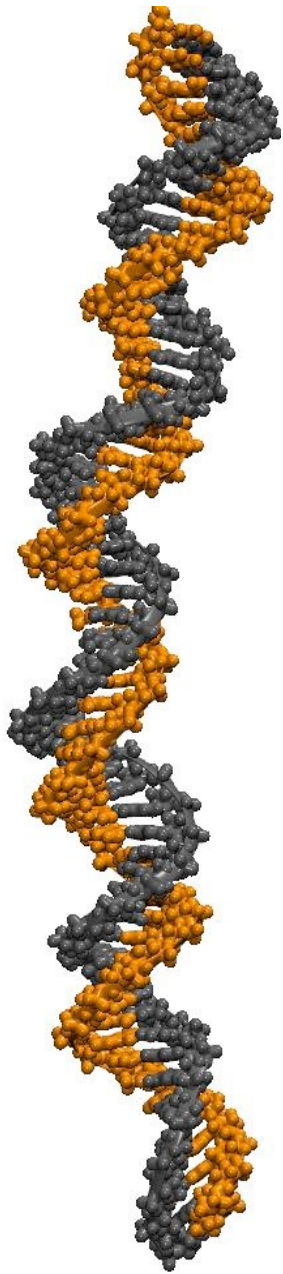


Reinventing a DNA sequence reader

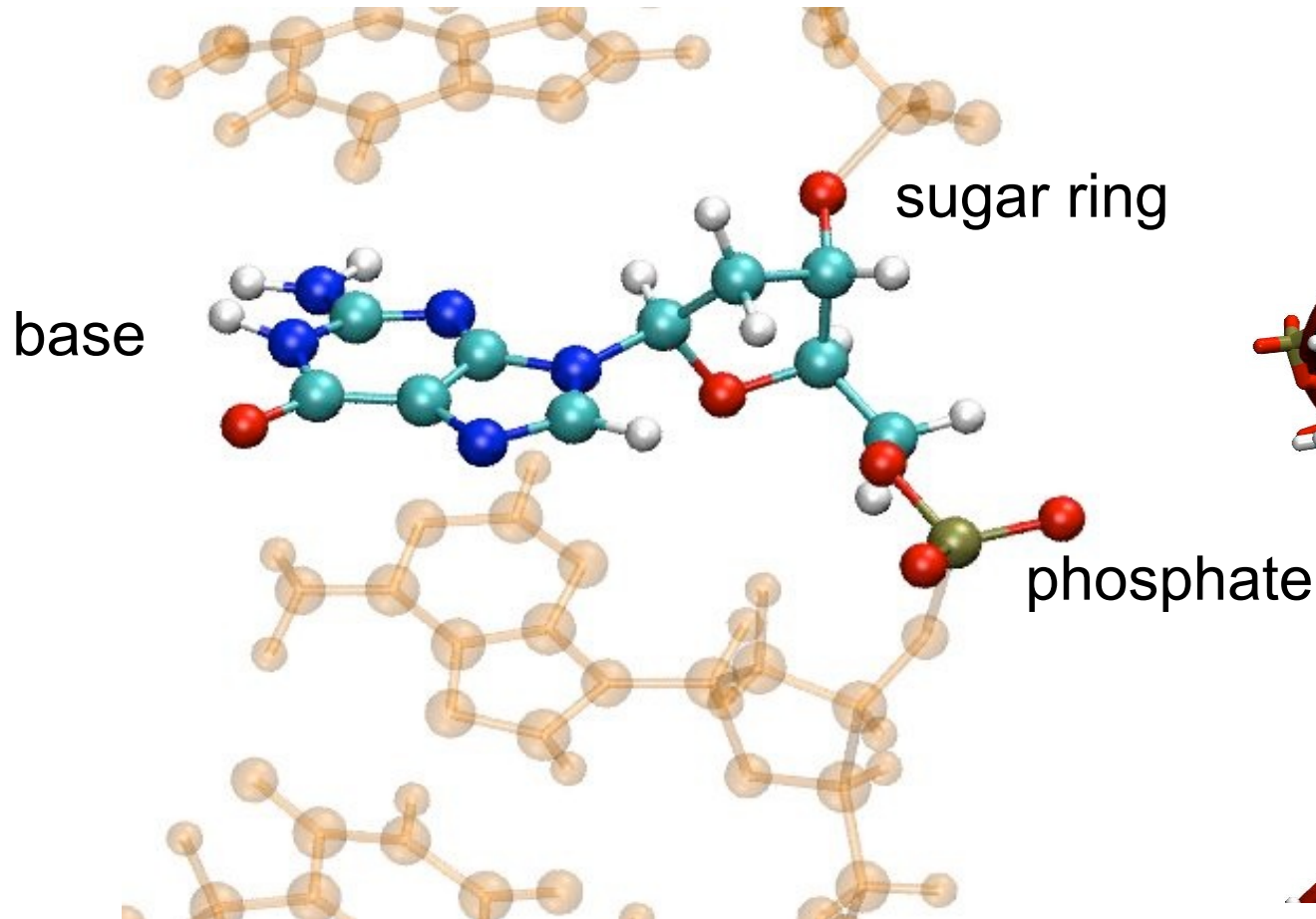
Aleksei Aksimentiev
University of Illinois at Urbana-Champaign

DNA code is written in atoms

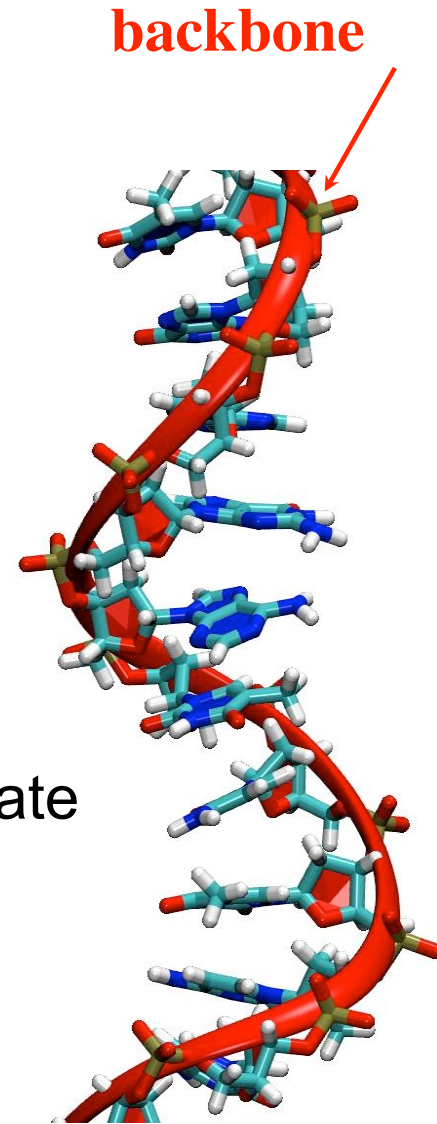
Highly charged: 2 electron charges per 0.32nm



Double stranded DNA
(persist. length ~50nm)



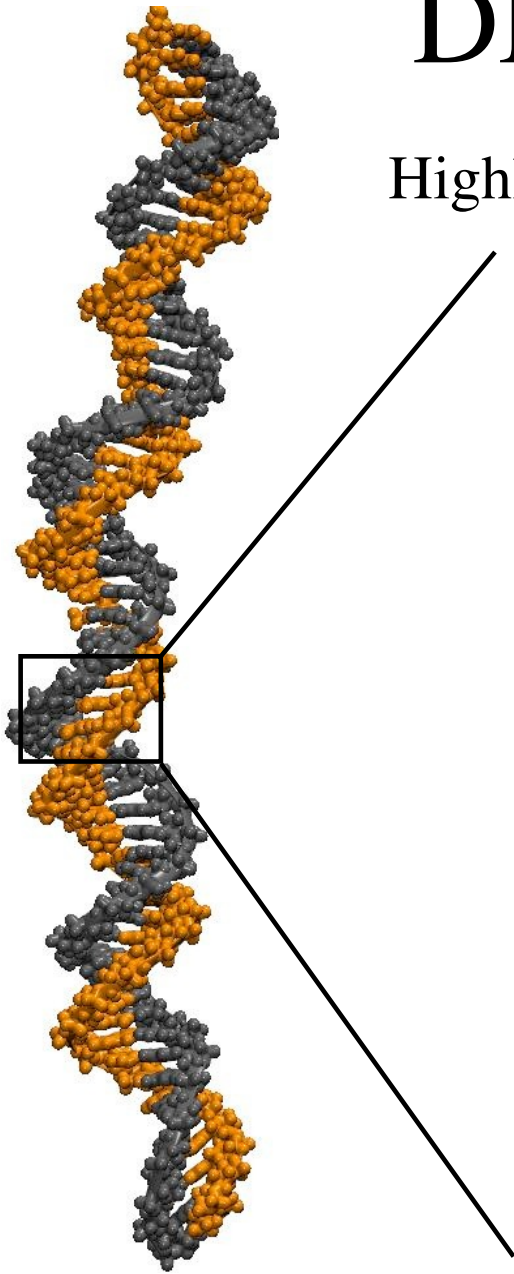
The sequence has direction:
5'-AAGCTGGTTCAG-3'



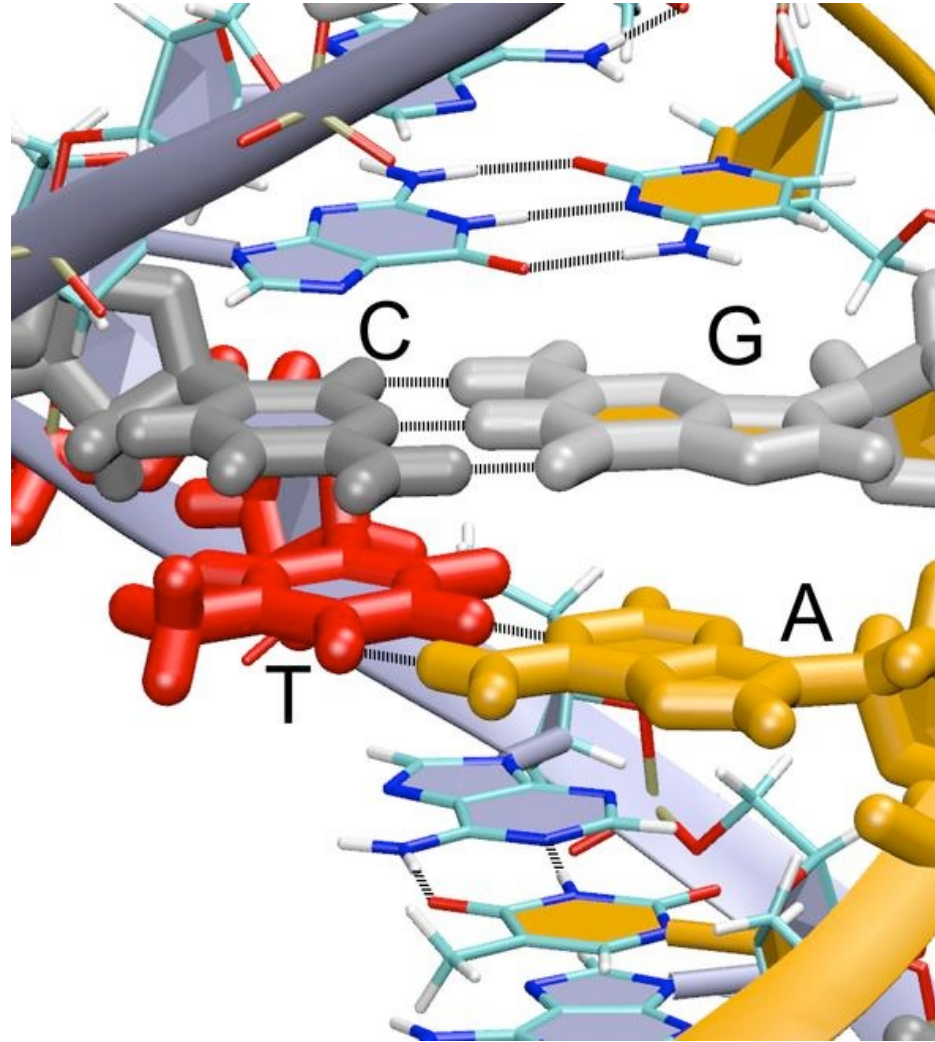
Single stranded DNA
(persist. length ~1.5nm)

DNA code is written in atoms

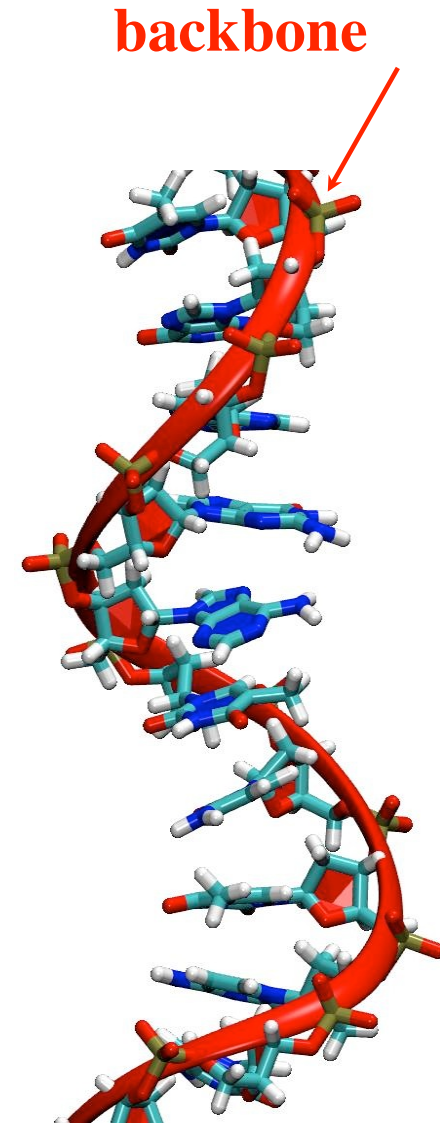
Highly charged: 2 electron charges per 0.32nm



Double stranded DNA
(persist. length ~50nm)



The sequence has direction:
5'-AAGCTGGTTCAG-3'

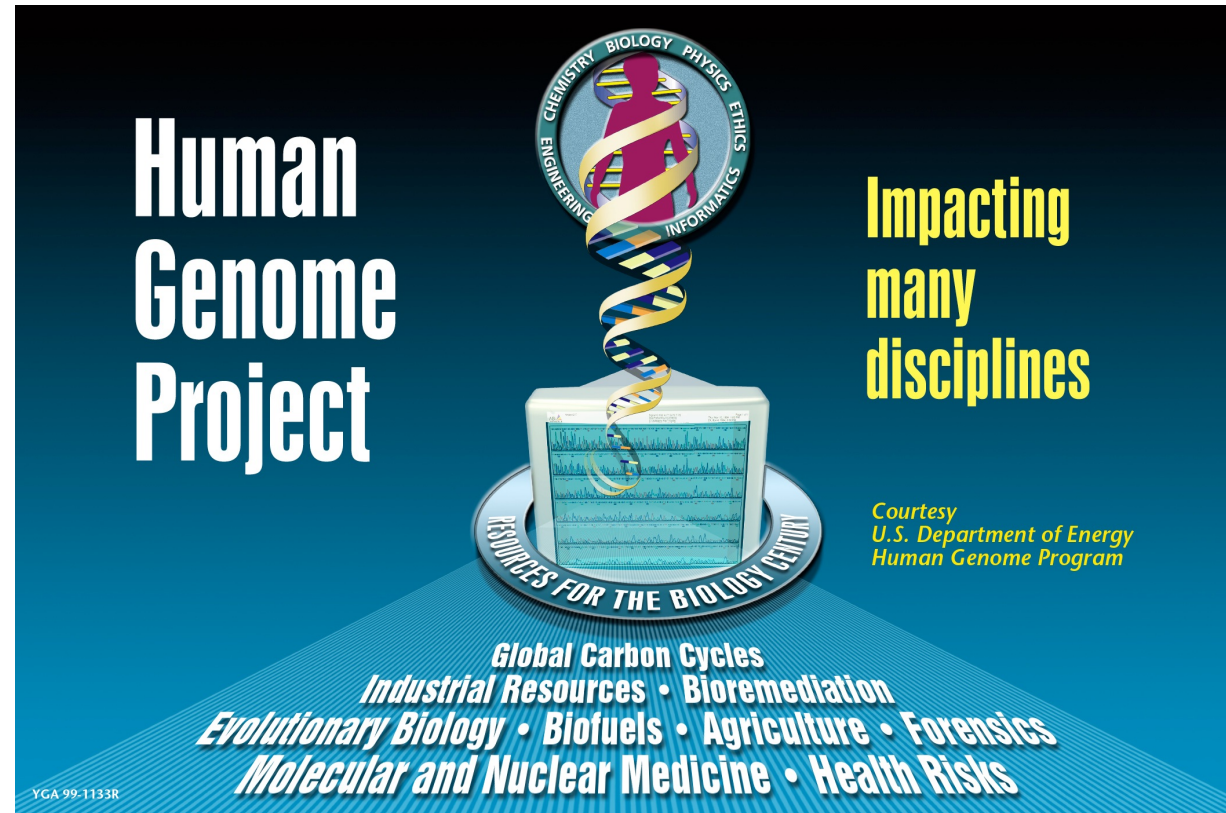


Single stranded DNA
(persist. length ~1.5nm)

The Human Genome Project

Duration:
October 1990 - 2003

Discovered ALL
20,000-25,000
human genes



Determined complete sequence of the 3 billion DNA bases

5'-ACCGGTGGGTGCATAGCTGTGCTGTAAGTGAAGTG
AGGCGGCAGGTGTTGAAAGTCGATGTAGTTCGTAG
GTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTG
GACAGGGTGACTAGTGAATCGATGCTAGCCTAGCTA
GTCAGTGGTGCTAGCTACGATCGATTTCAGGCTGCT

GTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGGCGGCAGGTGTTGAAAG
TCGATGTAGTTCGTAGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGT
GGACAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTA
GCTACGATCGATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAA
GTGAGGGCGGCAGGTGTTGAAAGTCGATGTAGTTCGTAGGTCAGTTGATGTC
GATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAG
CCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTCAGGCTGCTGTGGGTG
CATAGCTGTGCTGTAAGTGAAGTGAGGGCGGCAGGTGTTGAAAGTCGATGTA
GTTTCGTAGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGACAGGG
TGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATC
GATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGGCGG
CAGGTGTTGAAAGTCGATGTAGTTCGTAGGTCAGTTGATGTCGATGTGAAAT
GCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGT
CAGTGGTGCTAGCTACGATCGATTTCAGGCTGCT CCTAGCTAGTCAGTGGT
GTTTCGTAGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGACAGGG
TGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATC
GATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGGCGG
CAGGTGTTGAAAGTCGATGTAGTTCGTAGGTCAGTTGATGTCGATGTGA TC
GATGTAGTTCGTAGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGA
CAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTATTGT
GCTACGATCGATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAA
GTGAGGGCGGCAGGTGTTGAAAGTCGATGTAGTTCGTAGGTCAGTTGATGTC
GATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAG
CCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTCAGGCTGCTGTGGGTG

GATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAG
CCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTCAGGCTGCTGTGGGTG
CATAGCTGTGCTGTAAGTGAAGTGAGGCGGGCAGGTGTTGAAAGTCGATGTA
GTTTCGTAGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGACAGGG
TGA CTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATC
GATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGCGG
CAGGTGTTGAAAGTCGATGTAGTTCGTAGGTCAGTTGATGTCGATGTGAAAT
GCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGT
CAGTGGTGCTAGCTACGATCGATTTCAGGCTGCT CCTAGCTAGTCAGTGGT
GTTTCGTAGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGACAGGG
TGA CTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATC
GATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGCGG
CAGGTGTTGAAAGTCGATGTAGTTCGTAGGTCAGTTGATGTCGATGTGA TC
GATGTAGTTCGTAGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGA
CAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTATTGT
GCTACGATCGATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAA
GTGAGGCGGGCAGGTGTTGAAAGTCGATGTAGTTCGTAGGTCAGTTGATGTC
GATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAG
CCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTCAGGCTGCTGTGGGTG
AAACGATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATG
CTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTCAGGCTGCTGTG
GGTG
GCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGT
CAGTGGTGCTAGCTACGATCGATTTCAGGCTGCT CCTAGCTAGTCAGTGGT

CAGGTGTTGAAAGTCGATGTAGTTCGTAGGGTCAGTTGATGTCGATGTGATC
GATGTAGTTCGTAGGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGA
CAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTATTGT
GCTACGATCGATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAA
GTGAGGCGGCAGGTGTTGAAAGTCGATGTAGTTCGTAGGGTCAGTTGATGTC
GATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAG
CCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTCAGGCTGCTGTGGGTG
AAACGATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATG
CTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTCAGGCTGCTGTG
GGTG
GCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGT
CAGTGGTGCTAGCTACGATCGATTTCAGGCTGCT CCTAGCTAGTCAGTGGT
GATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAG
CCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTCAGGCTGCTGTGGGTG
CATAGCTGTGCTGTAAGTGAAGTGAGGCGGCAGGTGTTGAAAGTCGATGTA
GTTTCGTAGGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGACAGGG
TGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATC
GATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGCGG
CAGGTGTTGAAAGTCGATGTAGTTCGTAGGGTCAGTTGATGTCGATGTGAAAT
GCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGT
CAGTGGTGCTAGCTACGATCGATTTCAGGCTGCT CCTAGCTAGTCAGTGGT
GTTTCGTAGGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGACAGGG
TGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATC
GATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGCGG

... and ~ 3,000,000 more pages!

