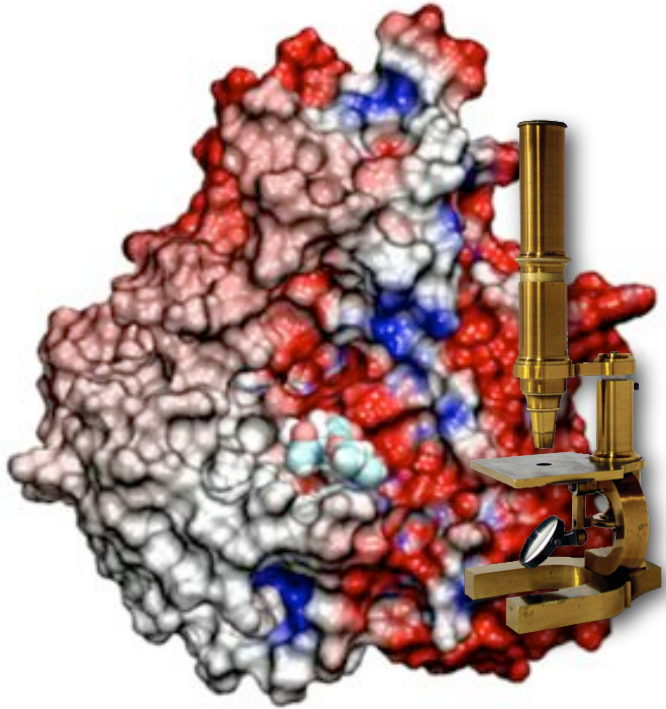# Discoveries Through the Computational Microscope

Accuracy • Speed-up • Unprecedented Scale

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

Klaus Schulten

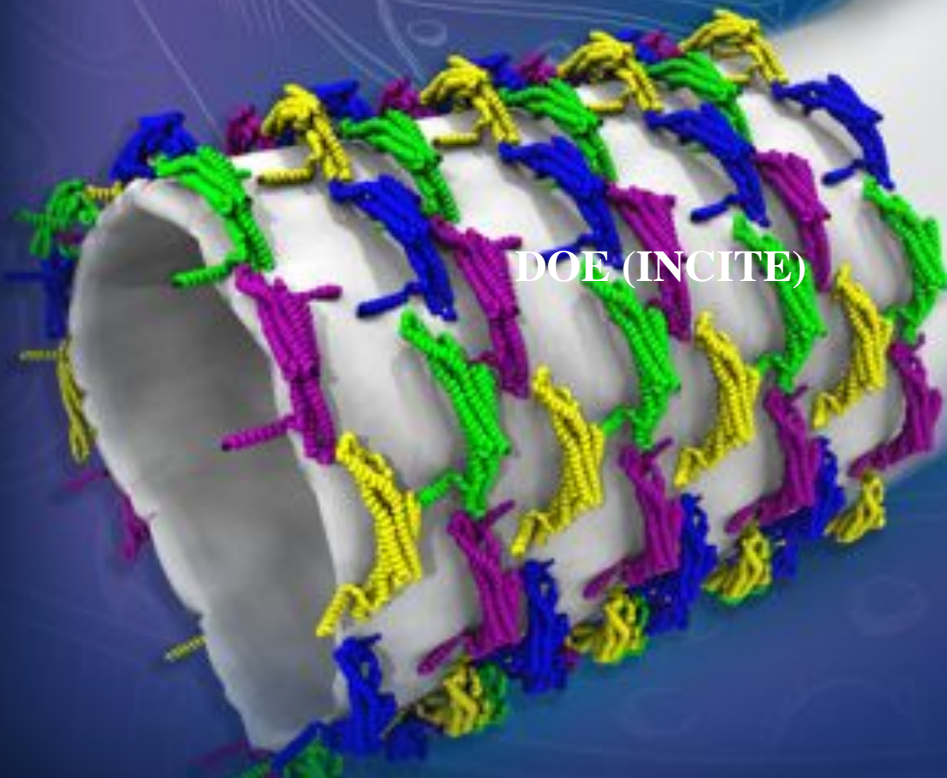Department of Physics and

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 μs

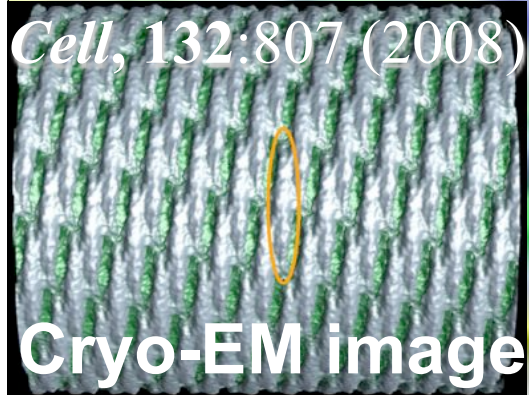DOE (INCITE)

