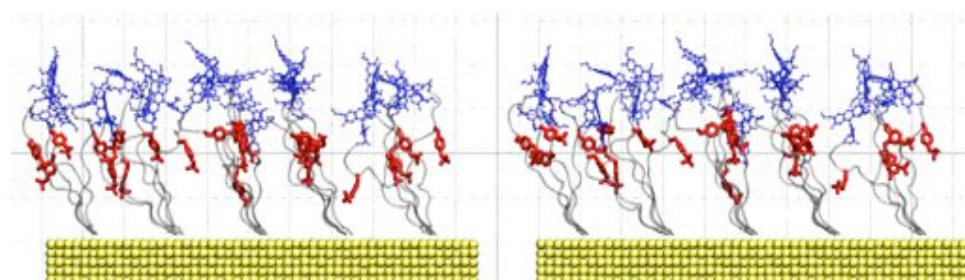
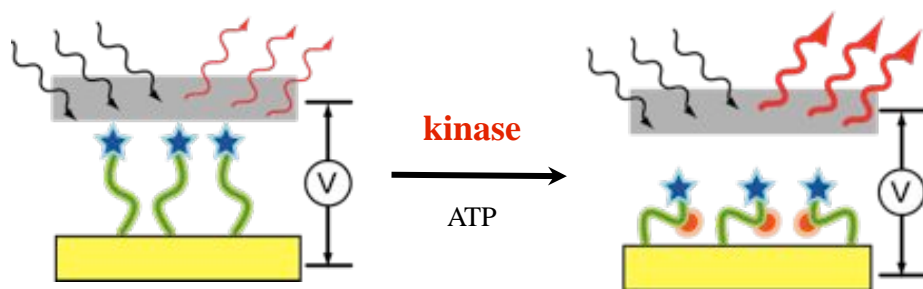
Recent progress

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

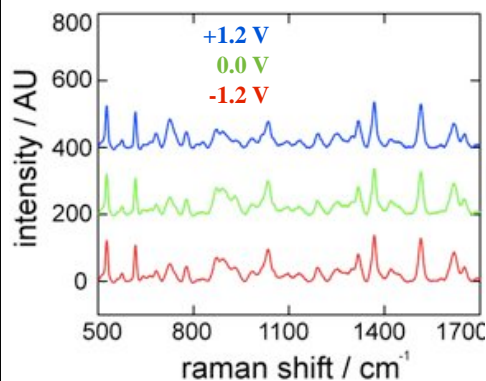
- ❑ Protein kinases are known to regulate the majority of biochemical pathways in the cell
- ❑ Disruption of kinase signaling pathways are frequent causes for diseases, such as cancer and diabetes
- ❑ New nanodevice to detect **kinase** activity

Key points for creating a functional device:

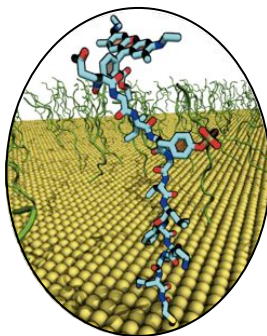
- ❑ Phosphorylated peptides must change conformation under different voltage polarities
- ❑ Peptide conformation must be sensitive to spectroscopic detection



Sequence insensitive to voltage polarity

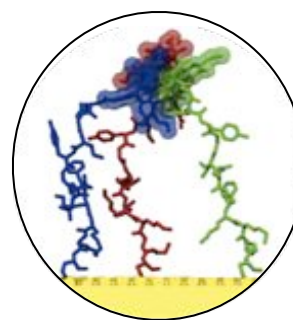


All-atom model



Sequence optimization through MD

MD reveals undesired effects



Optimized sequence responds to voltage polarity