(one month to show 24/7)

Just four letter:

~715 Mb

DNA code is
billion times more
efficient



A
C
G
T

2 bits

0 0
1 1

8 bits = 1b

$4/8 \times 3 \times 10^9$

Differences in the code are important

Among unrelated individuals, 99.4% of the sequence is similar

That is still over 1,000,000 differences.

(... and you and chimpanzee: 99%)

CAGGTGTTGAAAGTCGATGTAGTTTCGTAGGTCAGTTGATGTGCGATGTGATC
GATGTAGTTTCGTAGGTCAGTTGATGTGCGATGTGAAATGCTGATGCTAGTGGA
CAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTATTGT
GCTACGATCGATTTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAA
GTGAGGCGGCAGGTGTTGAAAGTCGATGTAGTTTCGTAGGTCAGTTGATGTC
GATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAG
CCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTTCAGGCTGCTGTGGGTG
AAACGATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATG
CTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTTCAGGCTGCTGTG
GGTGGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAGCCTAGCT
CAGTGGTGCTAGCTACGATCGATTTTCAGGCTGCT CCTAGCTAGTCAGTGGT
GATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAG
CCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTTCAGGCTGCTGTGGGTG
CATAGCTGTGCTGTAAGTGAAGTGAGGCGGCAGGTGTTGAAAGTCGATGTA
GTTTCGTAGGTCAGTTGATGTGCGATGTGAAATGCTGATGCTAGTGGACAGGG
TGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATC
GATTTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGCGG
CAGGTGTTGAAAGTCGATGTAGTTTCGTAGGTCAGTTGATGTGCGATGTGAAAT
GCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGT
CAGTGGTGCTAGCTACGATCGATTTTCAGGCTGCT CCTAGCTAGTCAGTGGT
GTTTCGTAGGTCAGTTGATGTGCGATGTGAAATGCTGATGCTAGTGGACAGGG
TGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATC
GATTTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGCGG

CAGGTGTTGAAAGTCGATGTAGTTTCGTAGGGTCAGTTGATGTGCGATGTGATC
GATGTAGTTTCGTAGGGTCAGTTGATGTGCGATGTGAAATGCTGATGCTAGTGGA
CAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTATTGT
GCTACGATCGATTTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAA
GTGAGGCGGCAGCTGTTGAAAGTCGATGTAGTTTCGTAGGGTCAGTTGATGTC
GATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAG
CCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTTCAGGCTGCTGTGGGTG
AAACGATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATG
CTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTTCAGGCTGCTGTG
GGTGGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAGCCTAGCT
CAGTGGTGCTAGCTACGATCGATTTTCAGGCTGCT CCTAGCTAGTCAGTGGT
GATGTGAAATGCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAG
CCTAGCTAGTCAGTGGTGCTAGCTACGATCGATTTTCAGGCTGCTGTGGGTG
CATAGCTGTGCTGTAAGTGAAGTGAGGCGGCAGGTGTTGAAAGTCGATGTA
GTTTCGTAGGGTCAGTTGATGTGCGATGTGAAATGCTGATGCTAGTGGACAGGG
TGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATC
GATTTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGCGG
CAGGTGTTGAAAGTCGATGTAGTTTCGTAGGGTCAGTTGATGTGCGATGTGAAAT
GCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGT
CAGTGGTGCTAGCTACGATCGATTTTCAGGCTGCT CCTAGCTAGTCAGTGGT
GTTTCGTAGGGTCAGTTGATGTGCGATGTGAAATGCTGATGCTAGTGGACAGGG
TGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATC
GATTTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGCGG

Differences in the code are important

Among unrelated individuals, 99.4% of the sequence is similar
That is still over 1,000,000 differences.

You and chimpanzee: 99%

Advanced diagnostics

(early detection and,
possibly, prevention of 4,000
genetic disorders)

Research instrumentation

(reconstruction of the tree of life,
human history, psychology)

Personal pharmaceuticals

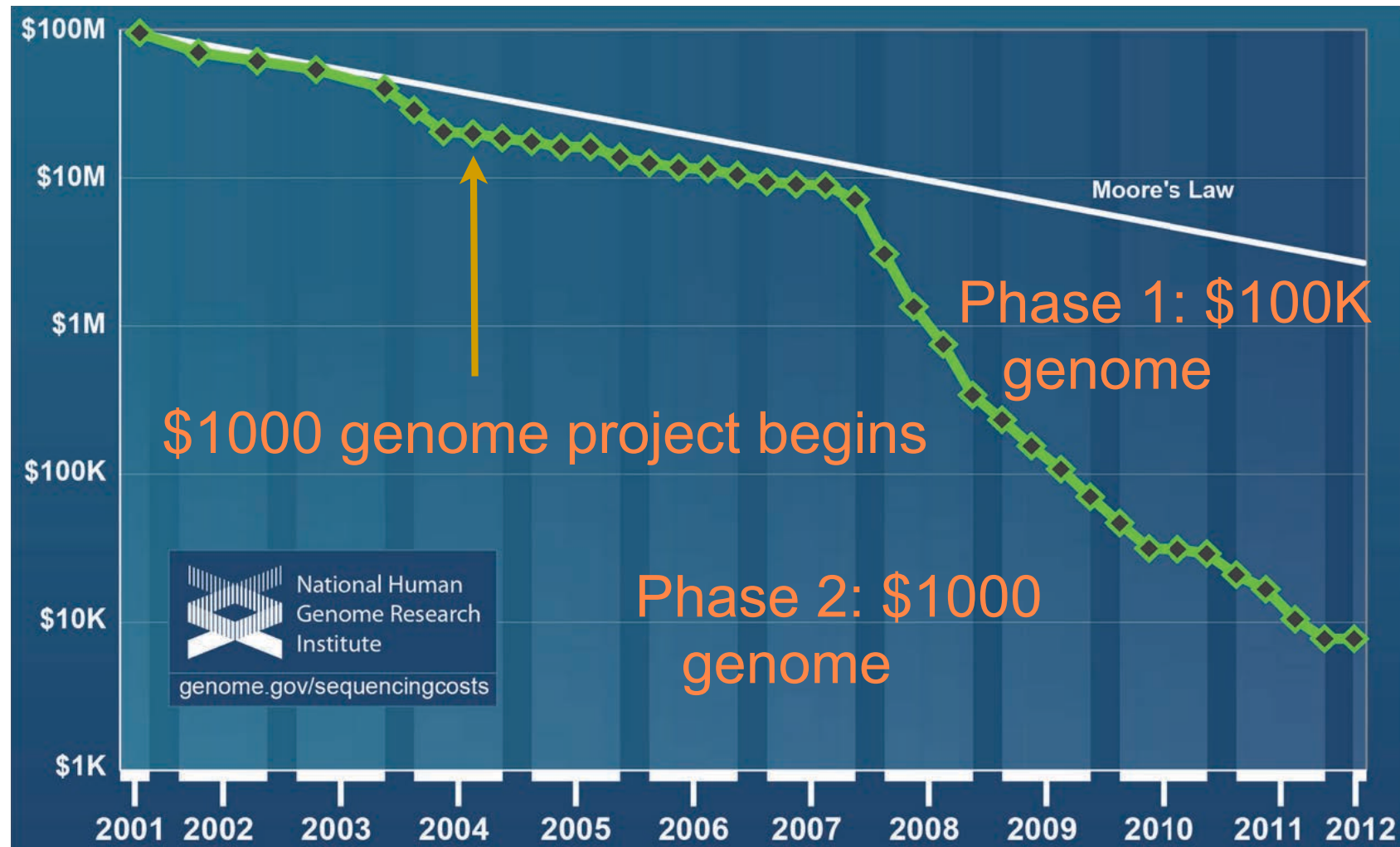
(tailor drugs to an individual's
genetic make-up)

Cancer: disease of DNA

Prenatal diagnostics

Single cell sequencing

Cost of sequencing a human genome (logarithmic scale)



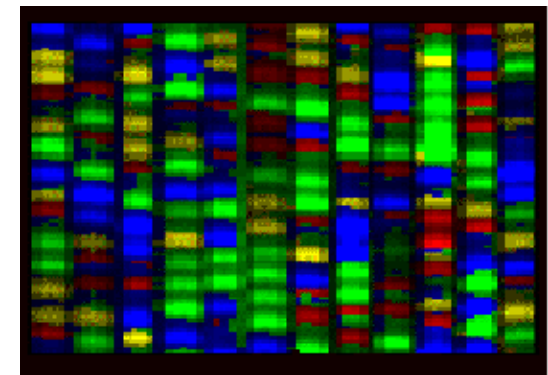
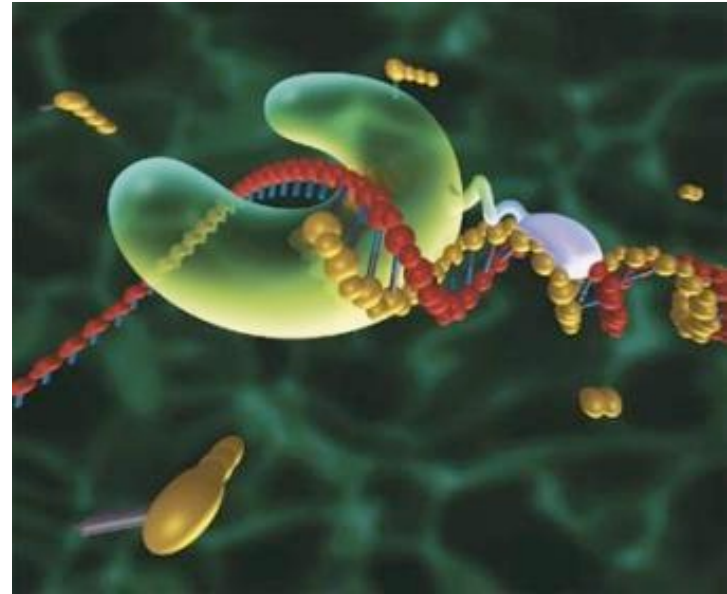
\$1,000 genome was claimed to be achieved (Jan 2014)

Conventional DNA sequencing

Nobel Prize in Chemistry 1980

As the DNA is synthesized, nucleotides are added on to the growing chain by the DNA polymerase.

The reactions start from the same nucleotide and end with a specific base



Fluorescence-based sequence gel

<http://bbrp.llnl.gov>

Next generation sequencing methods



Extremely small pH meter



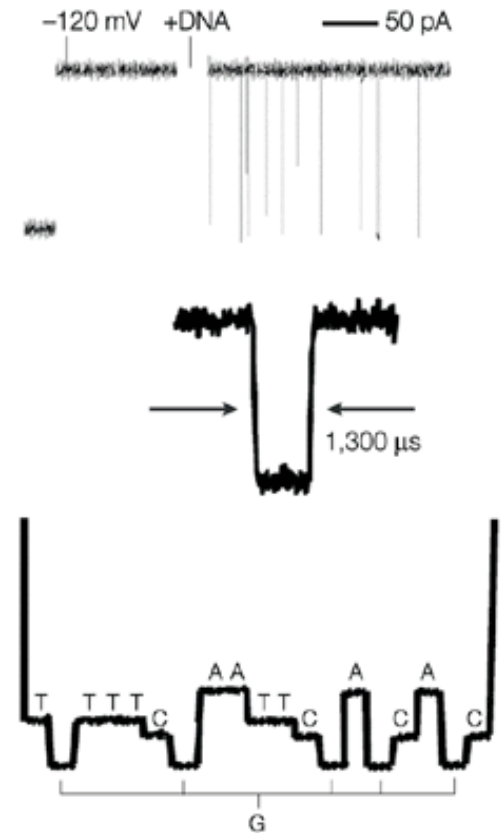
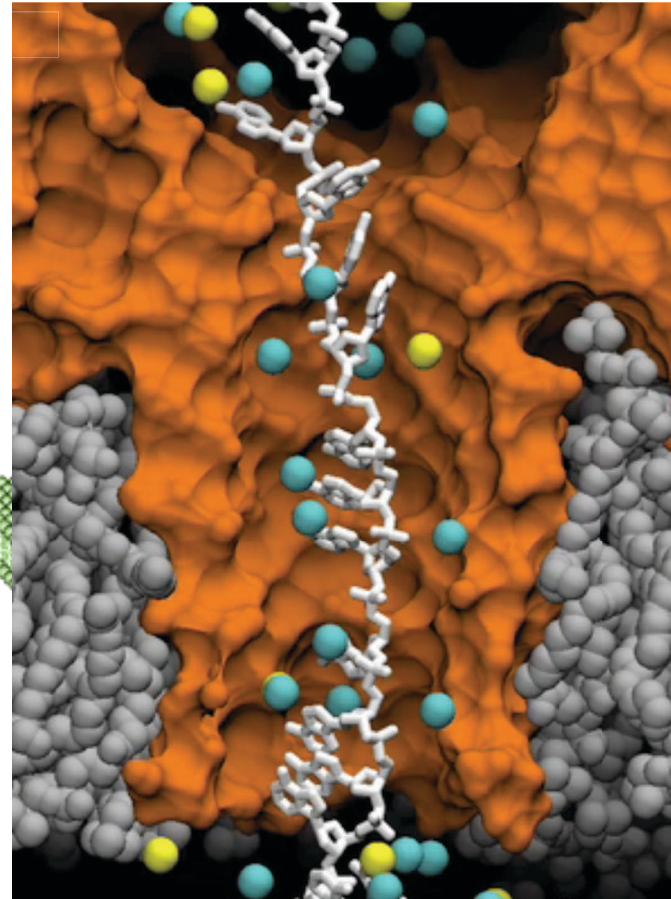
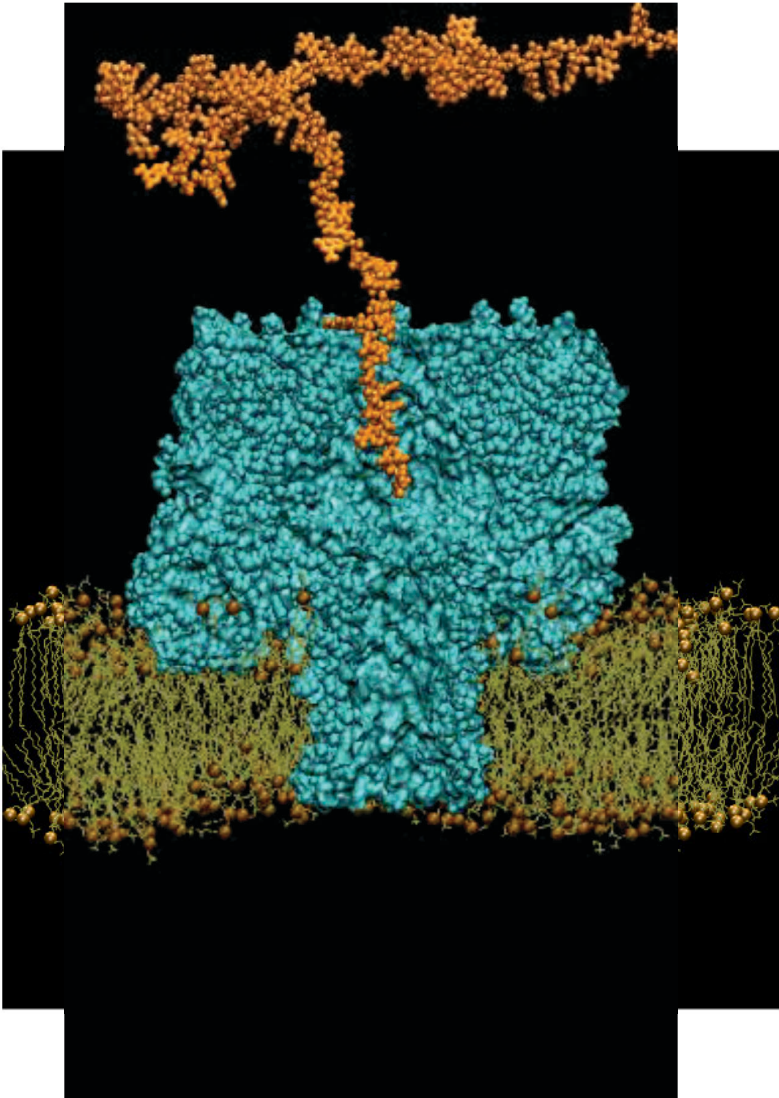
Multiplex optical readout

Problem: short reads, amplification, reagent and genome assembly costs



Single molecule optical readout
Problems: costs, accuracy, scalability

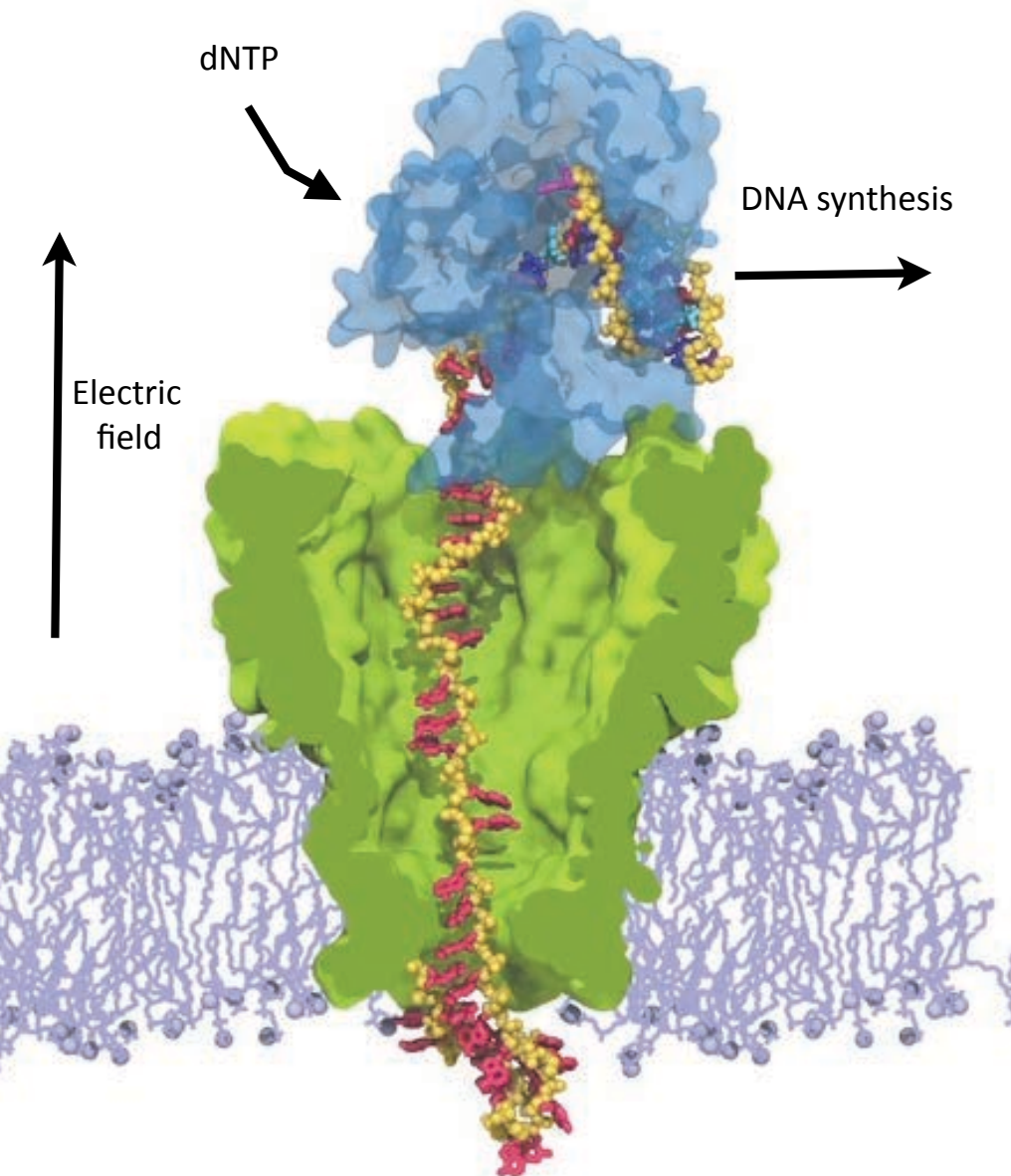
Nanopore sequencing of DNA



Nature Reviews Drug Discovery 1, 77-84 (January 2002)