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

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

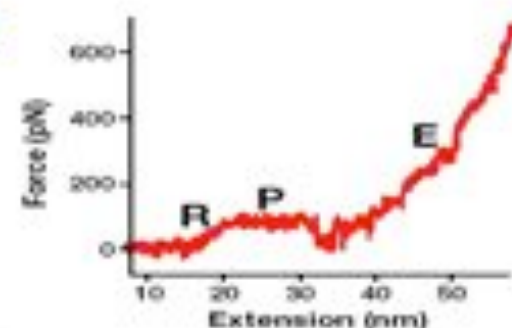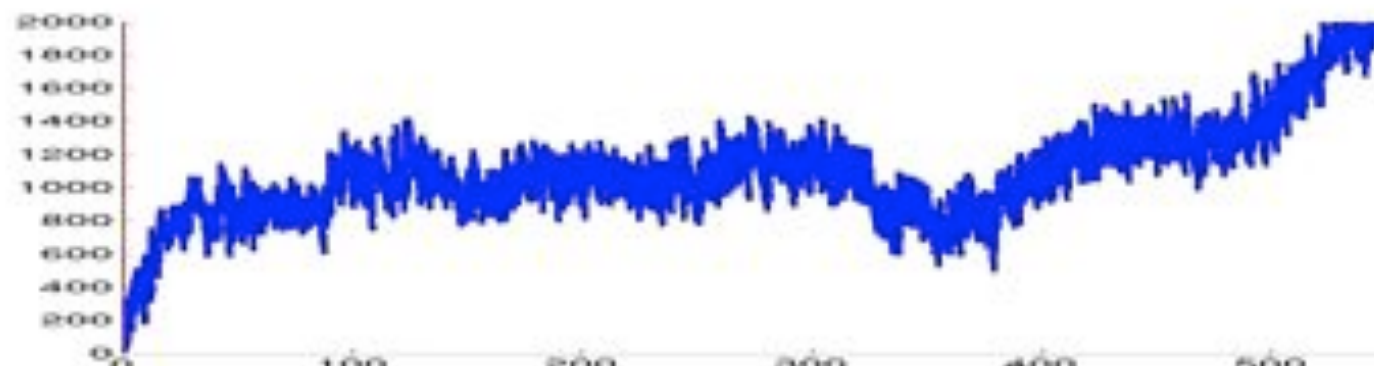Collaborator: Bernard C. Lim (Mayo Clinic College of Medicine)
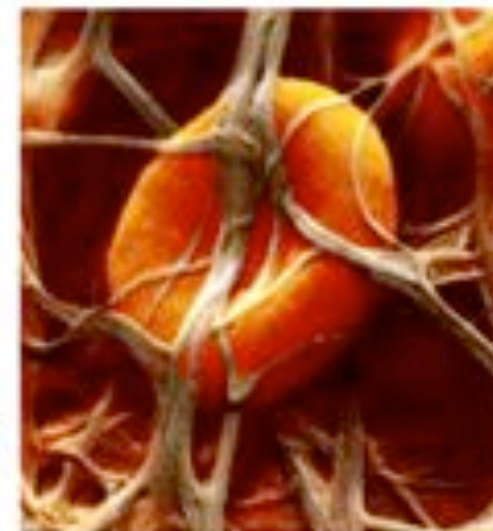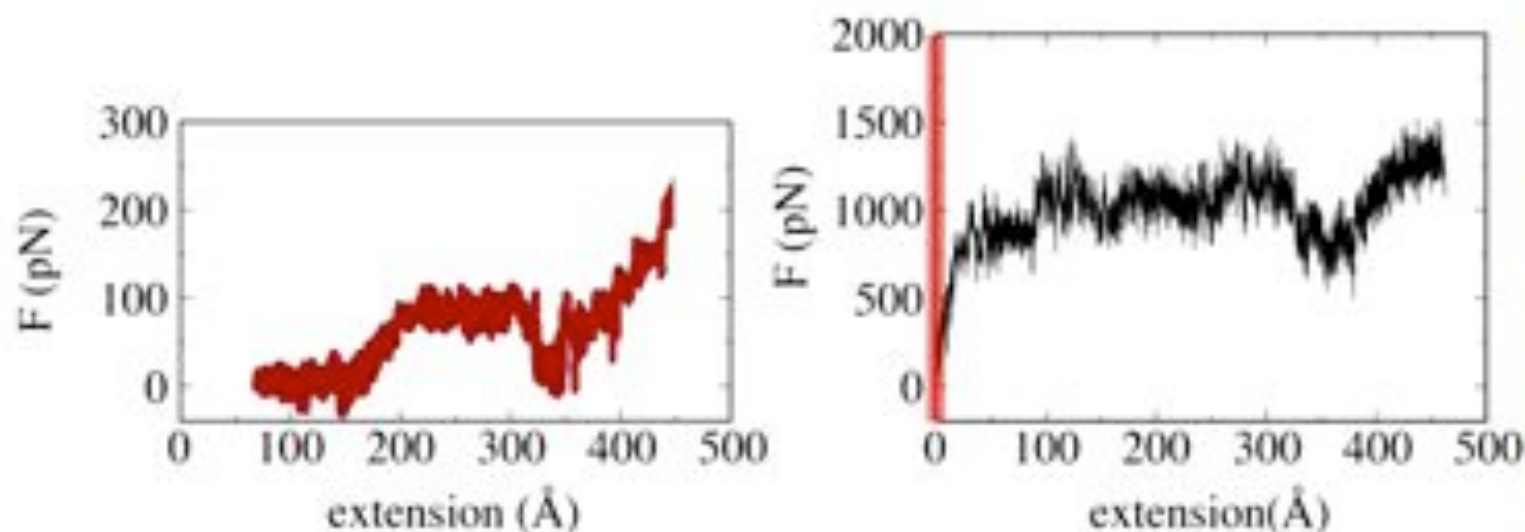
20ns SMD Simulation of <u>fibrinogen,</u> *1.06 million atoms,* *1.2 ns/day with pencil decomposition, 15 days on PSC XT3 Cray (1024 processors)*

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)