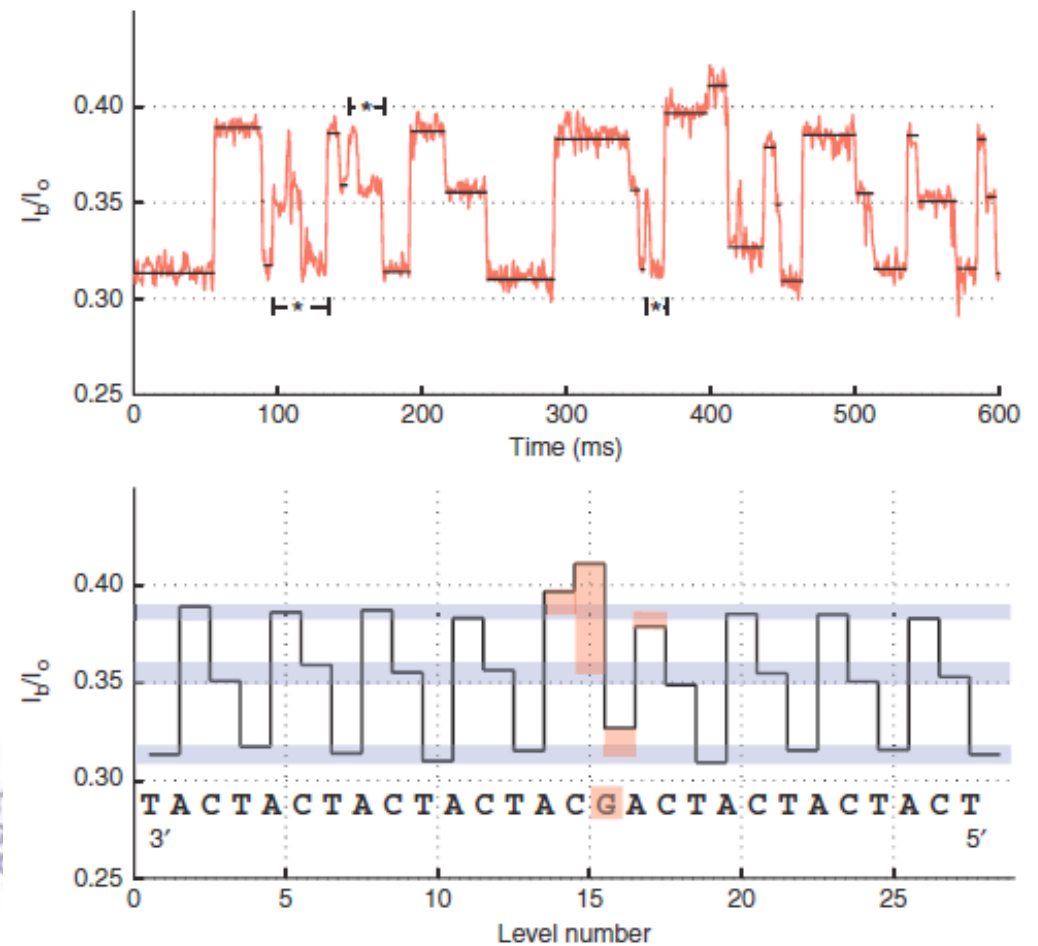
The ionic current blockade reveals the sequence of the confined nucleotides

Sequencing DNA using MspA



MD simulation ssDNA- DNA polymeraze complex

Experimentally measured ionic current blockades



Nature Biotech. 30: 349 - 353 (2012)

Oxford Nanopore Technologies



MinION: ~800 parallel detection wells

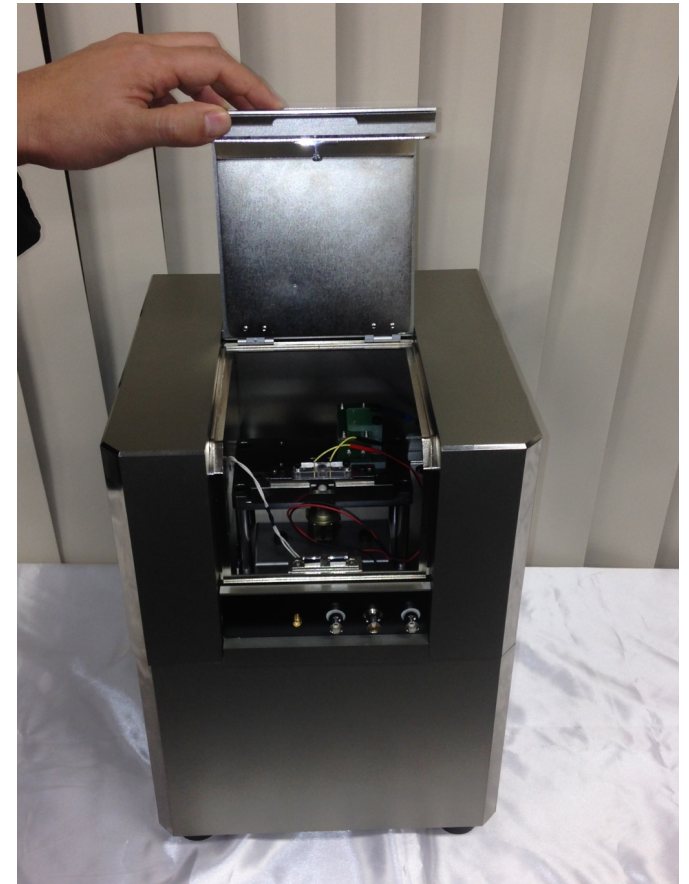
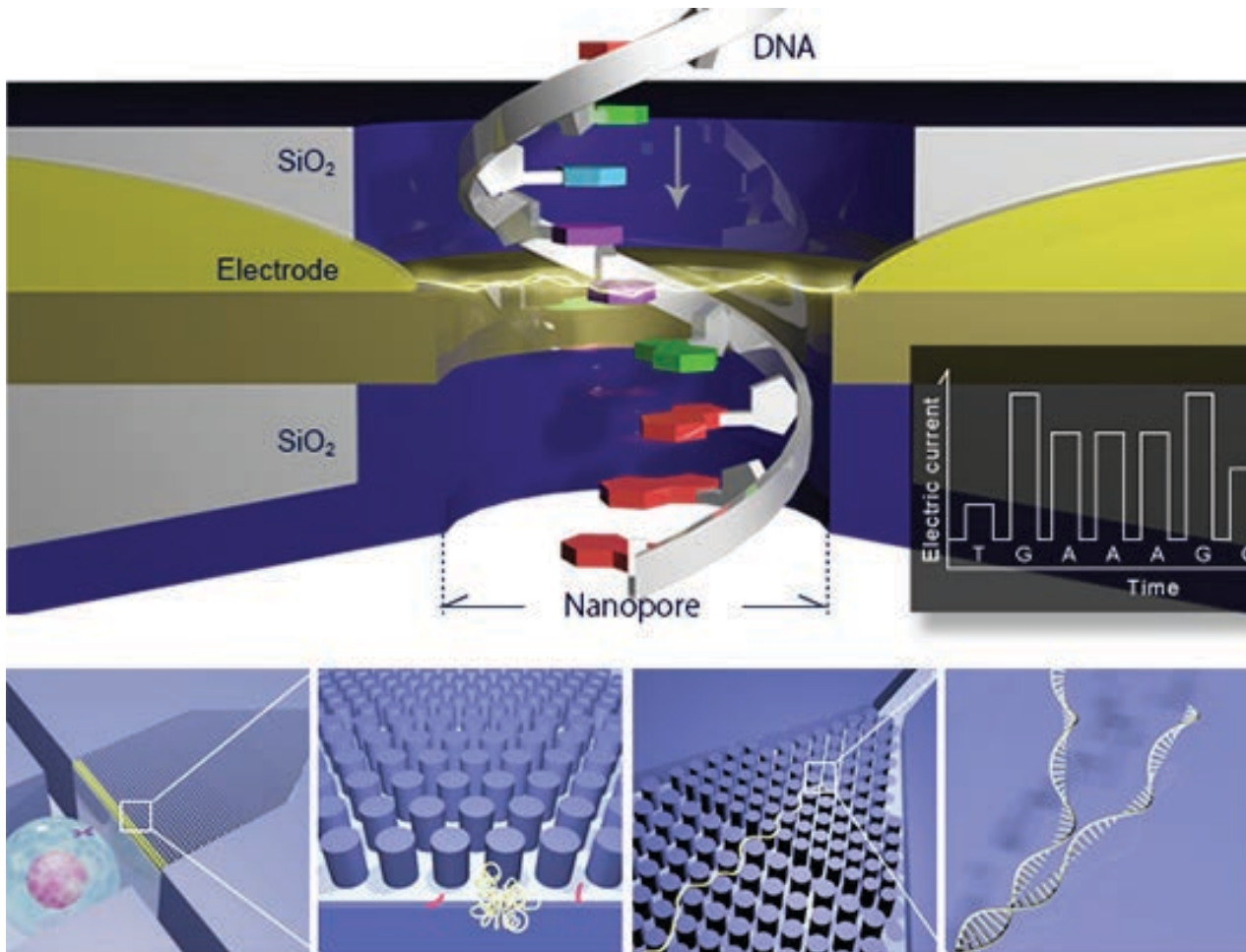
Read length: up to 100,000 nucleotides (2 strands of lambda phage genome)

Unknown pore (hemolysin, MspA, other?)

Unknown enzyme (better polymerase? Helicase?)

Accuracy: 96%

Nanopore sequencing: state of the art

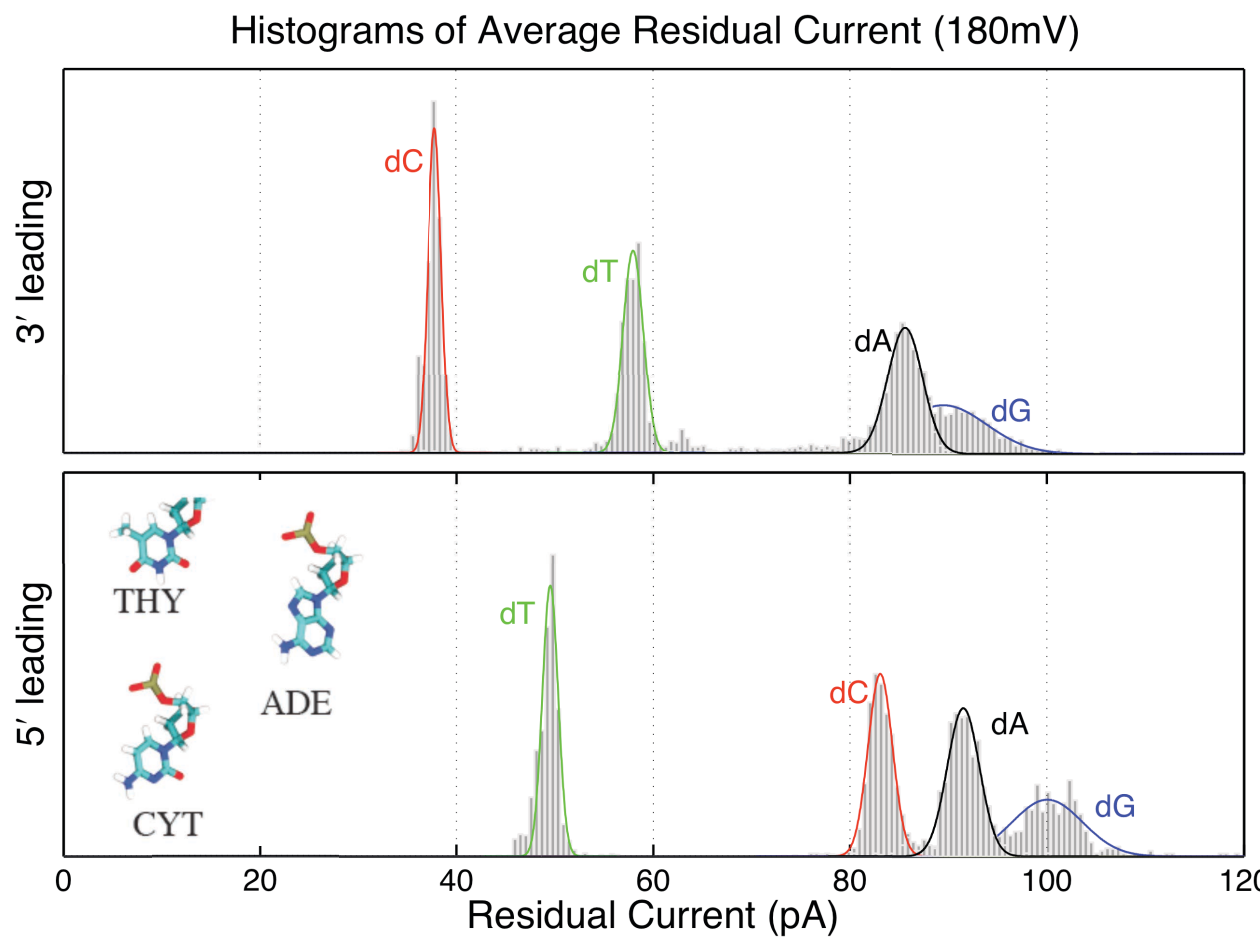
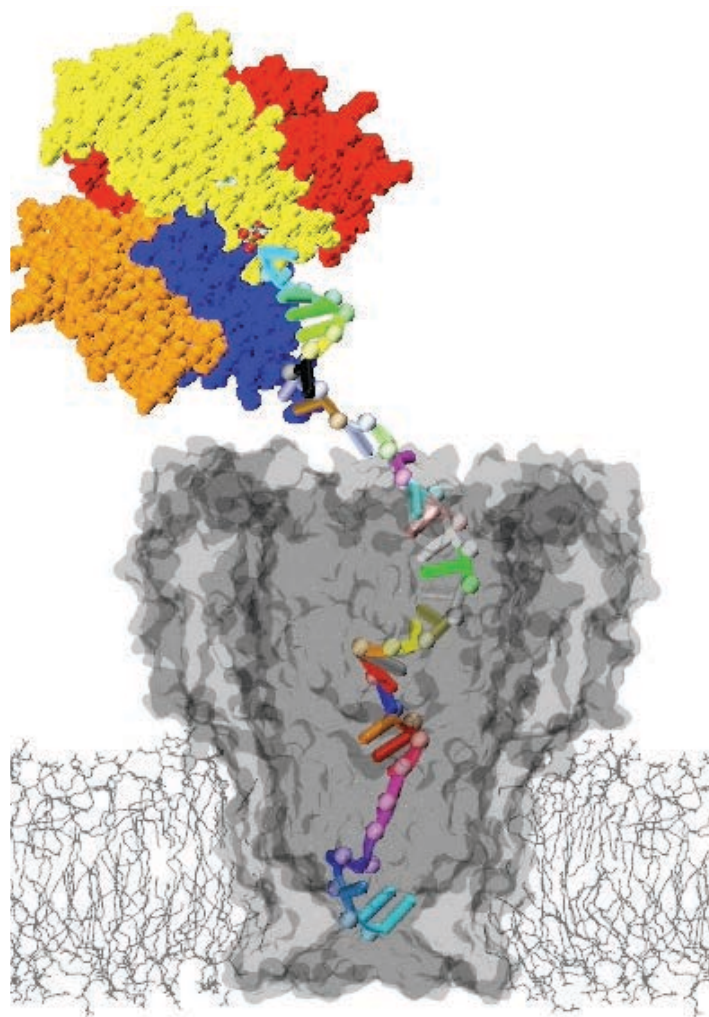


Quantum biosystems

... Genia, Nabsys ...
... Illumina, Roche ...

... also INTEL, IBM, HITACHI, TOSHIBA, SONY, SIEMENS ...

Homopolymer blockades in MspA



MD simulation neutravidin-anchored ssDNA
in MspA

Liz Manrao ... J Gundlach, U Washington
Plos One 2011, 6

Setting up a simulation is like cooking



A MEMBER OF THE  **MyPDB: Login | Register**

An Information Portal to Biological Macromolecular Structures

As of Tuesday Mar 31, 2009  there are 56751 Structures  | [PDB Statistics](#) 

[CONTACT US](#) | [FEEDBACK](#) | [HELP](#) | [PRINT](#)

 PDB ID or keyword  Author

[Site Search](#)  | [Advanced Search](#)

[Home](#) [Search](#)

- Home
- Getting Started
- Structural Genomics
- Electron Microscopy
- ▶ Download Files
- ▶ Deposit and Validate
- ▶ Dictionaries & File Formats
- ▶ Software Tools
- ▶ General Education
- ▶ Site Tutorials
- BioSync
- ▶ General Information
- Acknowledgements
- Frequently Asked Questions

Quick Tips: 

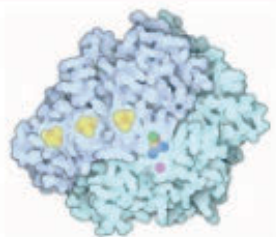
Try the [Web Services API](#)

A Resource for Studying Biological Macromolecules

The PDB archive contains information about experimentally-determined structures of proteins, nucleic acids, and complex assemblies. As a member of the [wwPDB](#), the RCSB PDB curates and annotates PDB data according to agreed upon standards.

The RCSB PDB also provides a variety of tools and resources. Users can perform simple and advanced searches based on annotations relating to sequence, structure and function. These molecules are visualized, downloaded, and analyzed by users who range from students to specialized scientists.

Molecule of the Month: Hydrogenase



Hydrogen gas is an unusual substance. Normally, it is stable and must be coaxed with powerful catalysts to enter into chemical reactions. But when mixed with oxygen, a tiny spark will set off an explosive chain reaction. Hydrogen gas holds great promise to be the greenest of green energy sources. It has many advantages: compared with many fuels, it releases a lot of energy for its weight, and the reaction forms only energy and pure water. It has substantial disadvantages, however. It is dangerous to store, and it is difficult to perform the reaction in a controlled, non-explosive manner.

■ [Read more ...](#) ■ [Previous Features](#)

News

- [Complete News](#)
- [Newsletter](#)
- [Discussion Forum](#)
- [Job Listings](#)

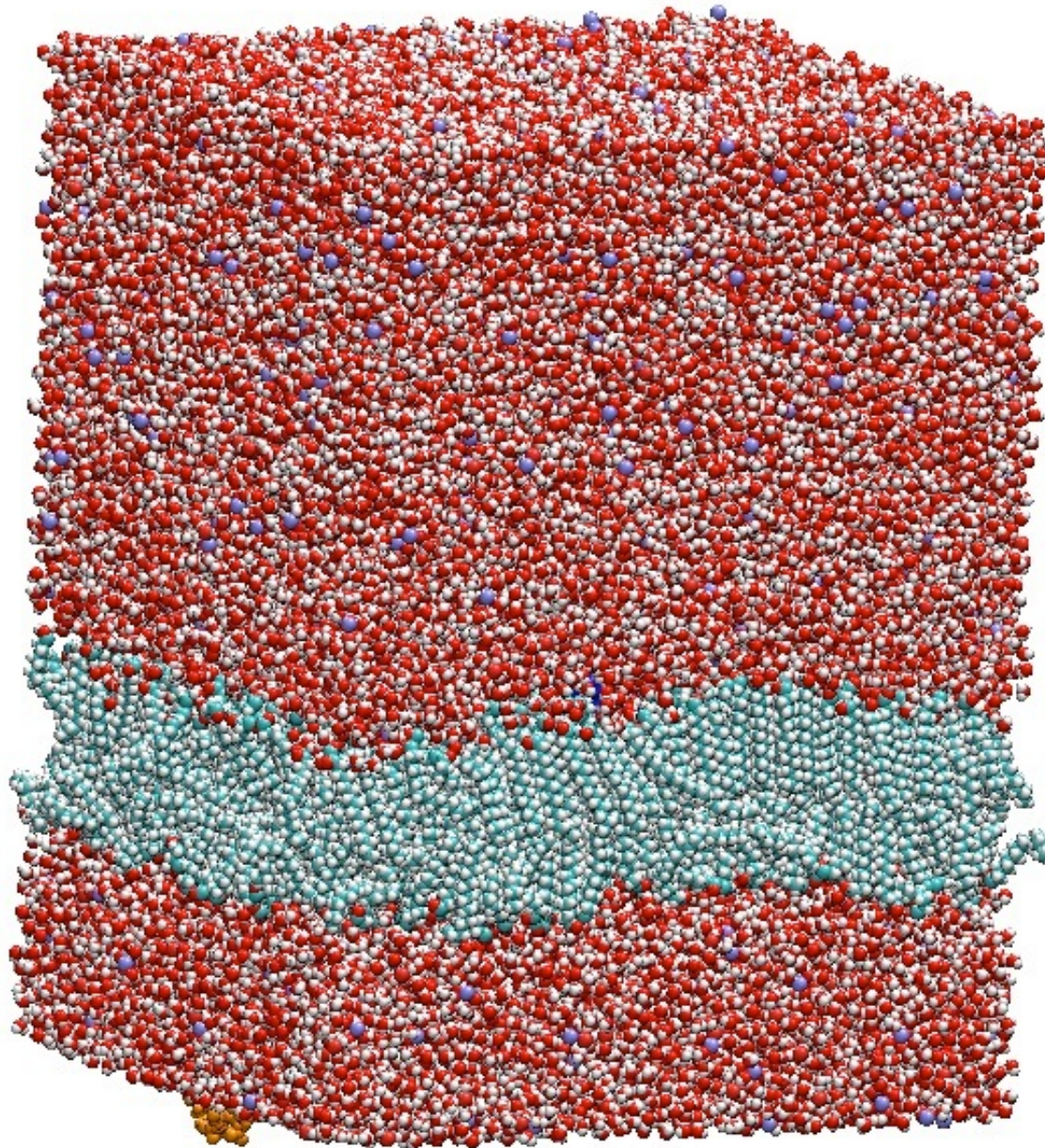
31-March-2009

Bridgewater-Raritan High School Wins New Jersey Science Olympiad Protein Modeling State Finals