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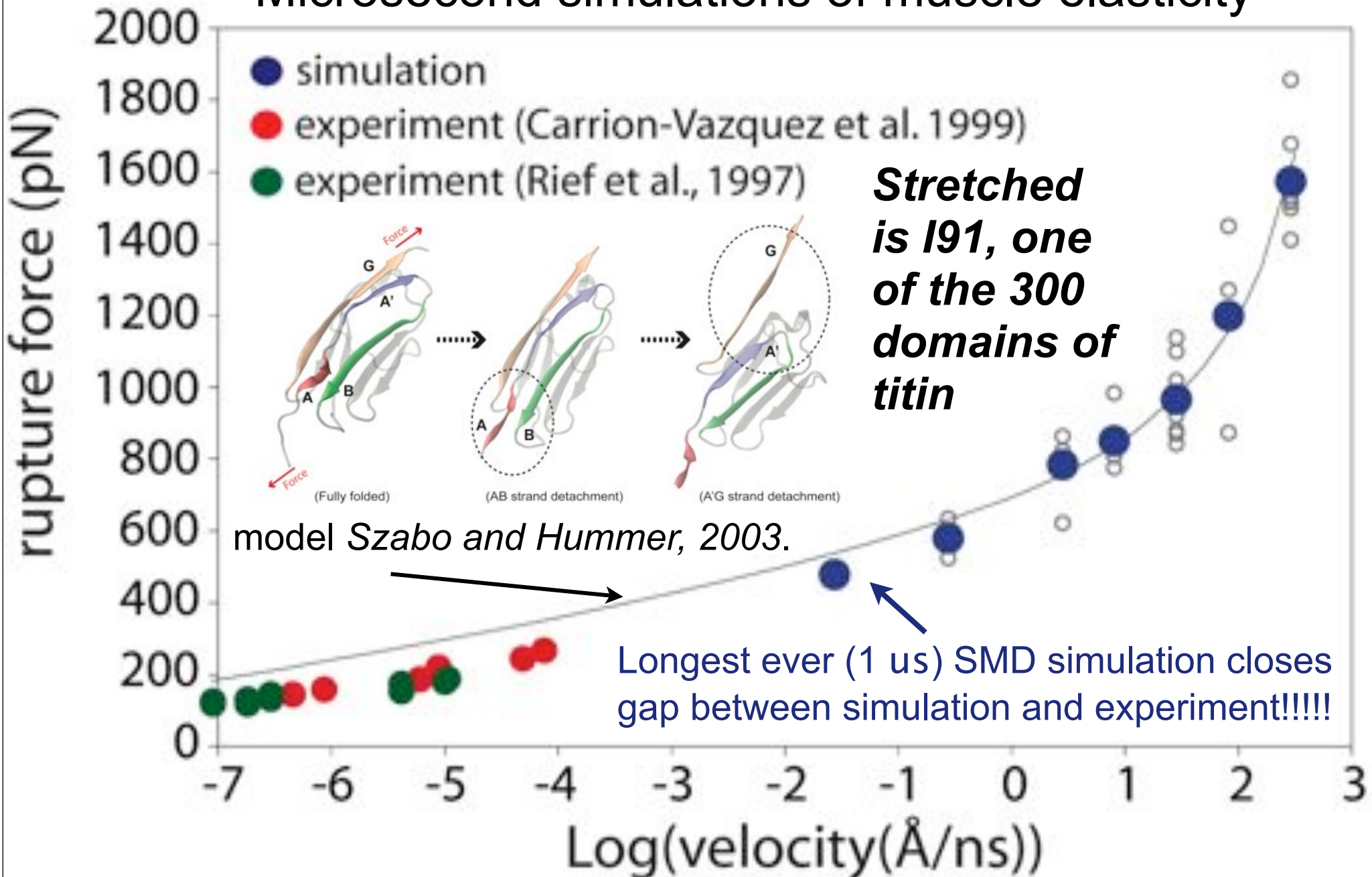
Petascale simulations will Permit Sampling
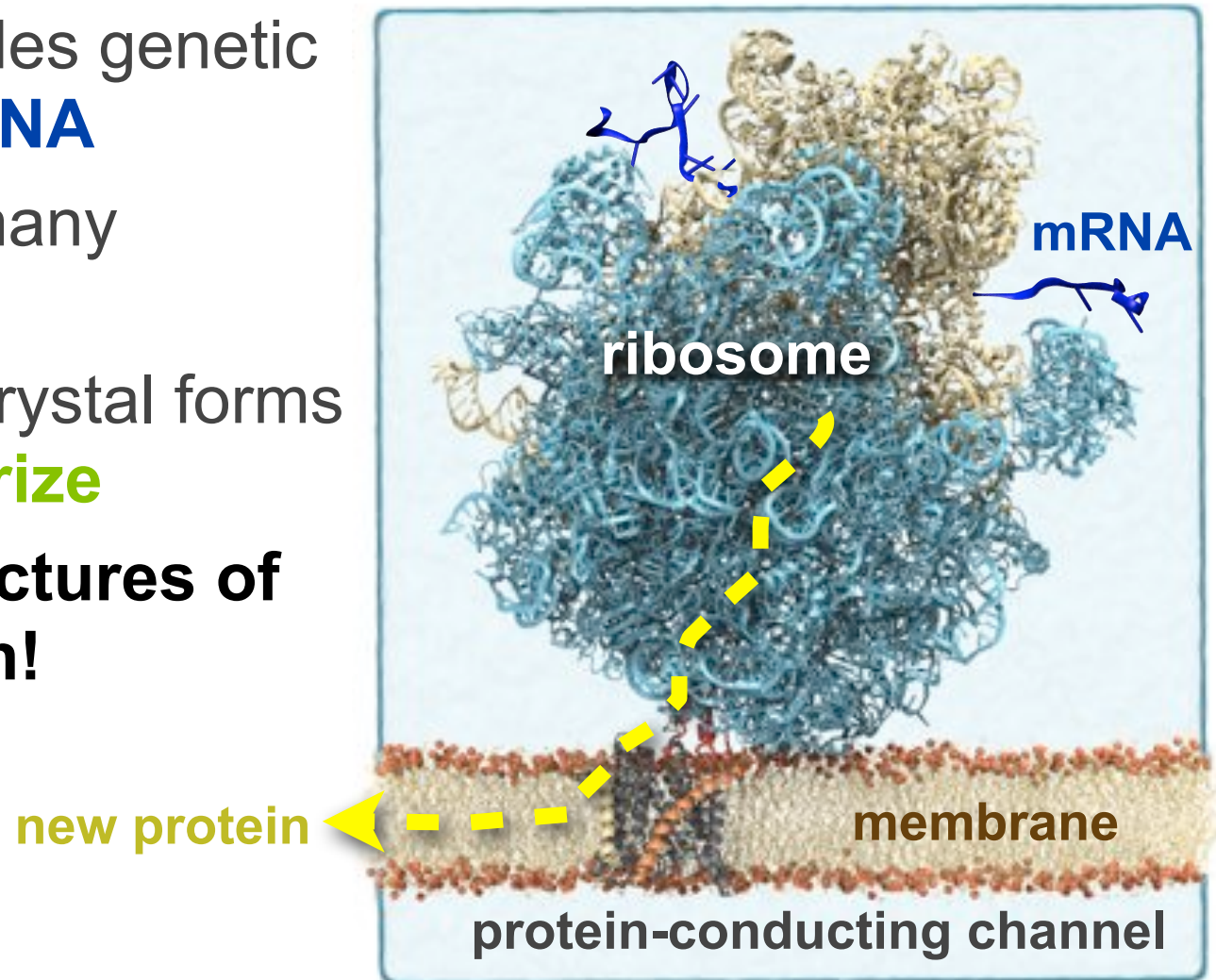## *For Example Carrying out a Second Simulation Required by a Referee*
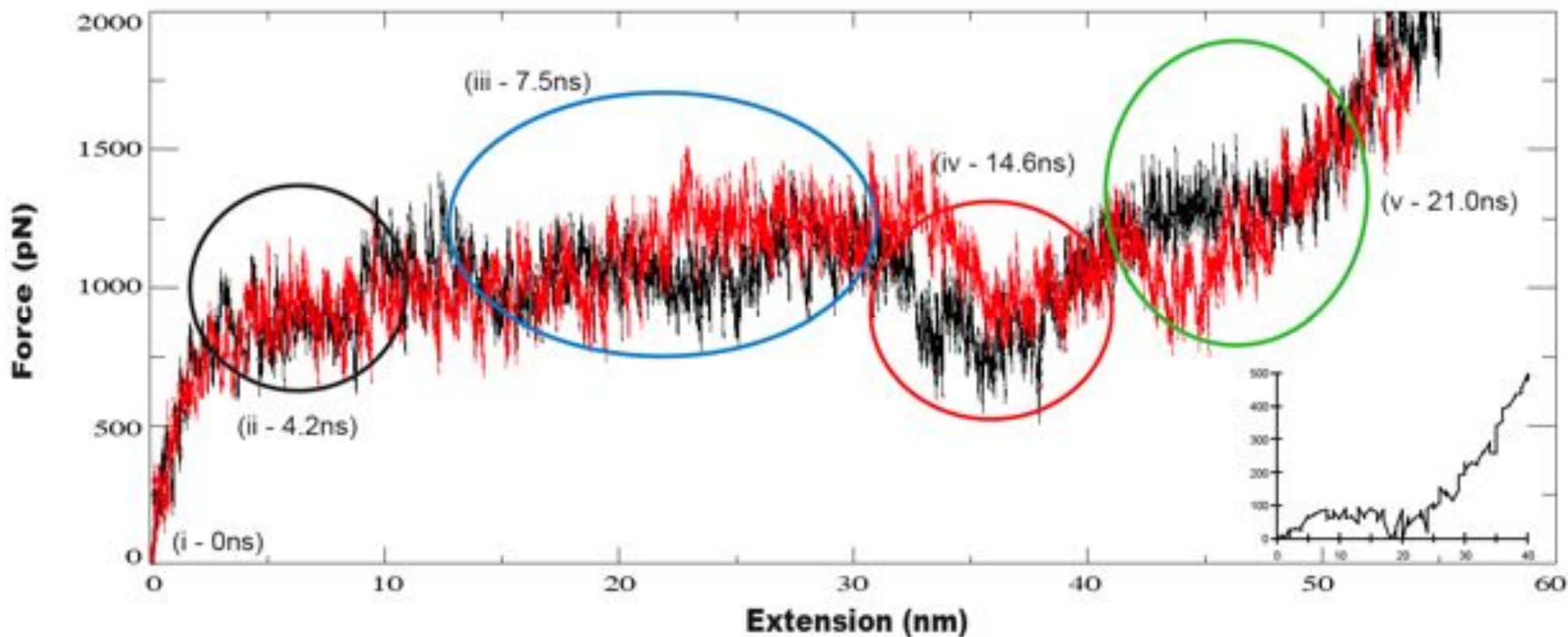
Reaching for Overlapping Time Scales