The team from

Setting up a simulation is like cooking



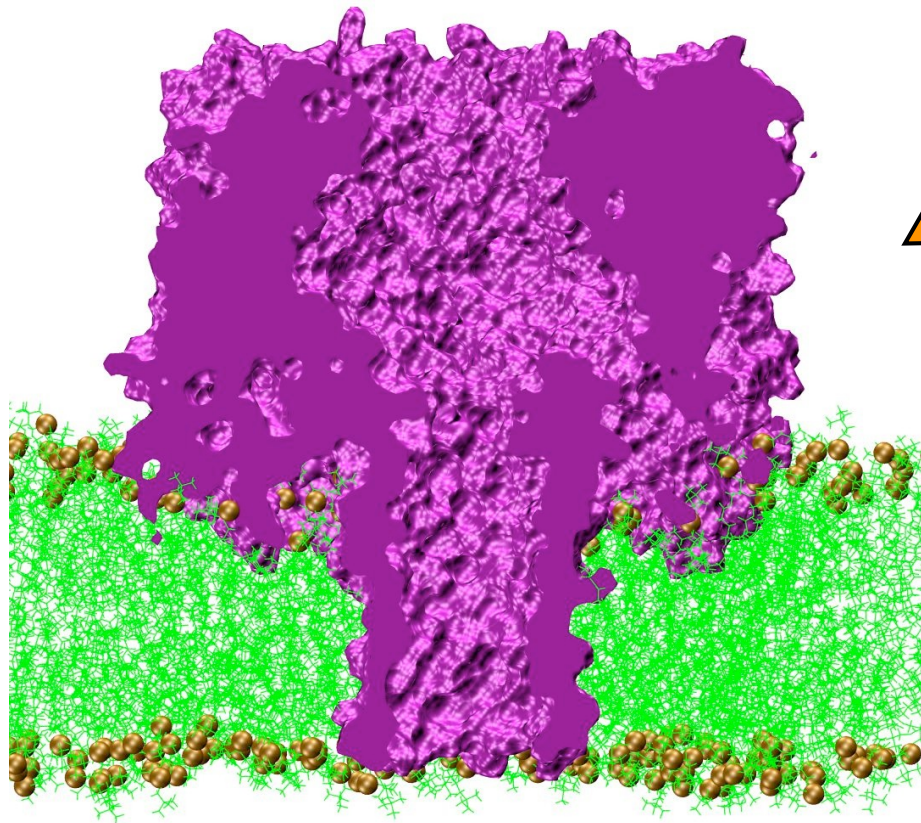
Components

- protein
- DNA
- lipid
- ions
- water

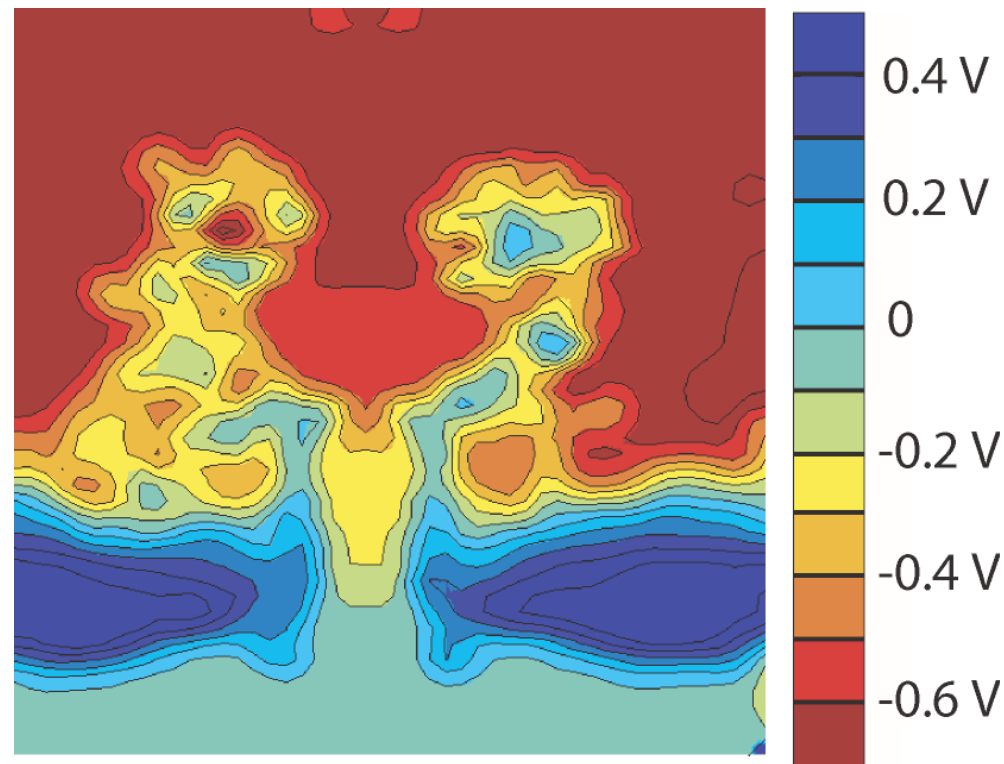
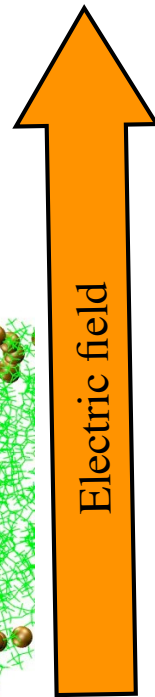
$F = ma$ @ 300 K

Time step = 1 fs

Computing conductance of α -hemolysin with molecular dynamics



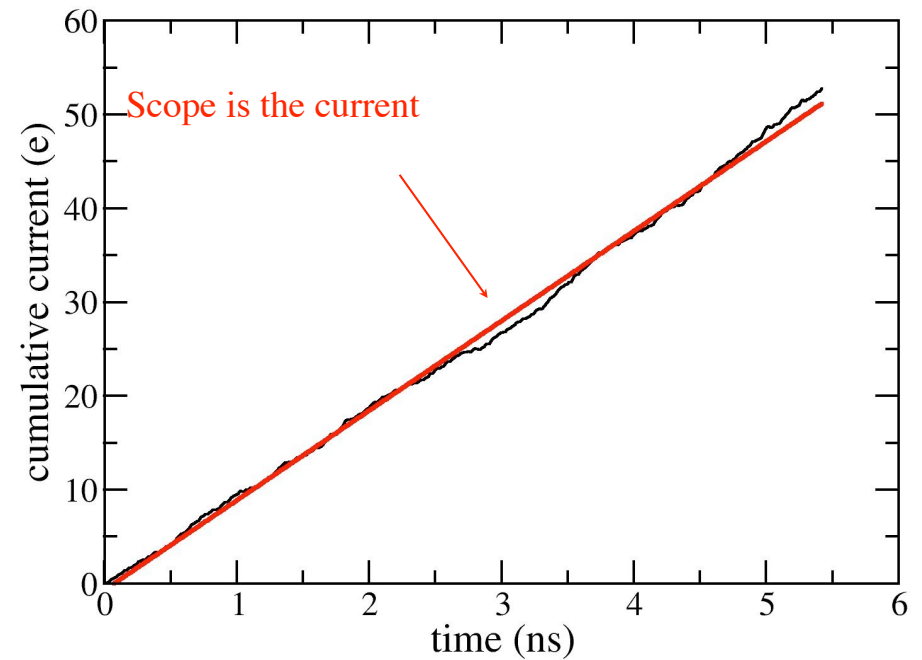
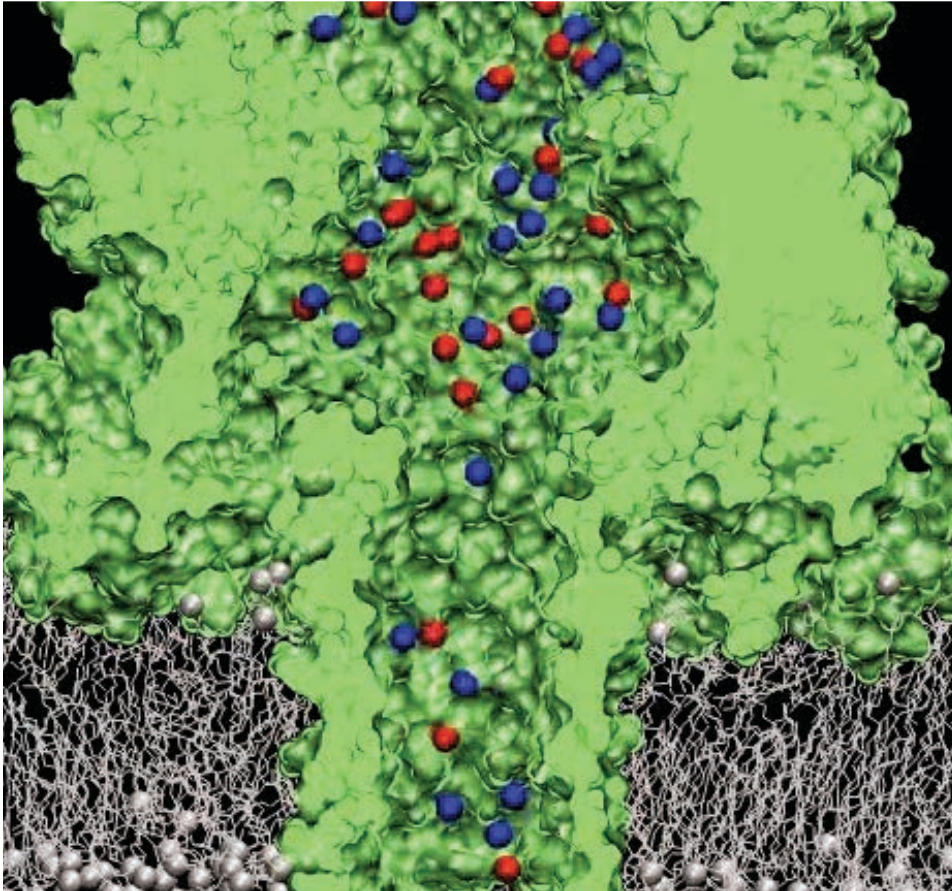
Protein + lipid bilayer membrane + 1M water
solution of KCl = $\sim 300,000$ atoms



Average electrostatic
potential map

Current-voltage curve of α -hemolysin

Biophys. J. 88:3745 (2005)

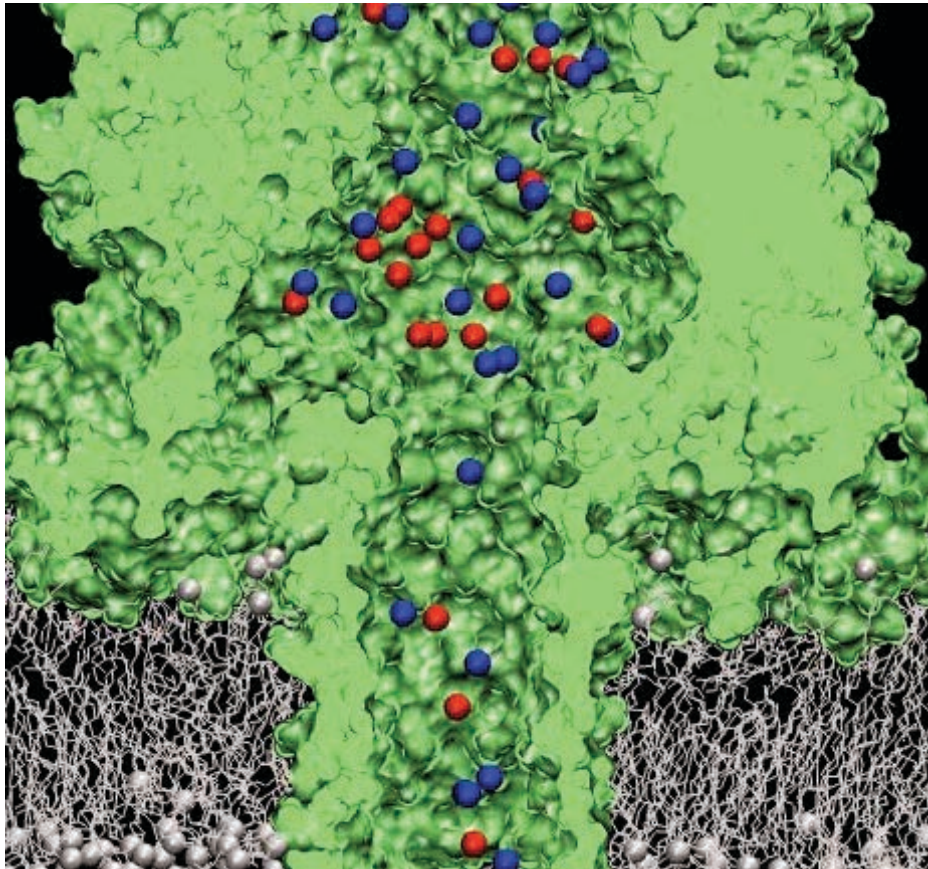


$$I(t) = \frac{1}{\Delta t L_z} \sum_{i=1}^N q_i (z_i(t + \Delta t) - z_i(t))$$

Instantaneous current

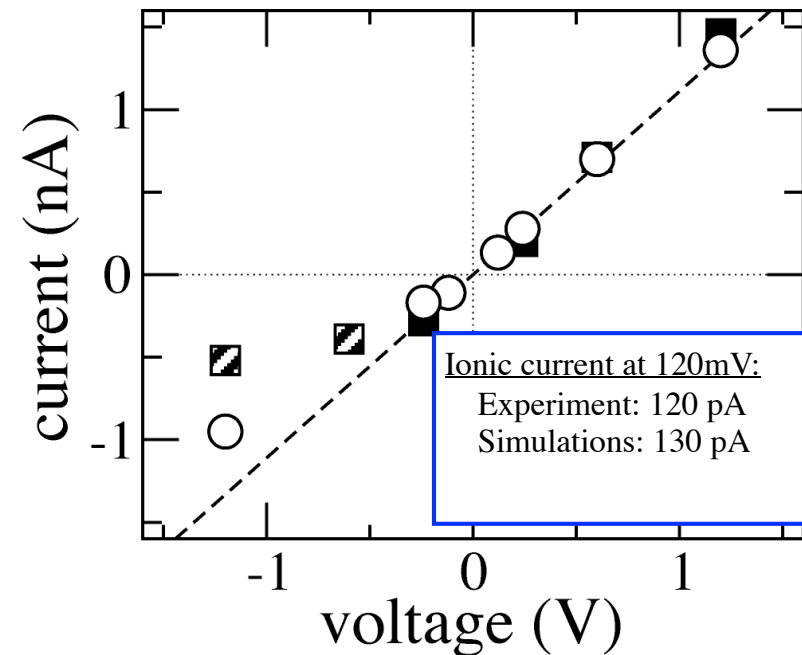
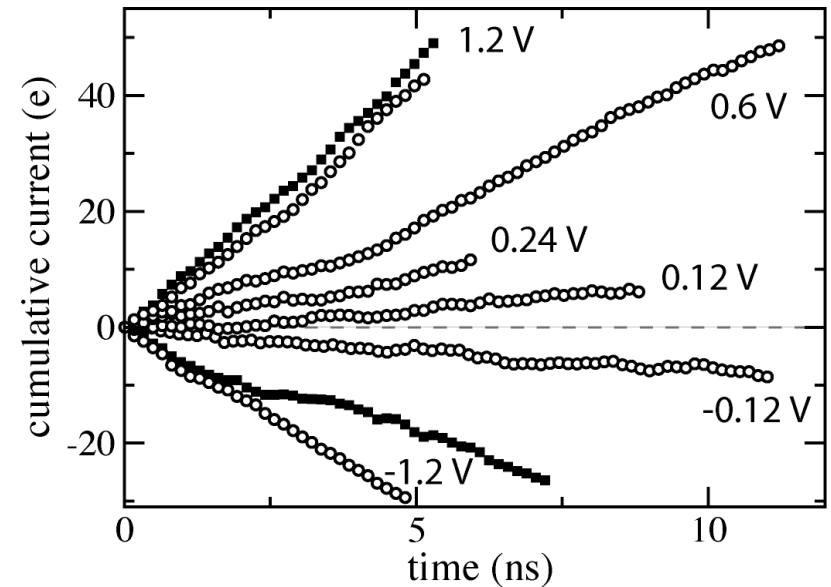
Current-voltage curve of α -hemolysin

Biophys. J. 88:3745 (2005)