Microsecond simulations of muscle elasticity

- **simulation** (blue)
- **experiment (Carrion-Vazquez et al. 1999)** (red)
- **experiment (Rief et al., 1997)** (green)

Stretched is I91, one of the 300 domains of titin

model *Szabo and Hummer, 2003*.

Longest ever (1 us) SMD simulation closes gap between simulation and experiment!!!!!

(Fully folded) → (AB strand detachment) → (A'G strand detachment)

y-axis: rupture force (pN)

x-axis: Log(velocity(Å/ns))

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!**

mRNA

ribosome

new protein

membrane

protein-conducting channel

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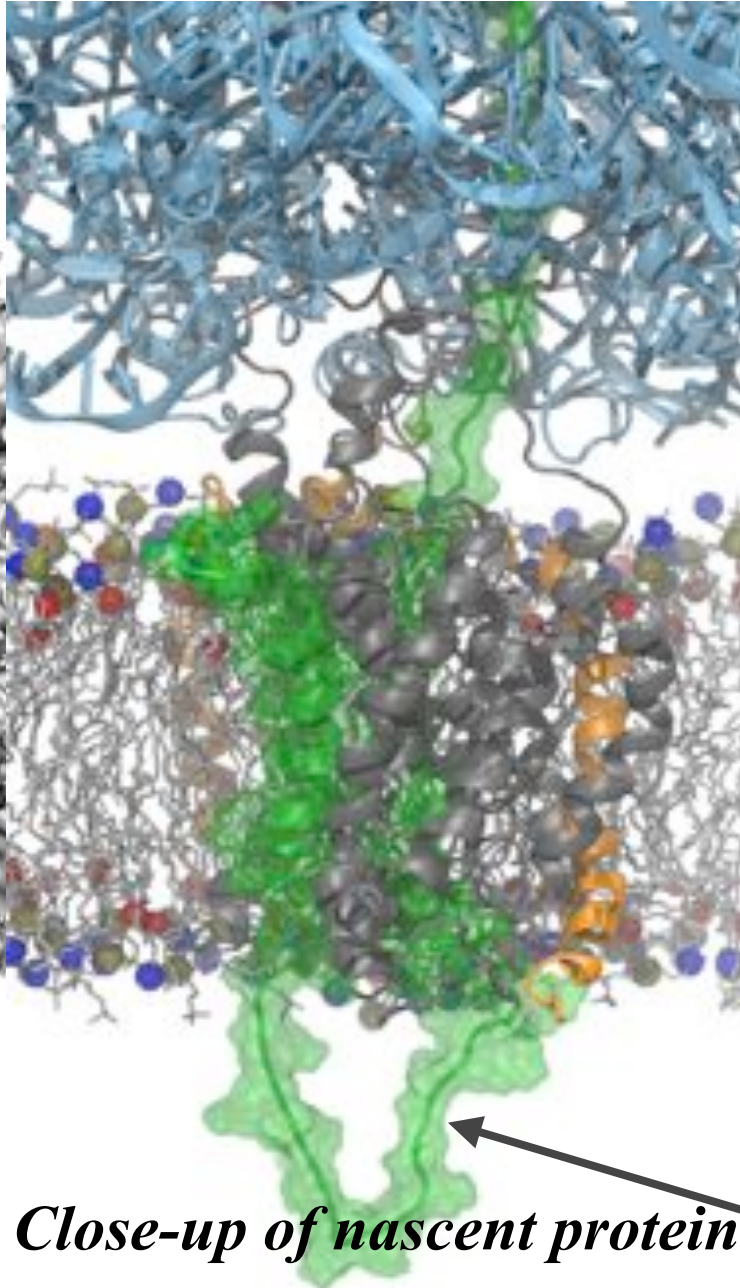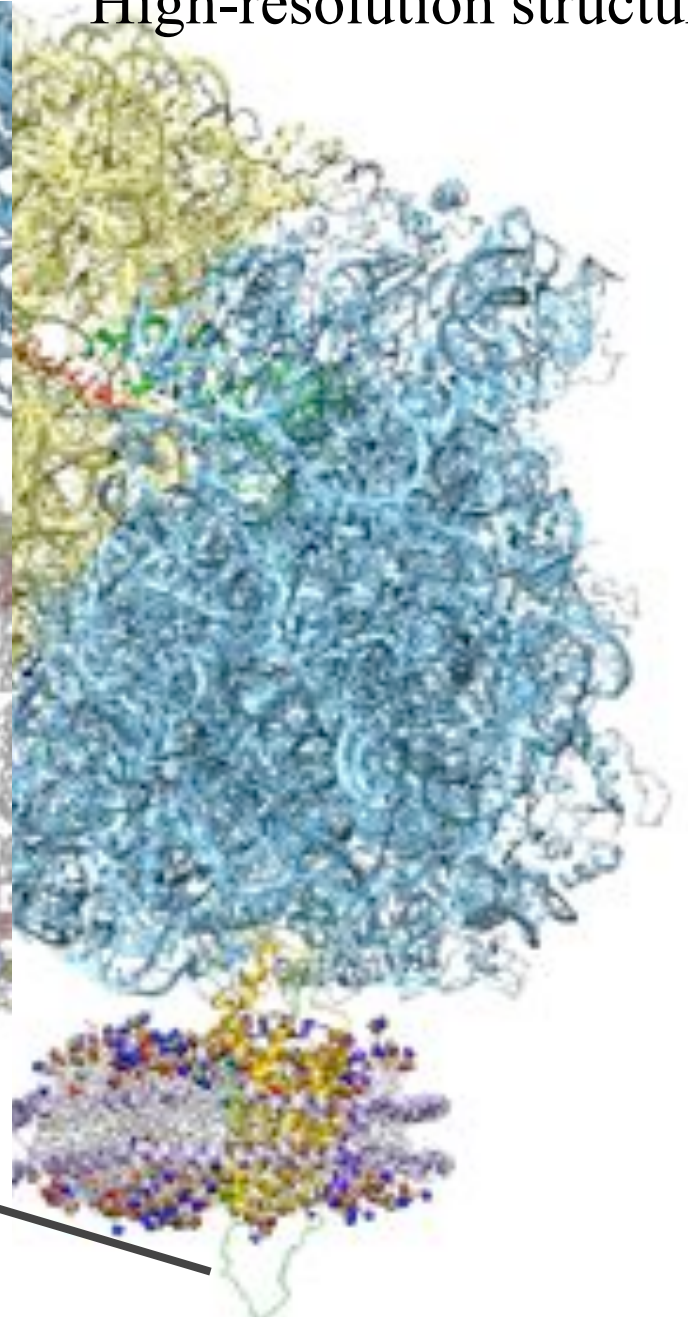- **But one needs structures of ribosomes in action!**