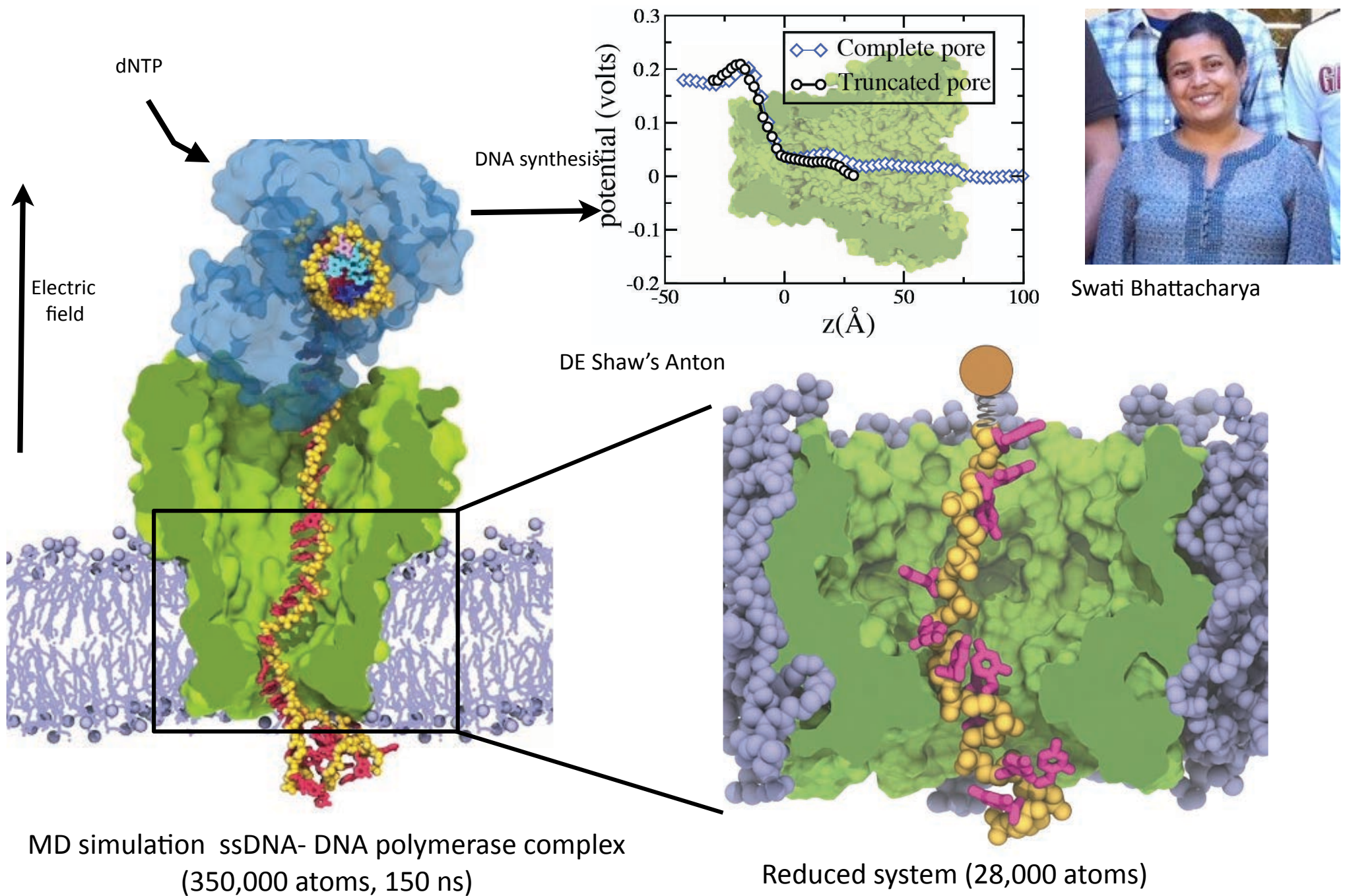


$$I(t) = \frac{1}{\Delta t L_z} \sum_{i=1}^N q_i (z_i(t + \Delta t) - z_i(t))$$

Instantaneous current



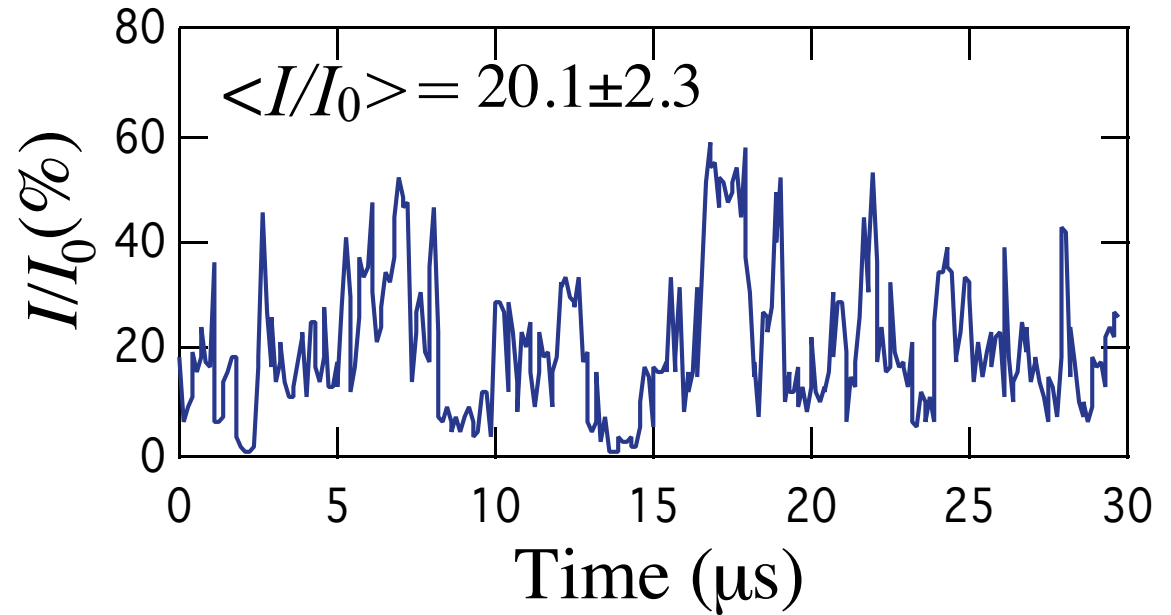
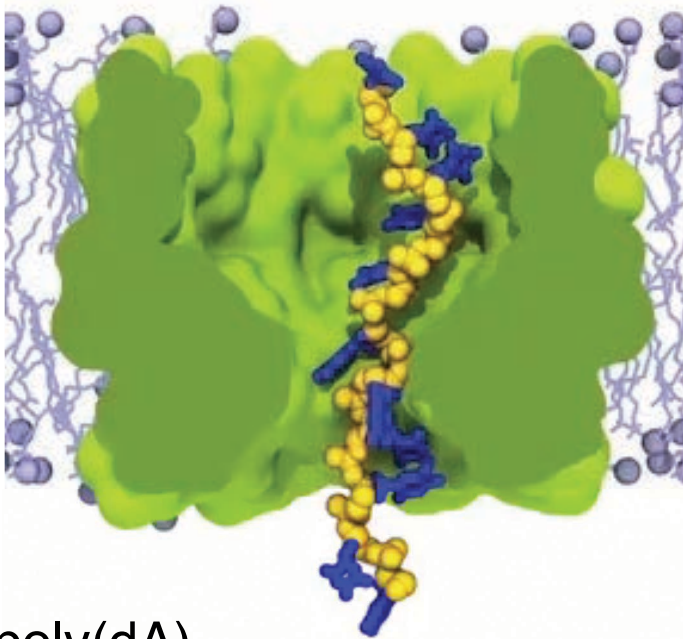
MD simulations of current blockades in MspA



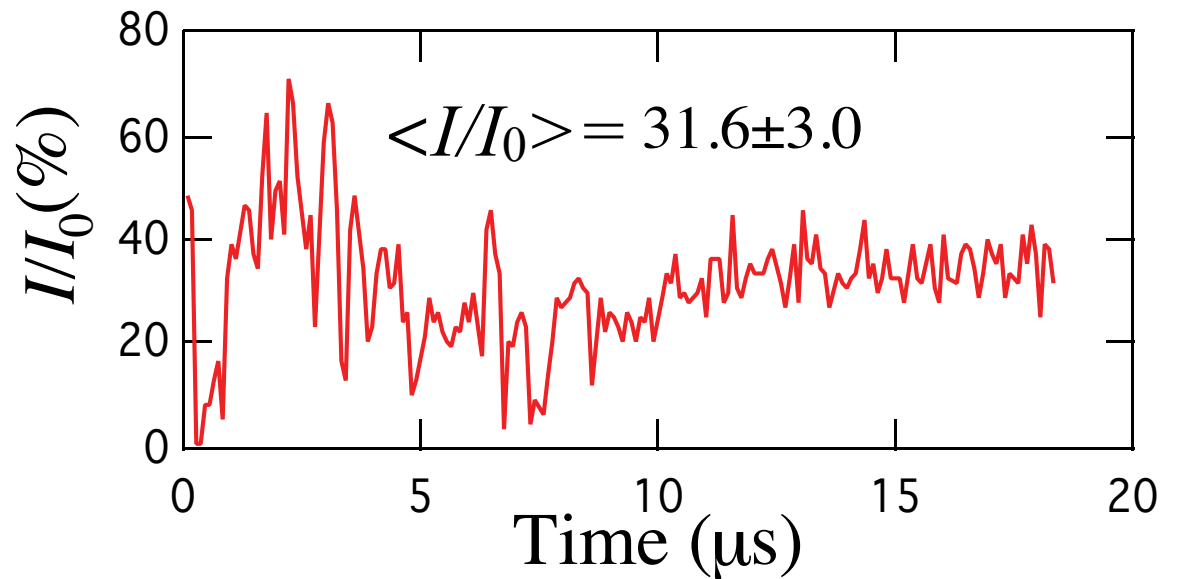
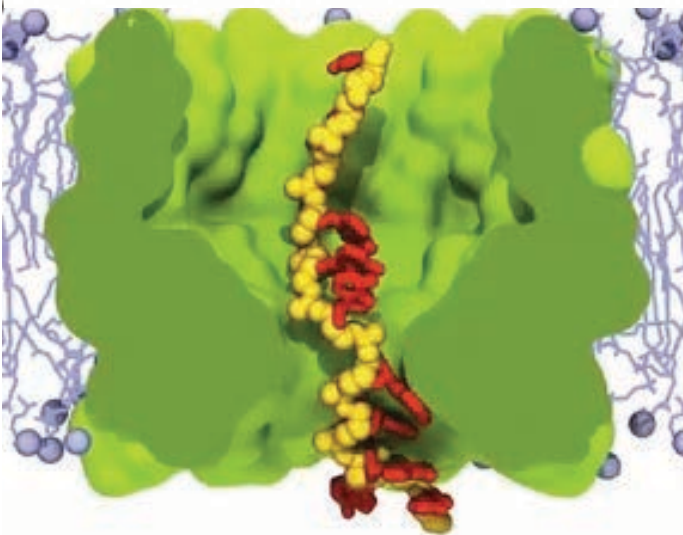
MD simulations of current blockades in MspA

5'-poly(dT)

Bhattacharya, Yoo, Aksimentiev, ACS Nano 10, 4644 (2016)



5'-poly(dA)

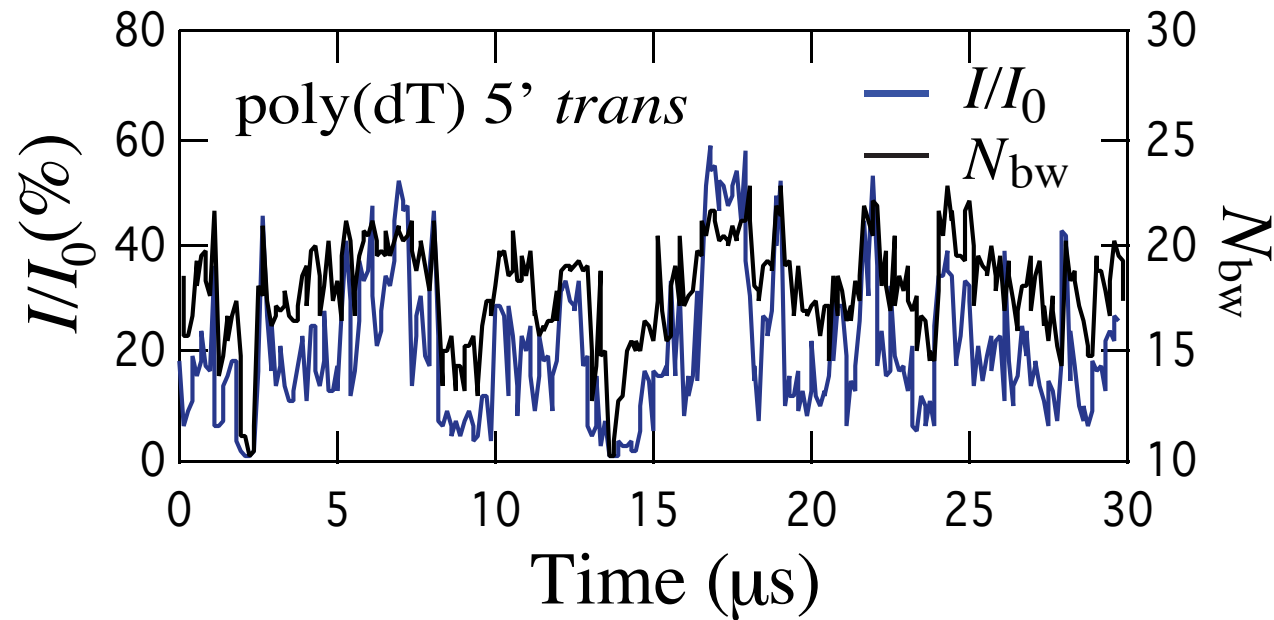
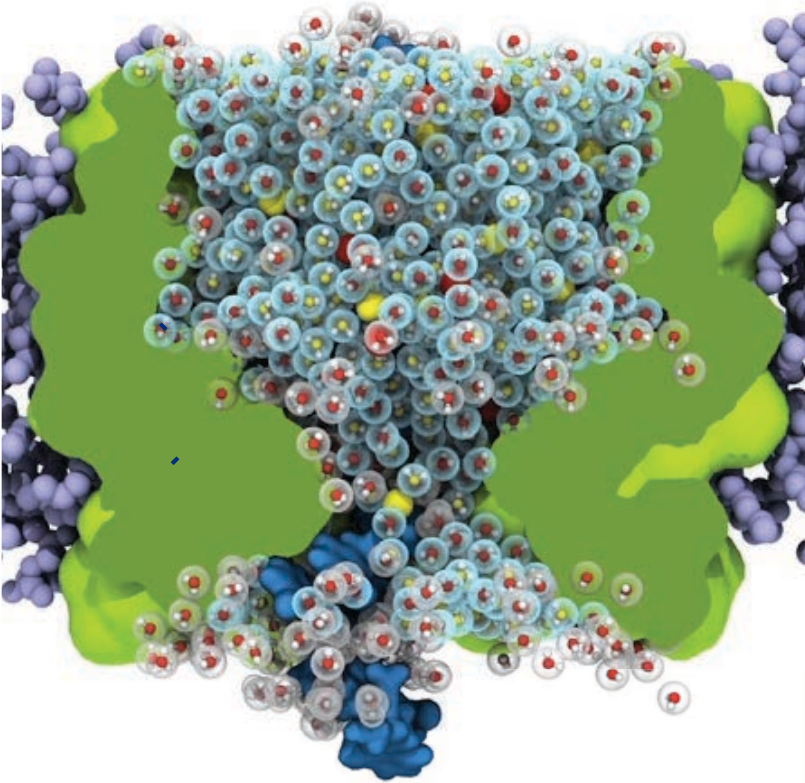


Water mediates DNA sequence recognition

Bhattacharya, Yoo, Aksimentiev, ACS Nano 10, 4644 (2016)

Red: structured water

Blue: unstructured water



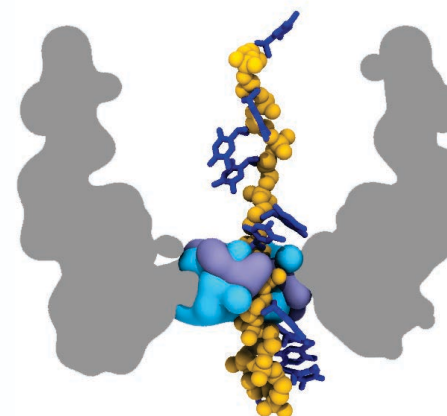
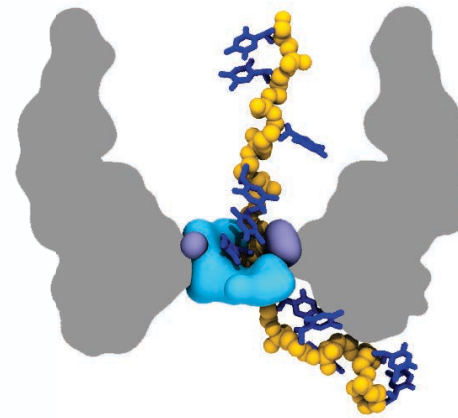
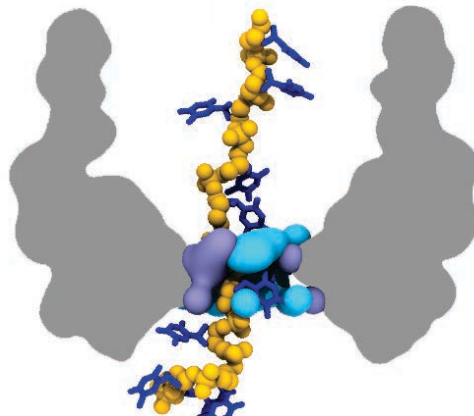
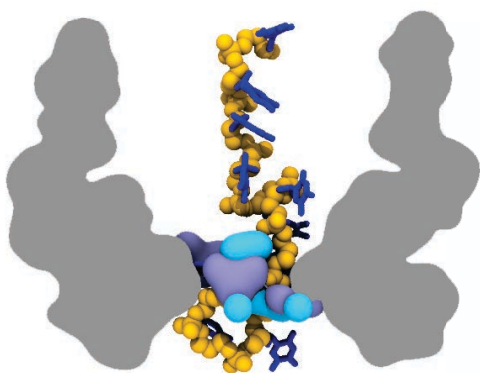
Current increase with the number of water molecules as $N^{1.7}$

$N_{bw}=10$

$N_{bw}=17$

$N_{bw}=21$

$N_{bw}=25$



Nanopore efforts around the world

Polymer

Darmstadt, UND,
UC Irvine, UF,
...

Proteins

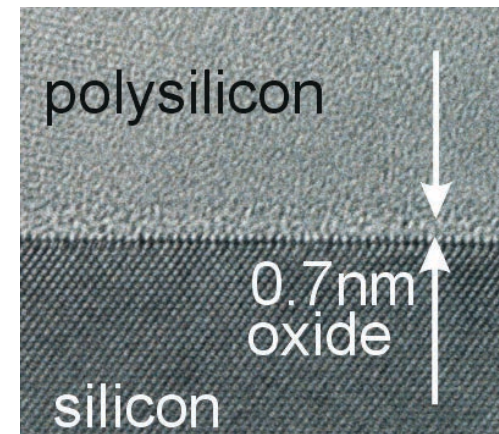
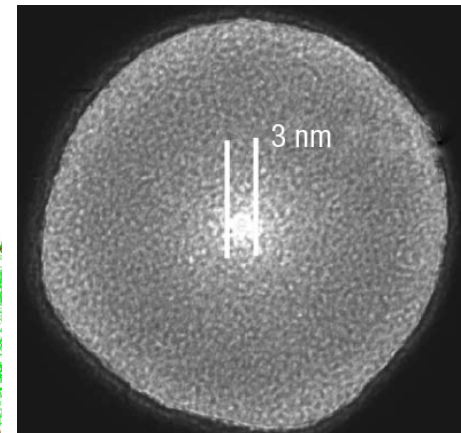
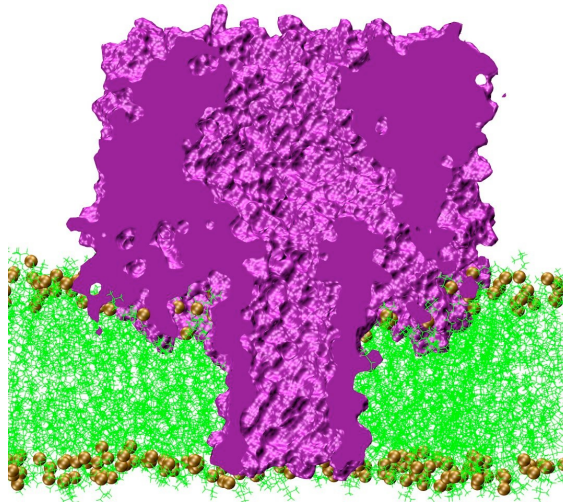
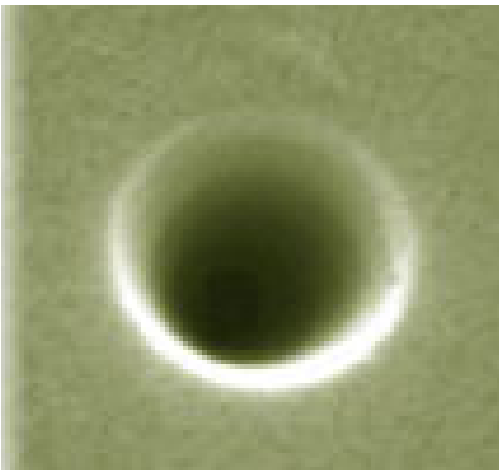
NIST, UCSC, Harvard, UBC,
Oxford, Evry, BU, U Wash.,
Syracuse, ...

Nitride/oxide

Harvard, UBC, BU,
UIUC, Delft, Arkansas,
Brown, UNC, NE(!),
...

Active hetero structures

IBM, UIUC,
Lausanne,...



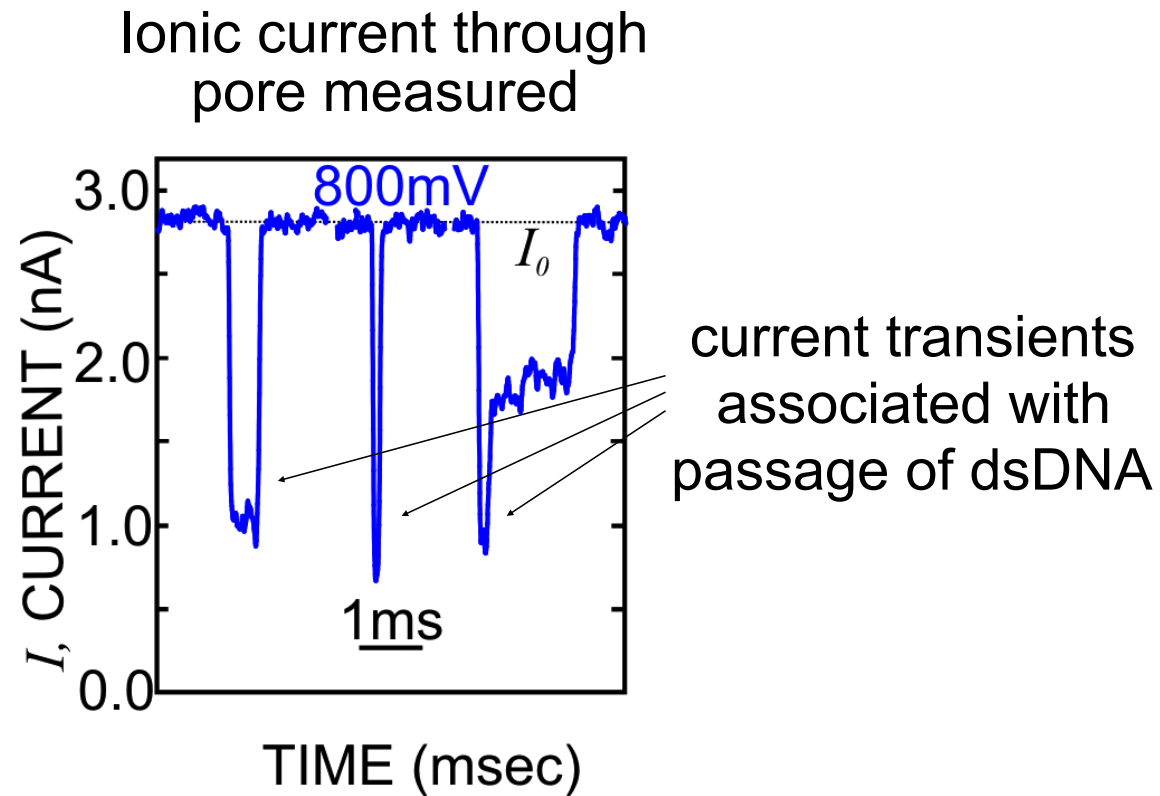
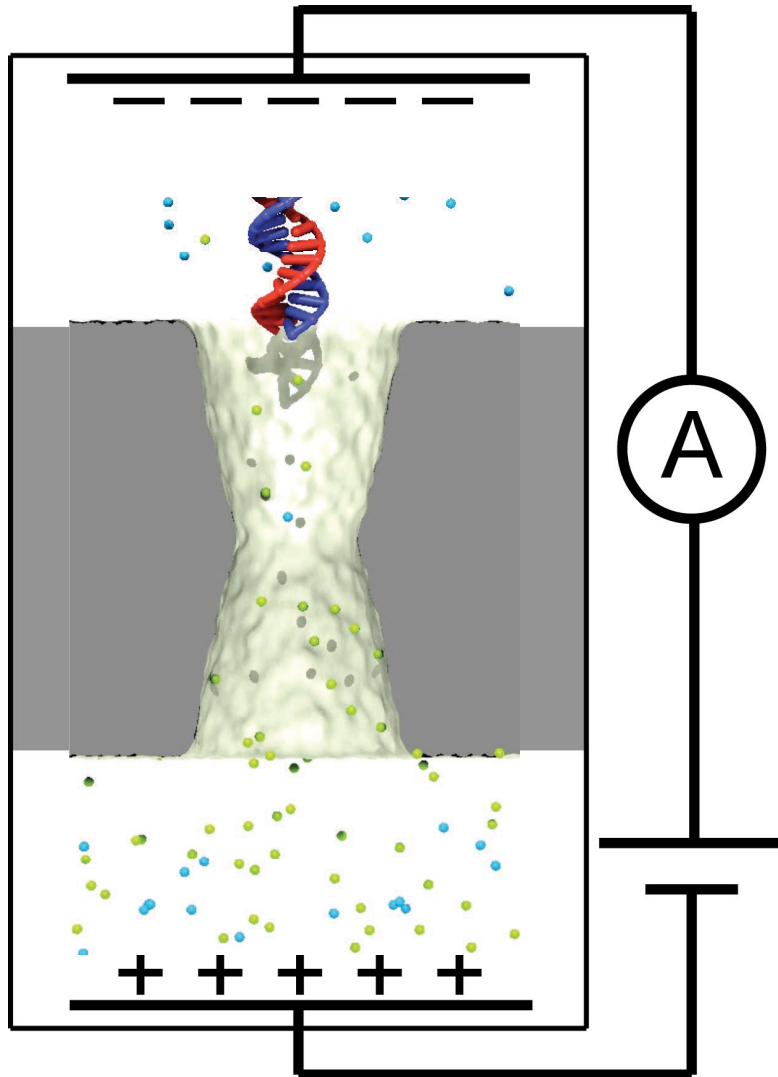
Ion track etched
Thick layers ($\sim \mu\text{m}$)
Robust
Fixed charge
Unknown dimensions
Surface modifications
High speed, low field
Indi address difficult