ribosome

protein-conducting channel
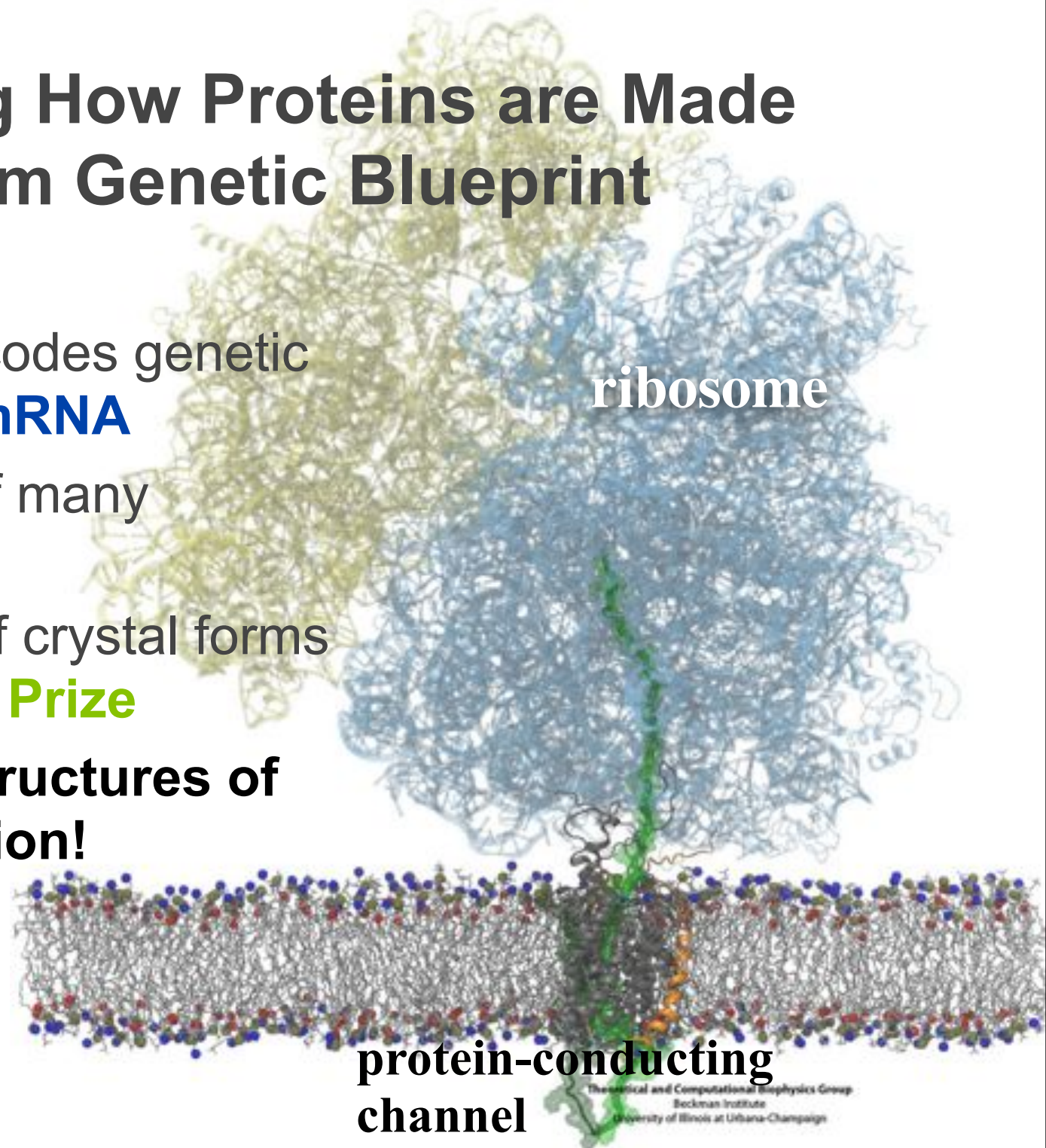
Viewing How Proteins Are Made from Genetic Blueprint

Low-resolution data
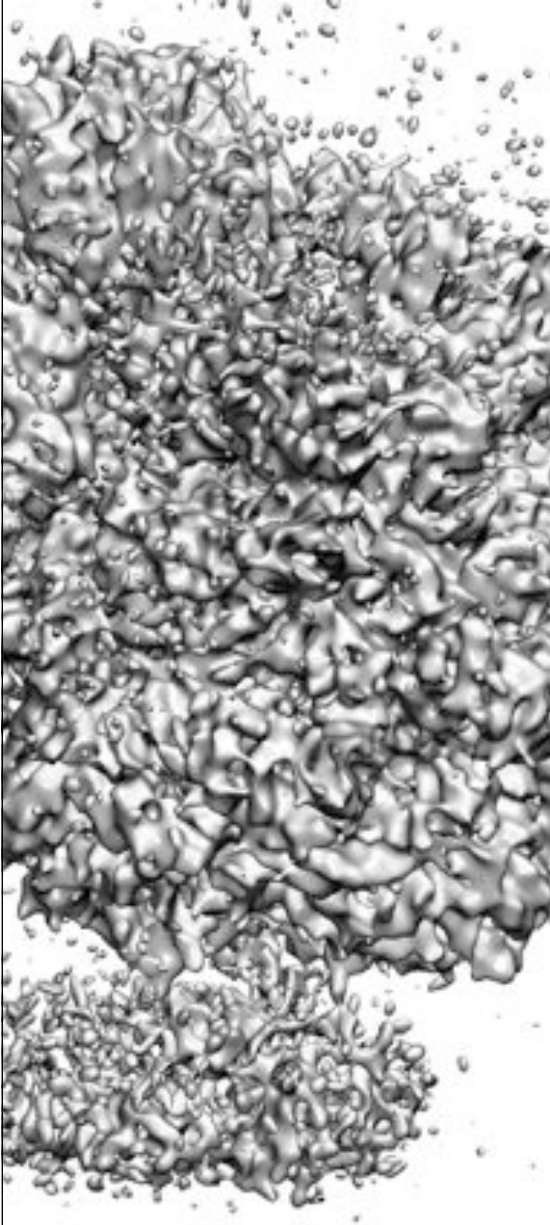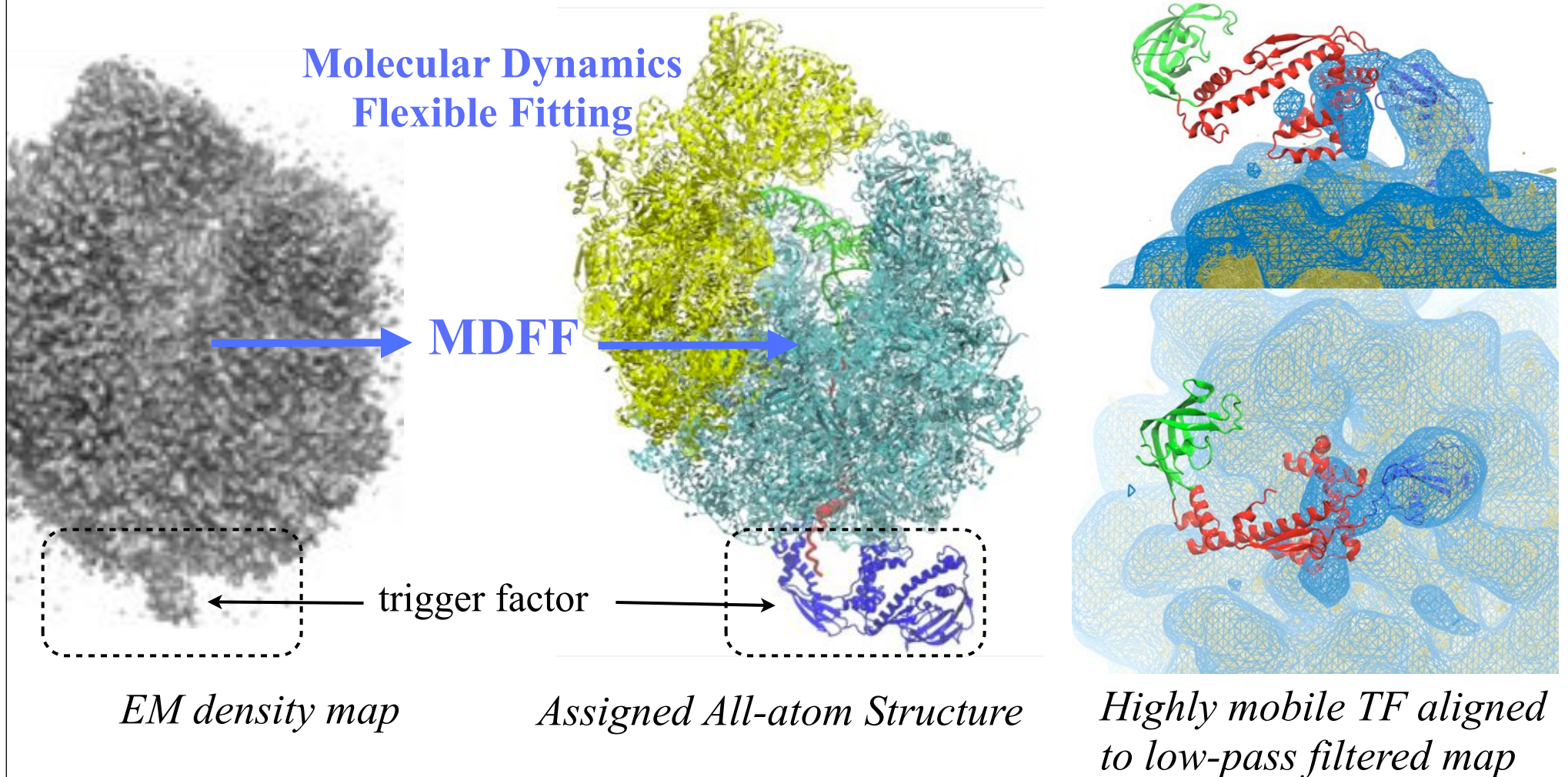
High-resolution structure

Close-up of nascent protein

Viewing how Proteins are Made from Genetic Blueprint
Trigger Factor Bound to Translating Ribosome

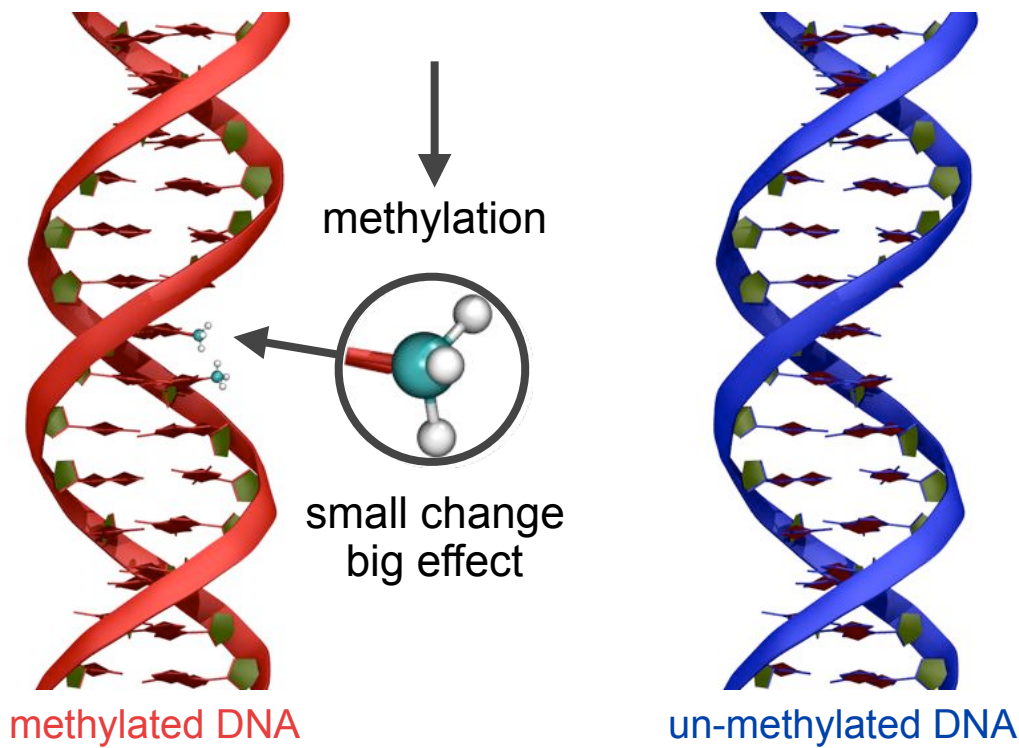Trigger factor (TF): ribosome-associated chaperon preventing misfolding of nascent chain