Self-assembled
Lipid membranes ($\sim 4\text{nm}$)
Fragile
Fixed charge
Atomically precise
Can be engineered
Low speed, high field
Indi address difficult

Fabricated
>5nm
Robust
Fixed charge
Sub-nm, but not atomic
Surface modifications
High speed, high field
Indi addressed

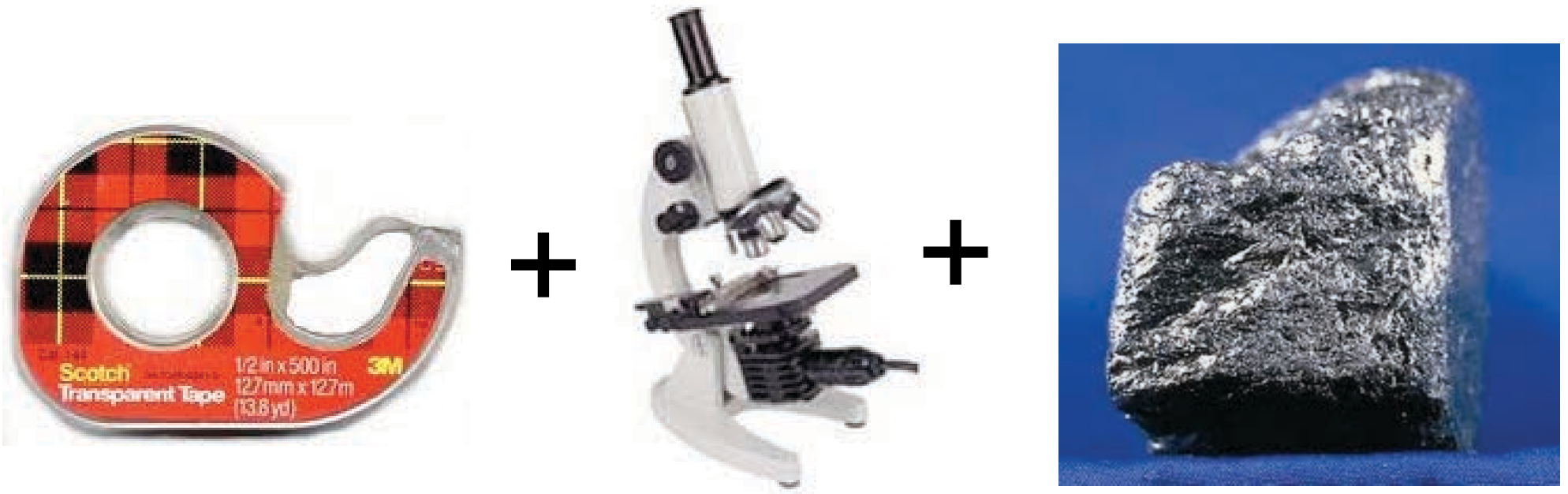
Fabricated
<1 nm
Robust
Field-effect adjustment
Sub-nm
Surface modifications
High speed, high field
Indi addressed

DNA transport through solid-state nanopore



- Isolates 1nm^3 of volume
- Automatic loading and reloading
- Highly processive, single-file transport
- Compatible with several detection schemes
- No limit on the read length

The thinner, the better!



Andre Geim

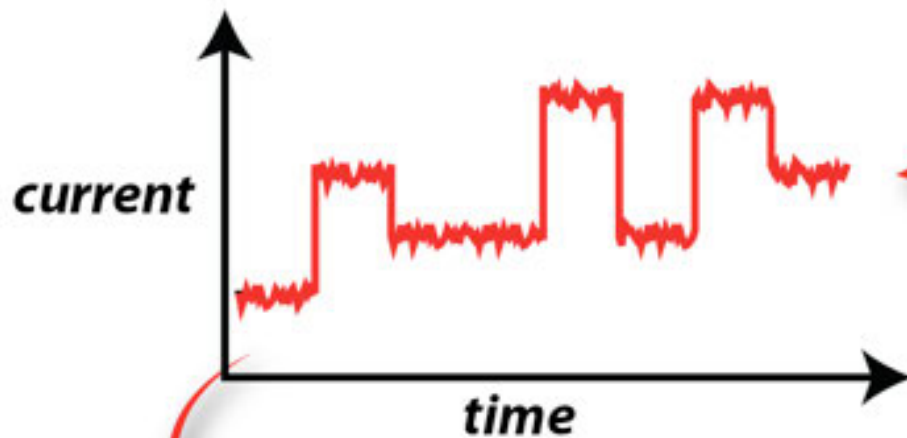
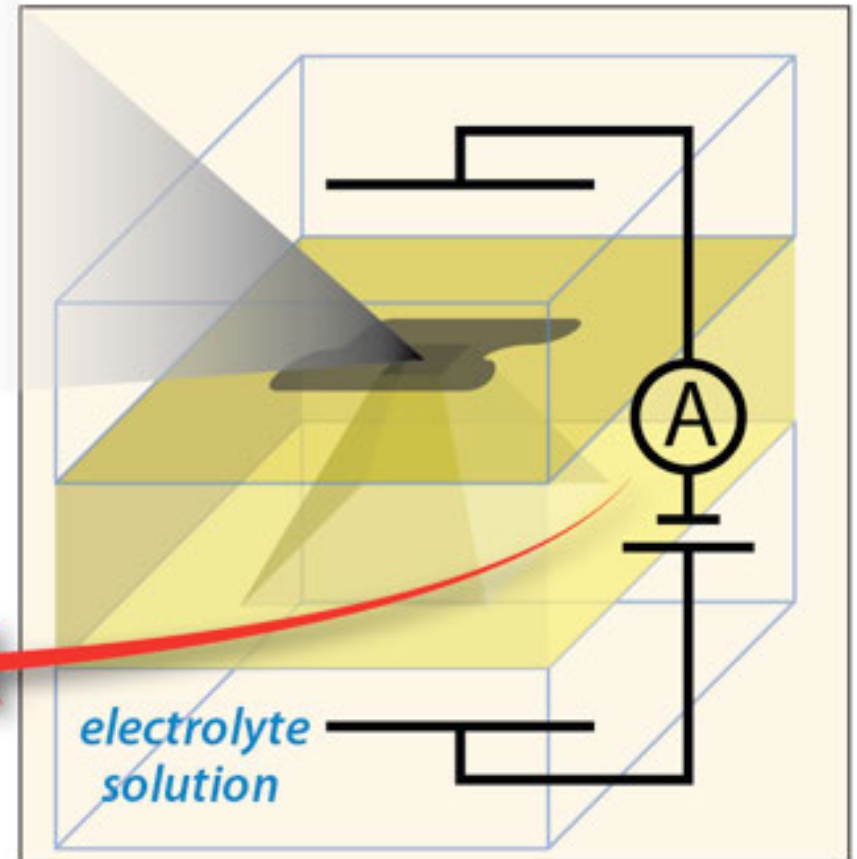
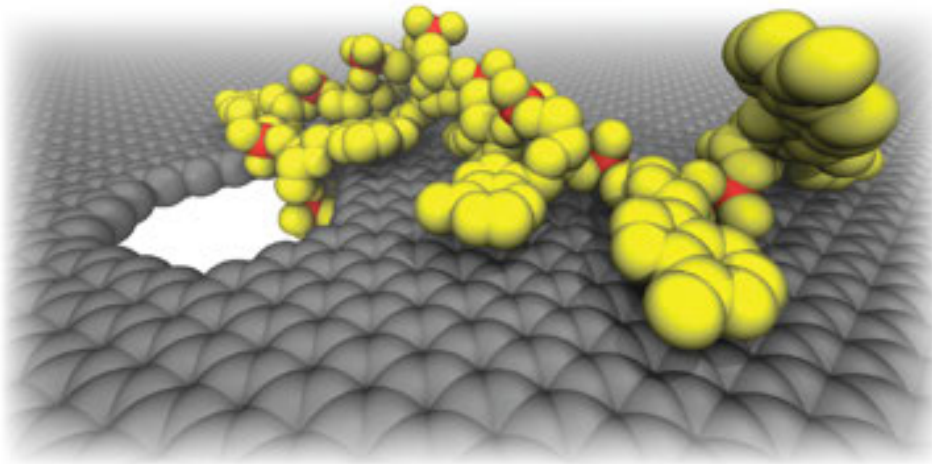


Konstantin Novoselov

=



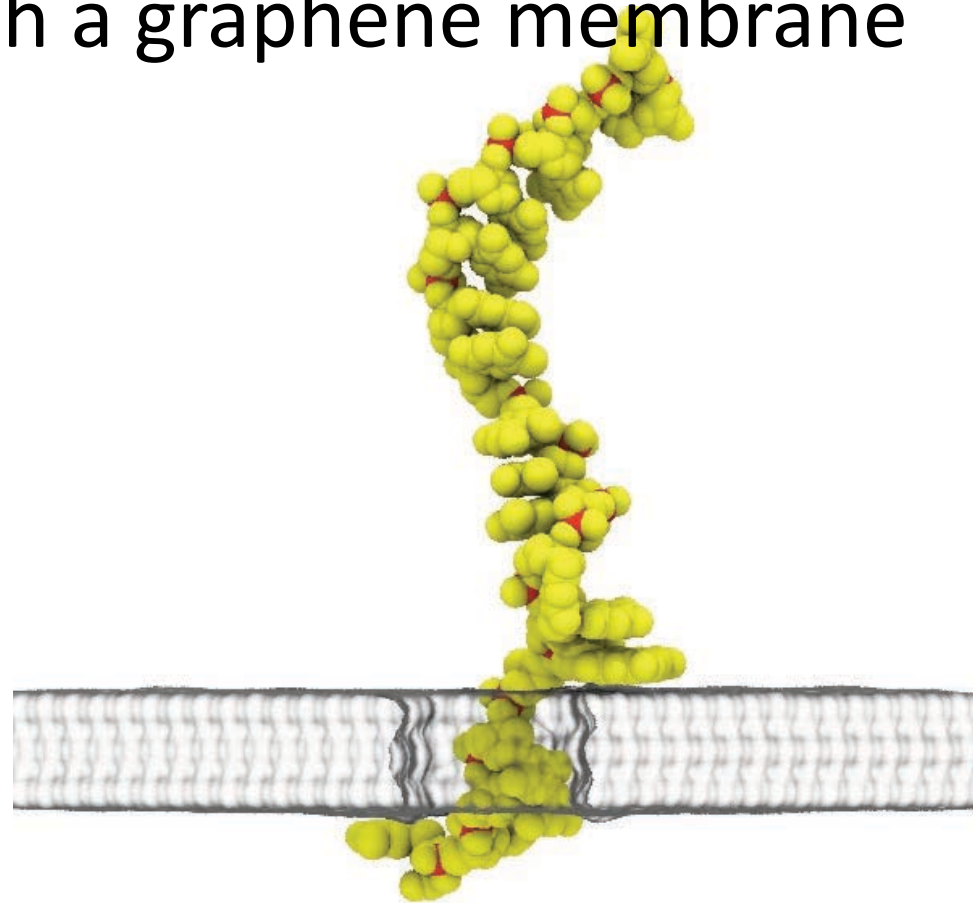
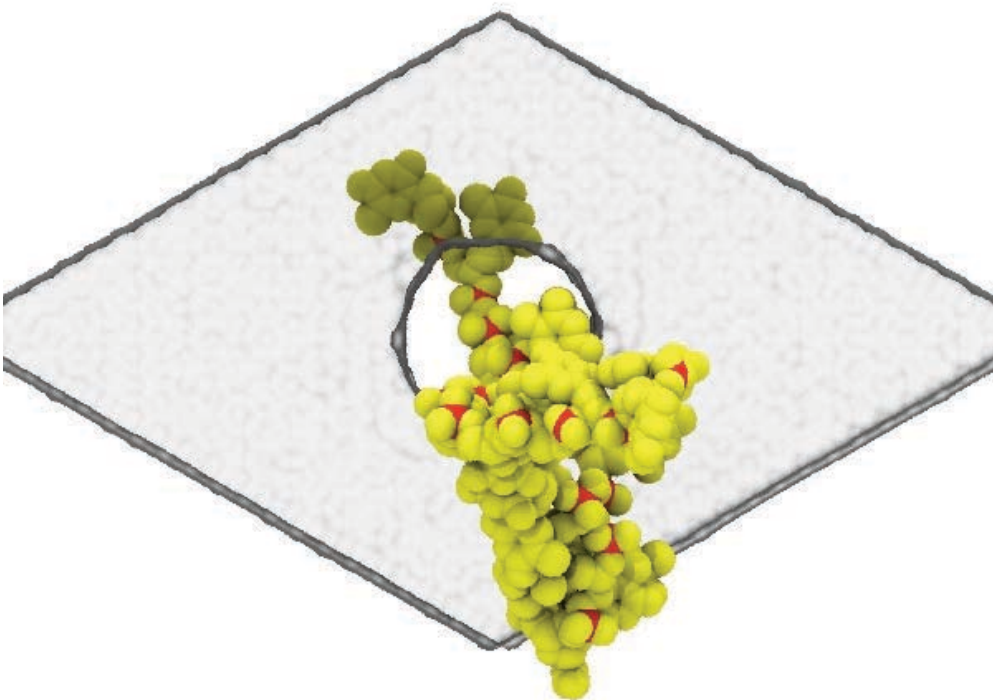
Graphene Nanopores



ACGGTGTTCGATTAC

Interaction of ssDNA with a graphene membrane

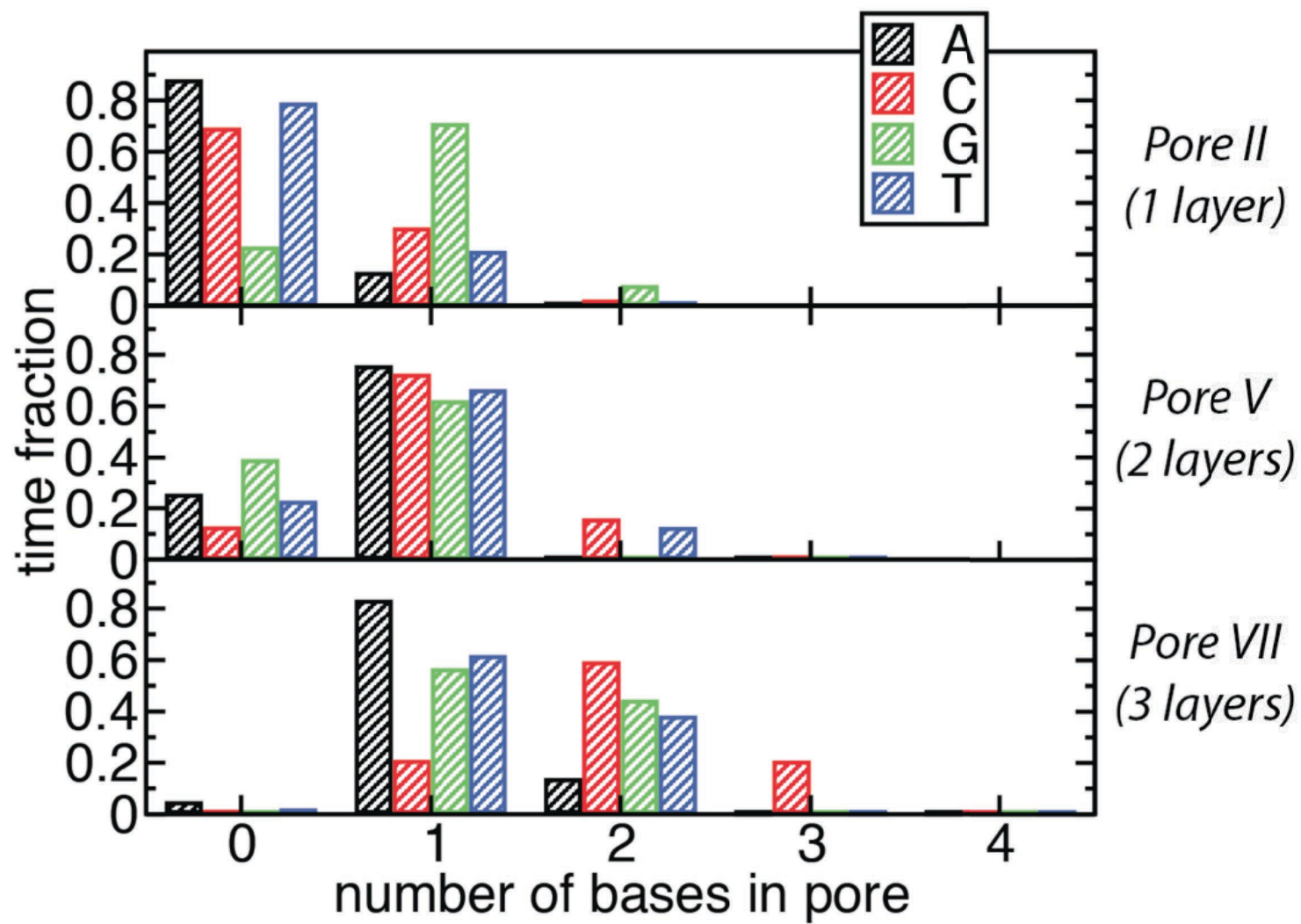
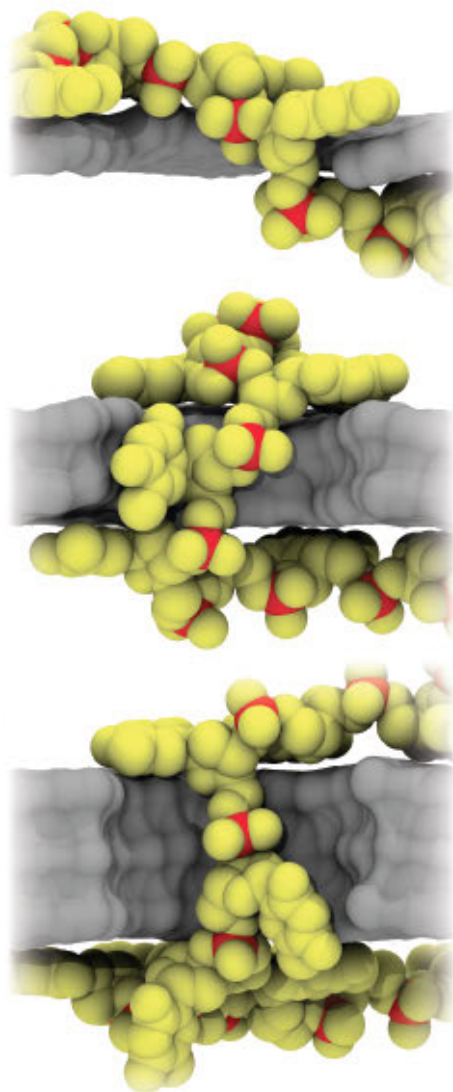
Top view



Side view

14-Å diameter pore (surface-to surface);
3-layer graphite;
poly(dT)₂₀ ; 500 mV bias

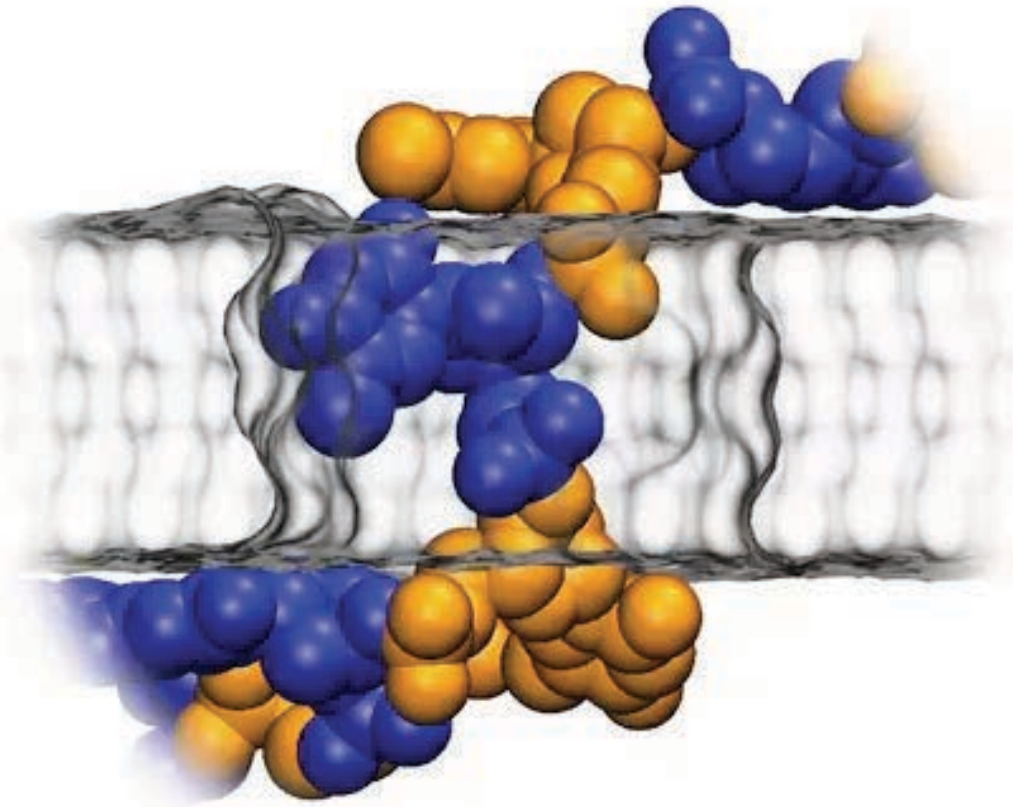
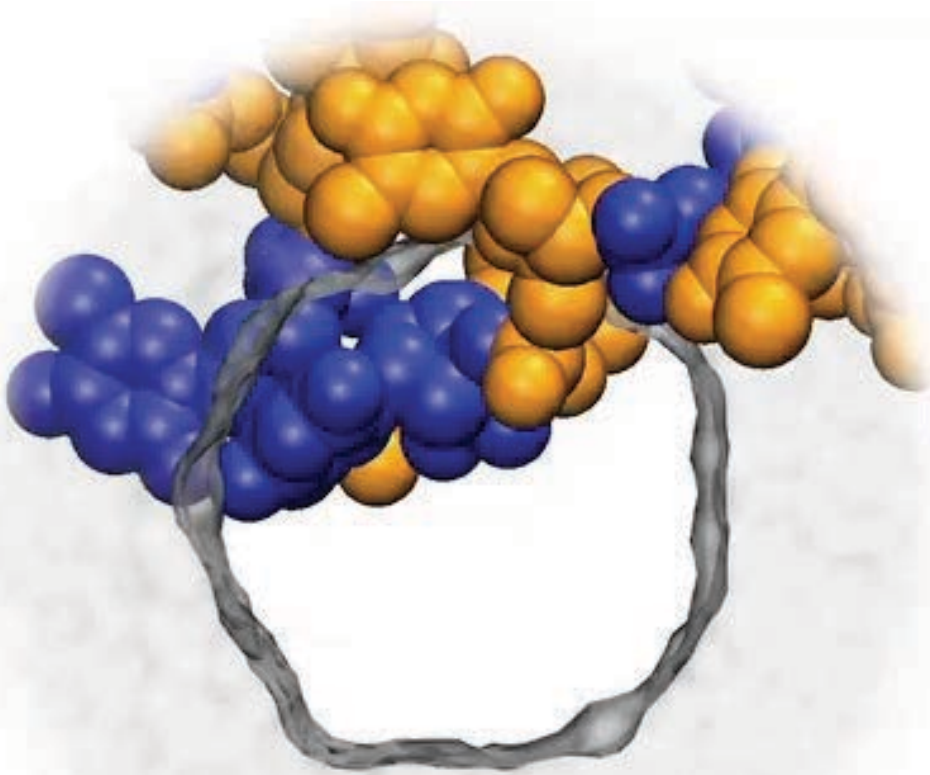
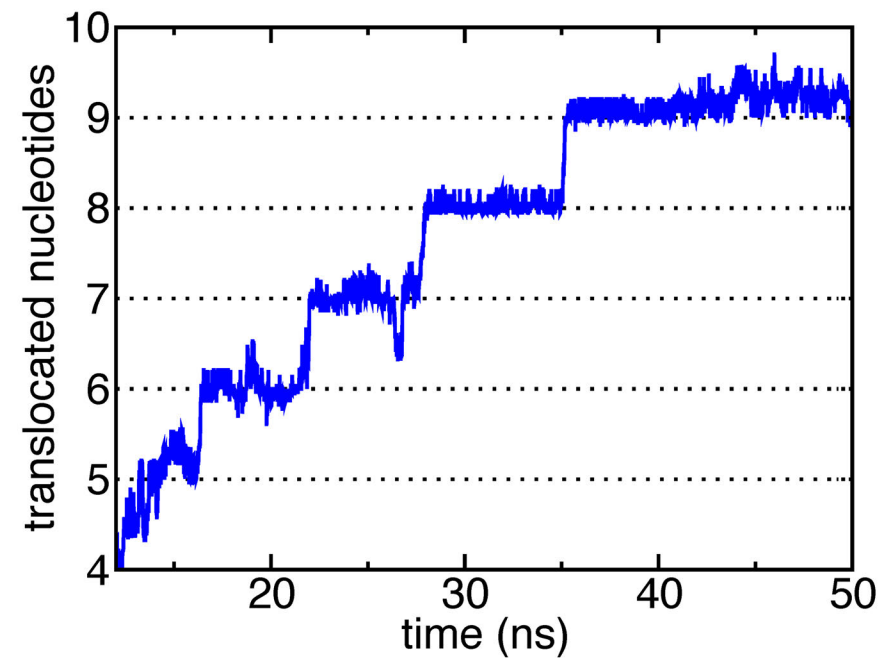
The thinner the better?



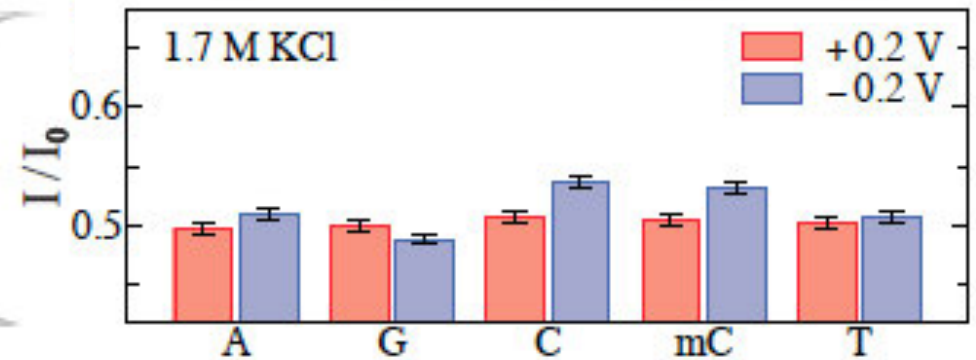
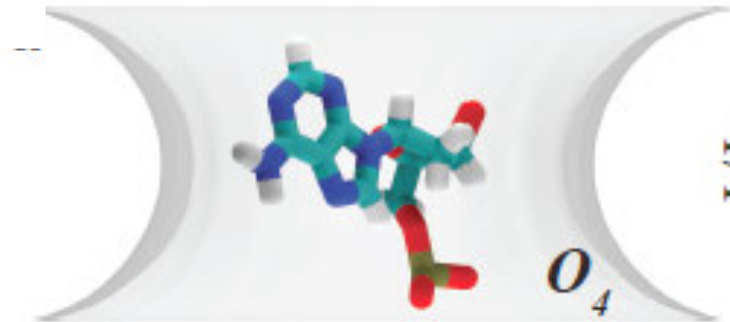
Stepwise transport of ssDNA through graphene nanopore

14-Å diameter pore (surface-to surface);
3-layer graphite;
poly(dT)₂₀; 500 mV bias

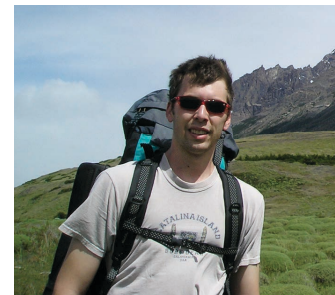
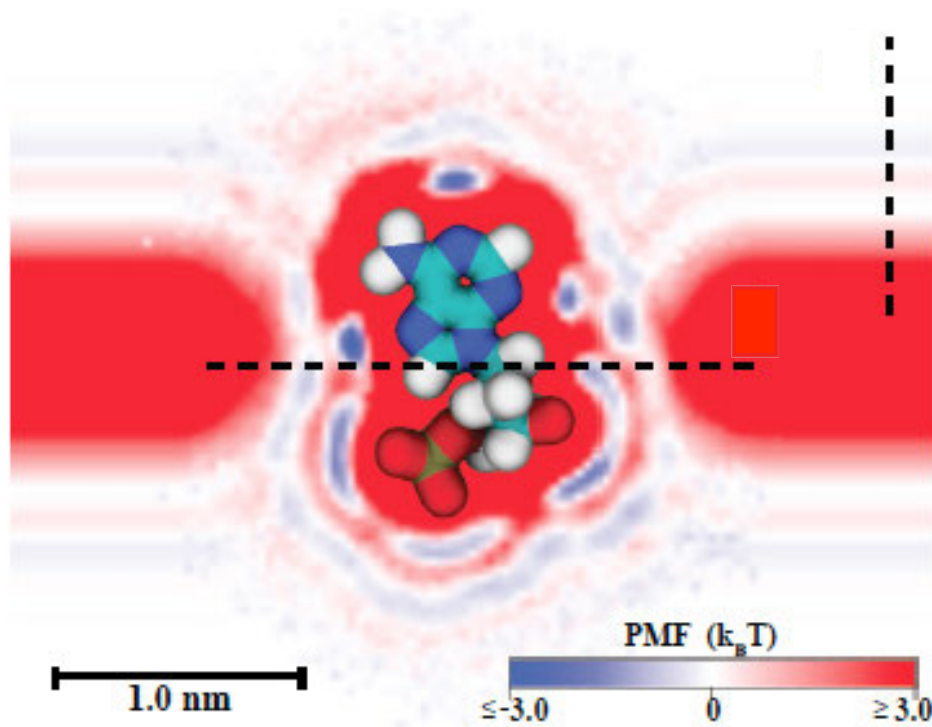
Acts like a polymerase!



Ionic current blockades can reveal the DNA sequence

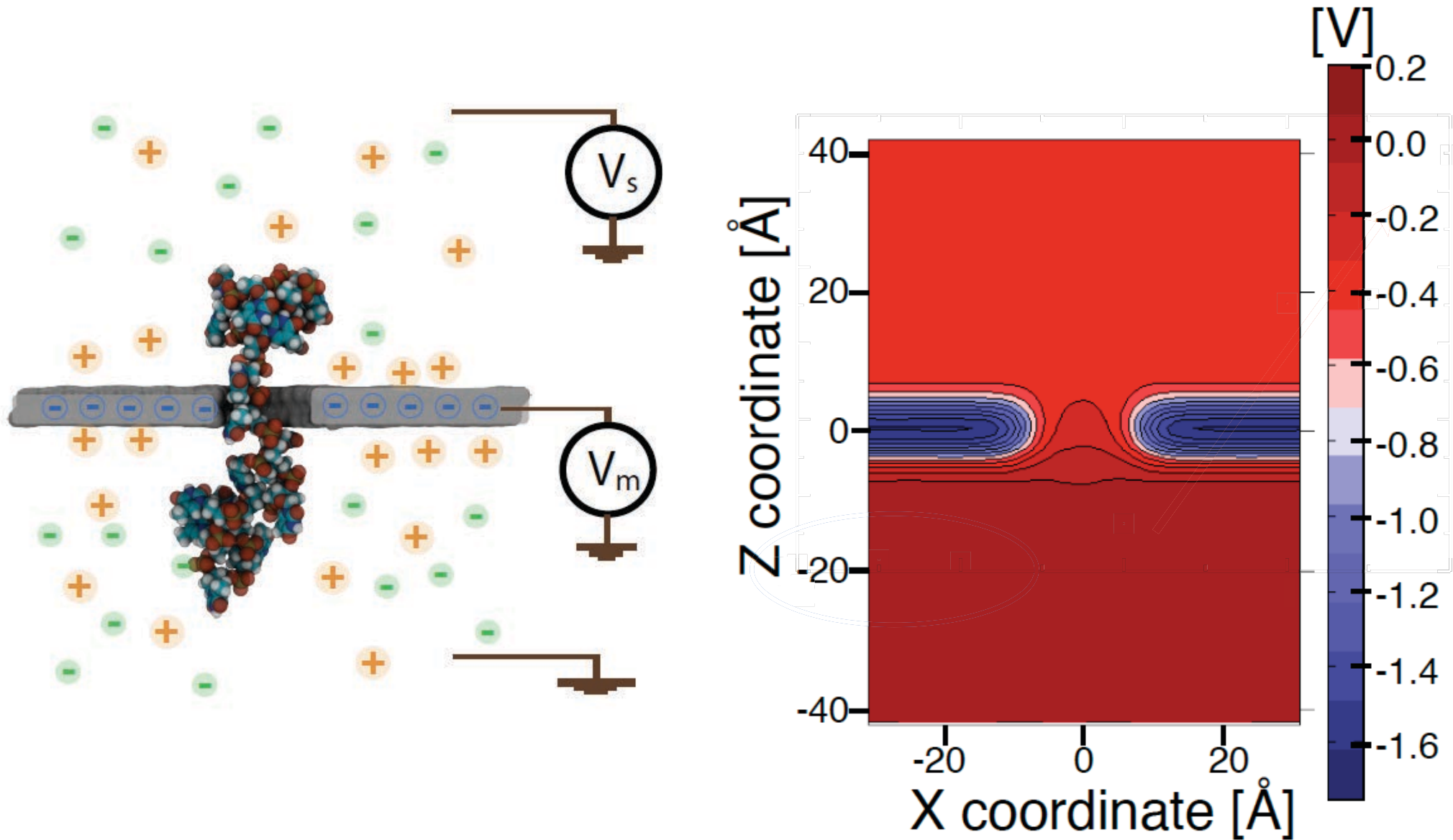


Atomic-Resolution Brownian Dynamics simulations of ionic current blockades in graphene nanopores

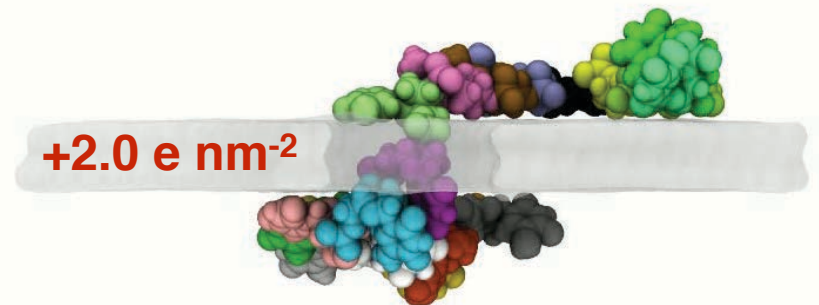
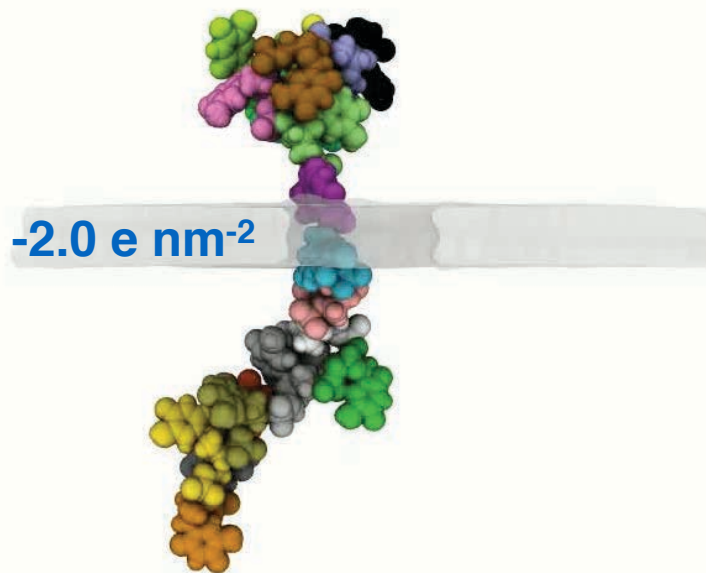
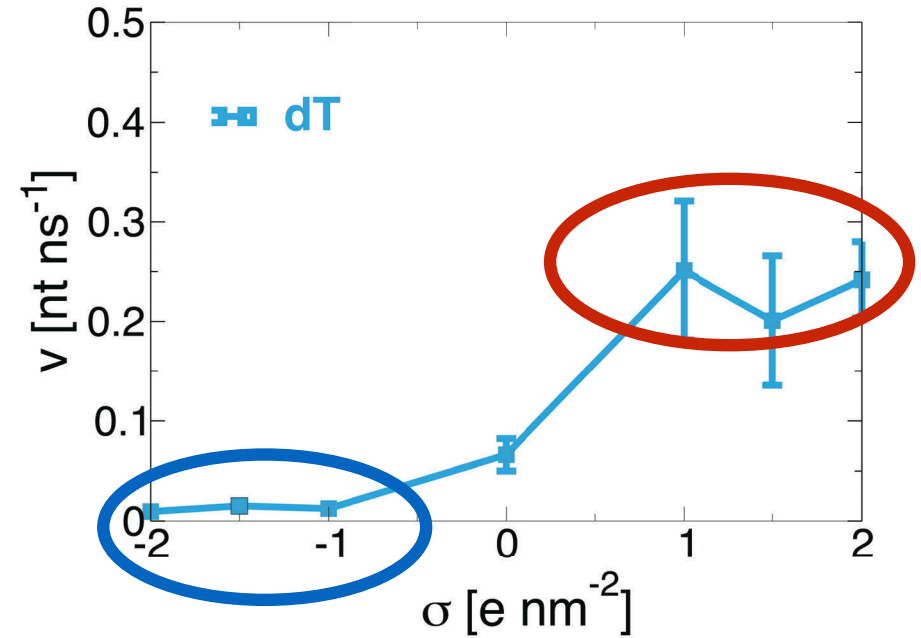
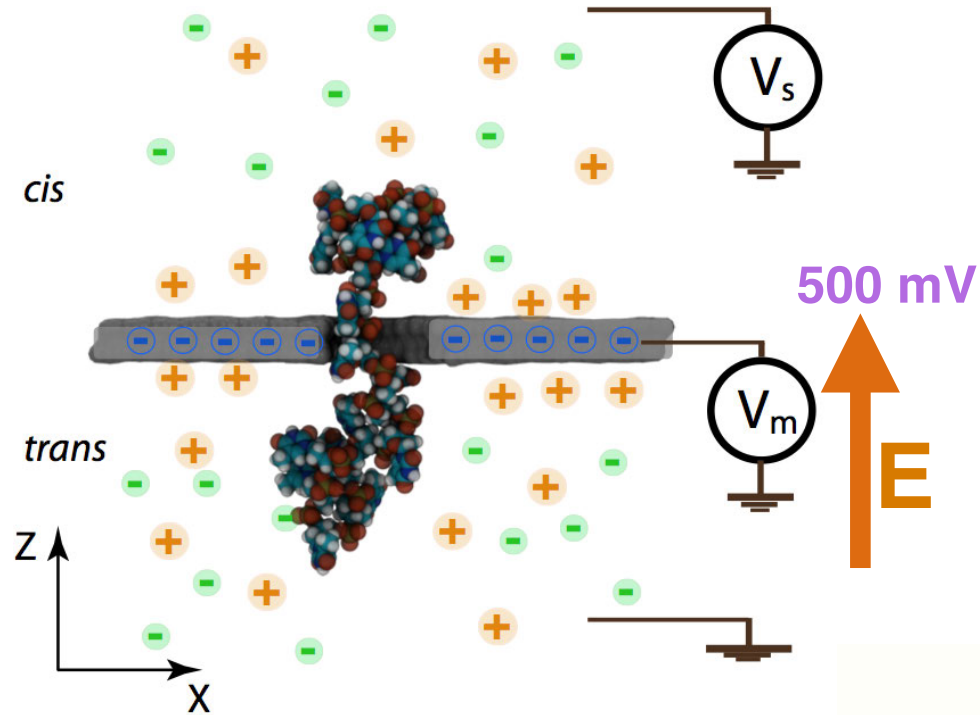