Molecular Dynamics Flexible Fitting

MDFF

trigger factor

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
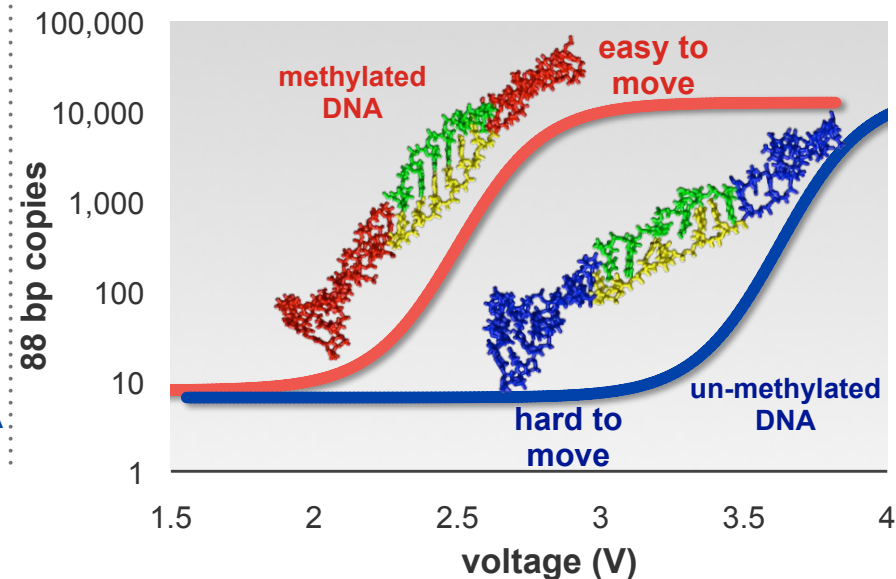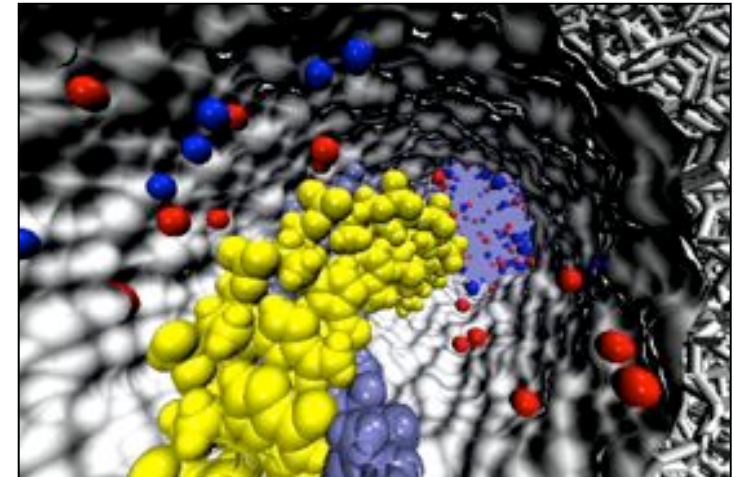
Viewing Nanopore Sensors

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

Epigenetics made possible through DNA methylation

methylation

small change
big effect

methylated DNA

un-methylated DNA

Related pathologies: obesity, depression, cancer

Detect methylation with **nanopores**

methylated DNA — easy to move

un-methylated DNA — hard to move

88 bp copies: 100,000 / 10,000 / 1,000 / 100 / 10 / 1

voltage (V): 1.5 2 2.5 3 3.5 4

Recent progress

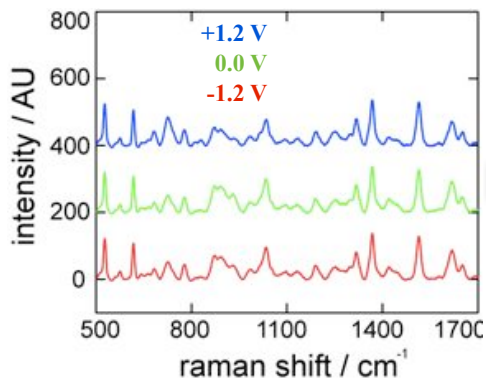## Building a nanodevice for kinase detection (*Collaborator: Logan Liu; UIUC*)

- 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

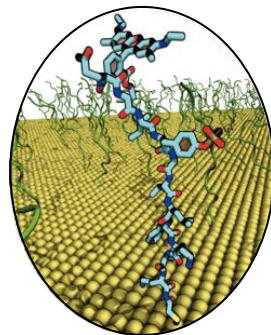**Key points for creating a functional device:**

- Phosphorylated peptides must change conformation under different voltage polarities

- Peptide conformation must be sensitive to spectroscopic detection

kinase

ATP
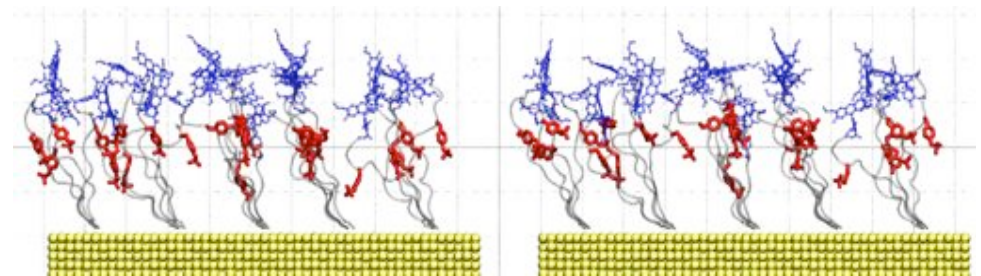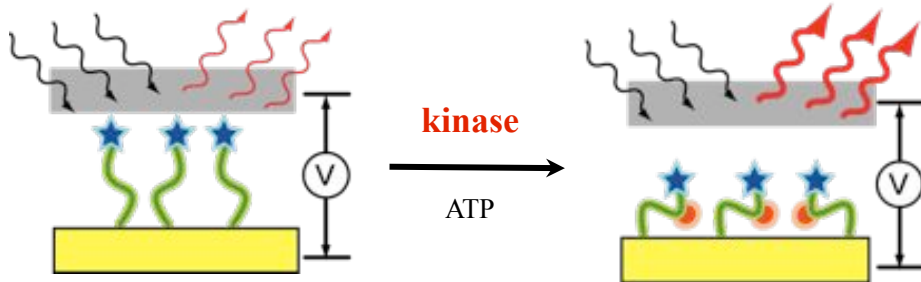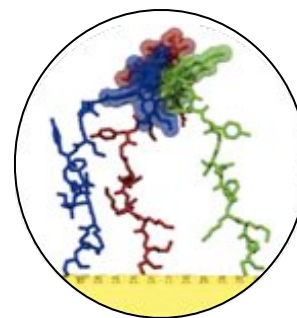
Sequence insensitive to voltage polarity

All-atom model

MD reveals undesired effects

Optimized sequence responds to voltage polarity

+1.2 V
0.0 V
-1.2 V

Sequence optimization through MD

+1.2 V
0.0 V
-1.2 V

intensity / AU

raman shift / cm⁻¹

BTRC for Macromolecular Modeling and Bioinformatics
http://www.ks.uiuc.edu/

Beckman Institute, UIUC