Wells, Belkin, Comer, Aksimentiev, Nano Letters 12:4117 (2012)

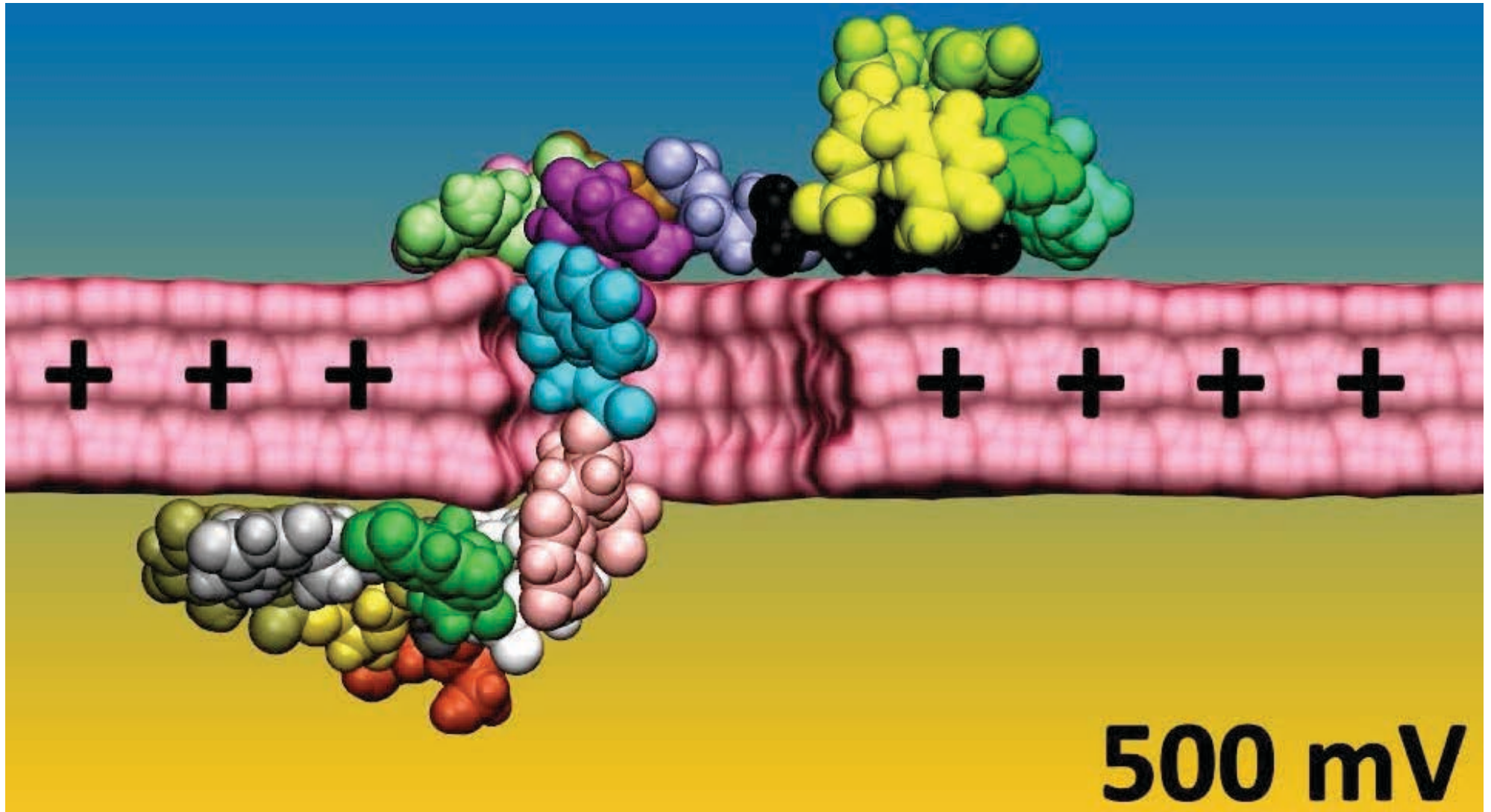
Charge modulates velocity of ssDNA translocation



Graphene charge controls DNA transport



Charge modulates velocity of ssDNA translocation

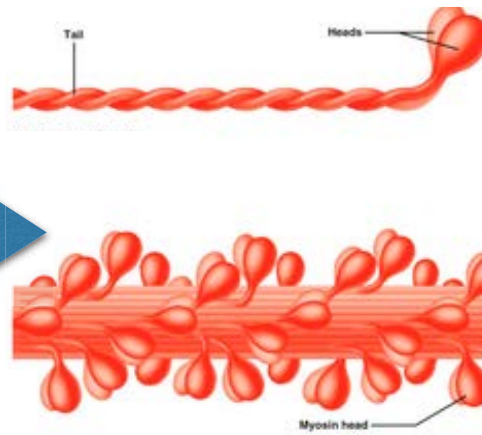


Manish Shankla et al. Nature Communications 5:5171

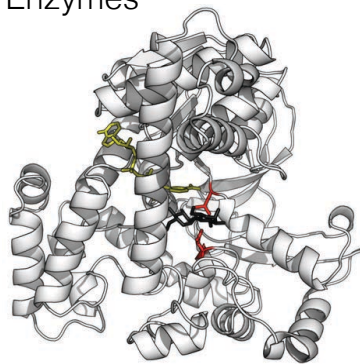
Protein sequencing



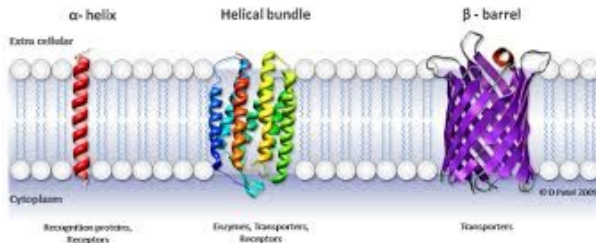
Structural proteins



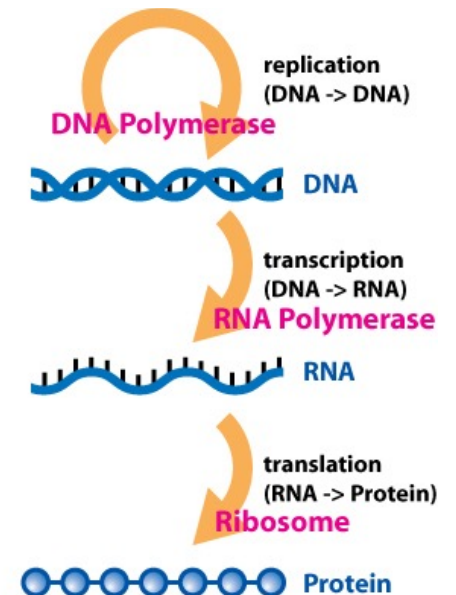
Enzymes



Membrane proteins



Central Dogma



In theory:

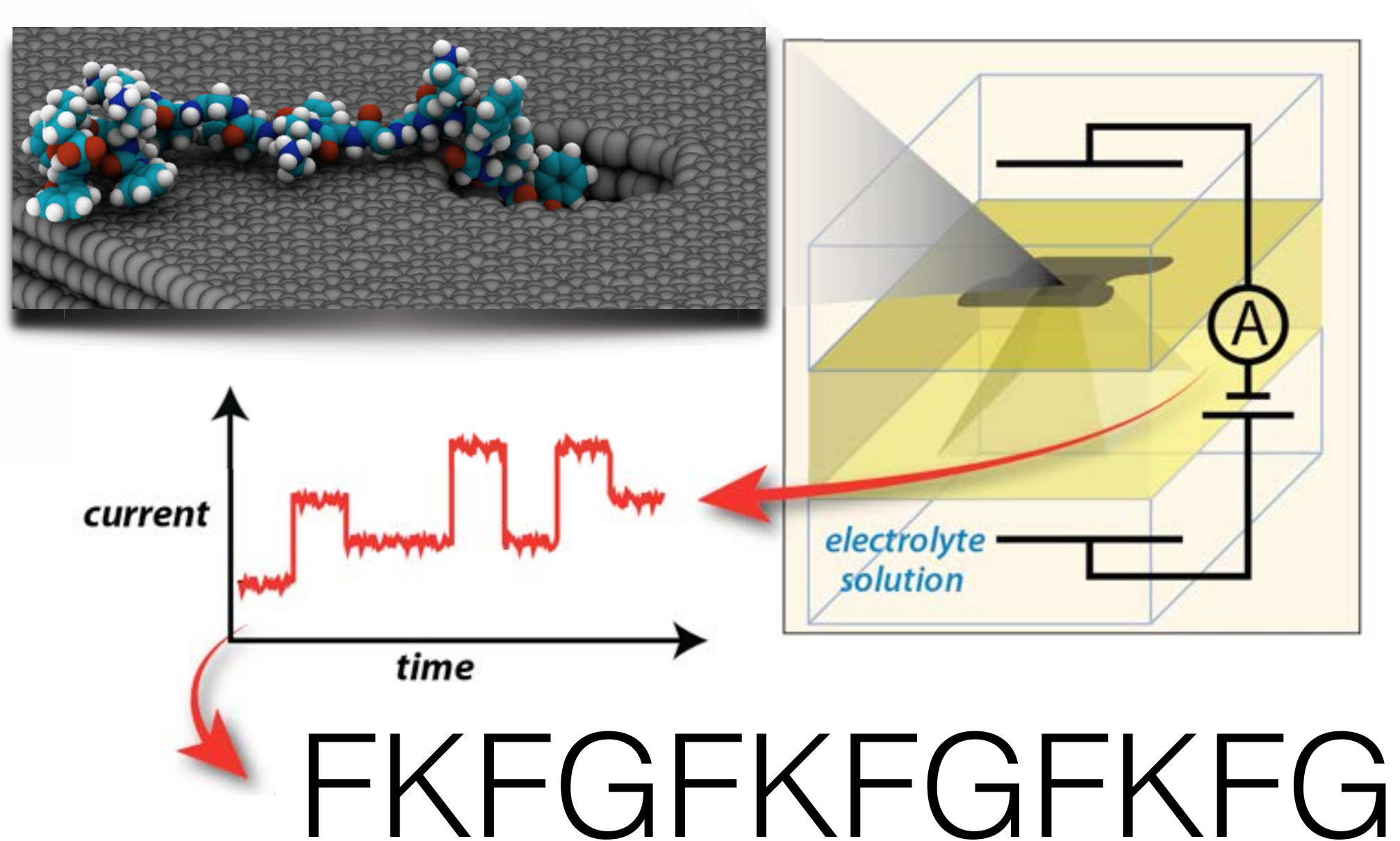
Knowing DNA == Knowing protein

In practice:

Post-translational modifications
Differences in expression level

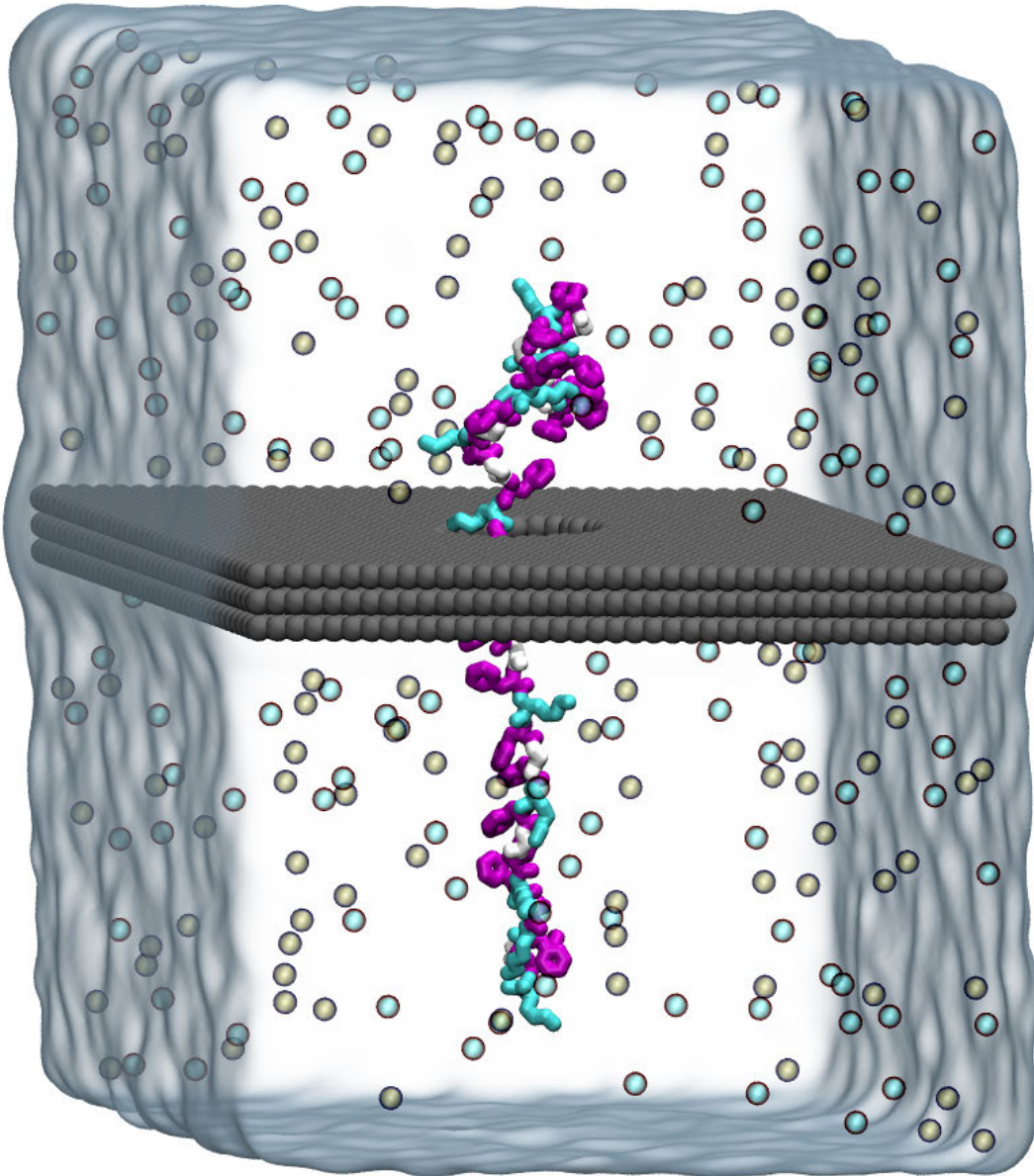
Sequencing proteins using graphene nanopores?

Wilson et al., Adv. Func. Mat. 10.1002/adfm.201601272 (2016)



Peptide adsorption to graphene

FKFGFKFGFKFGFKFGFKFGFKFGFKFGFKFGFKFGFKFGFKFGFKFGFKFGFKFGFKFGFKFGFKFGFKFG



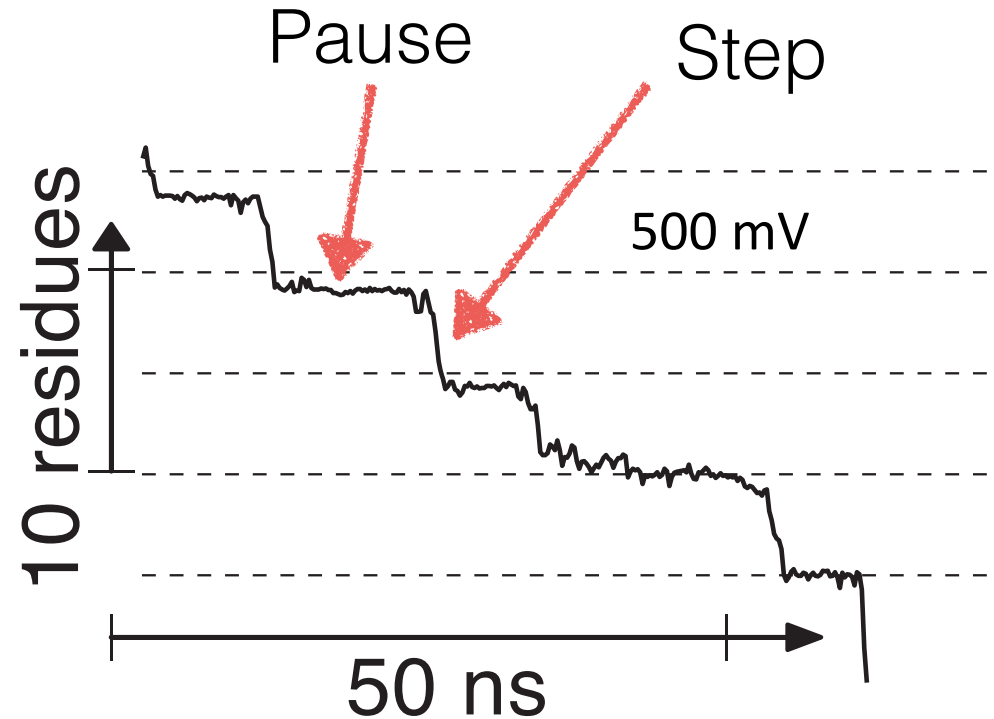
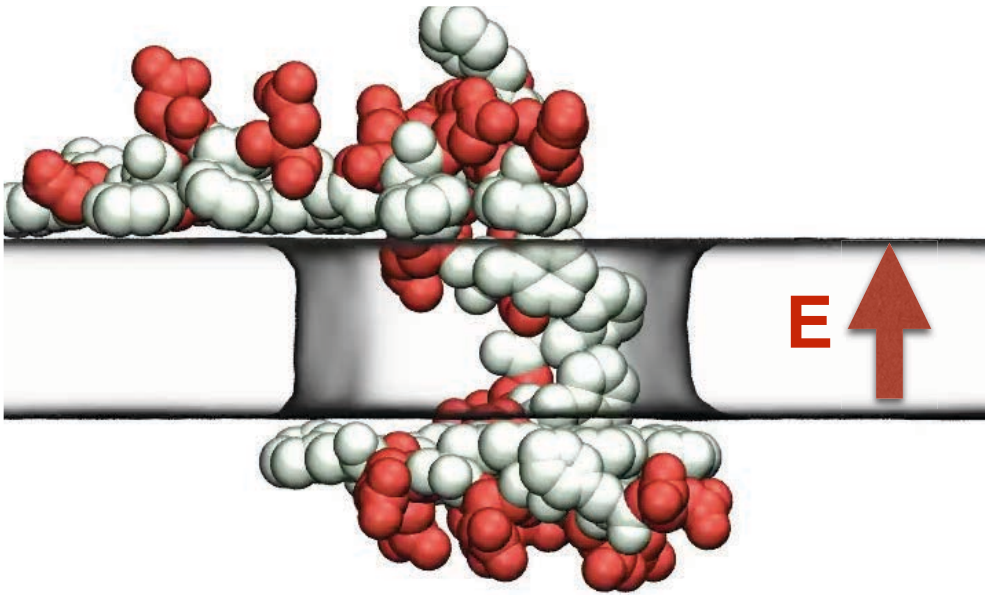
All atom model
with 2.2 nm 3-
layer graphene
membrane

Phenylalanine stacks to graphene

All peptide chains we tried adsorb to the graphene

Voltage driven transport is stepwise

FDFD FDFD FDFD FDFD FDFD FDFD FDFD FDFD FDFD FDFD FDFD FDFD FDFD FDFD FDFD FDFD

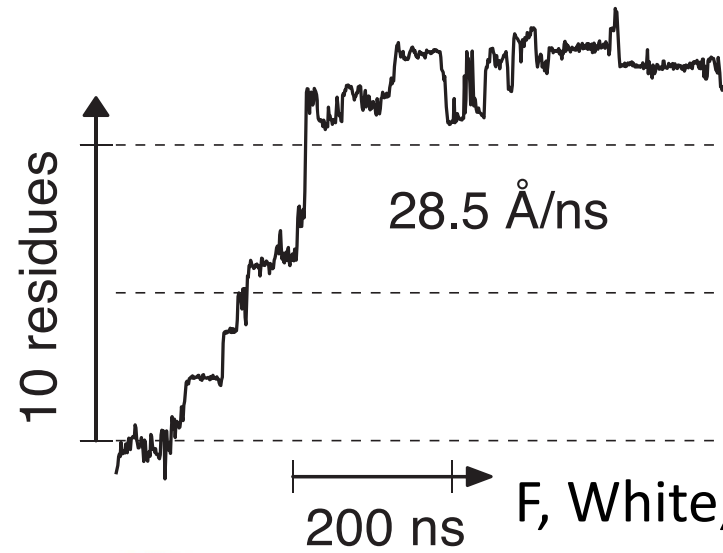
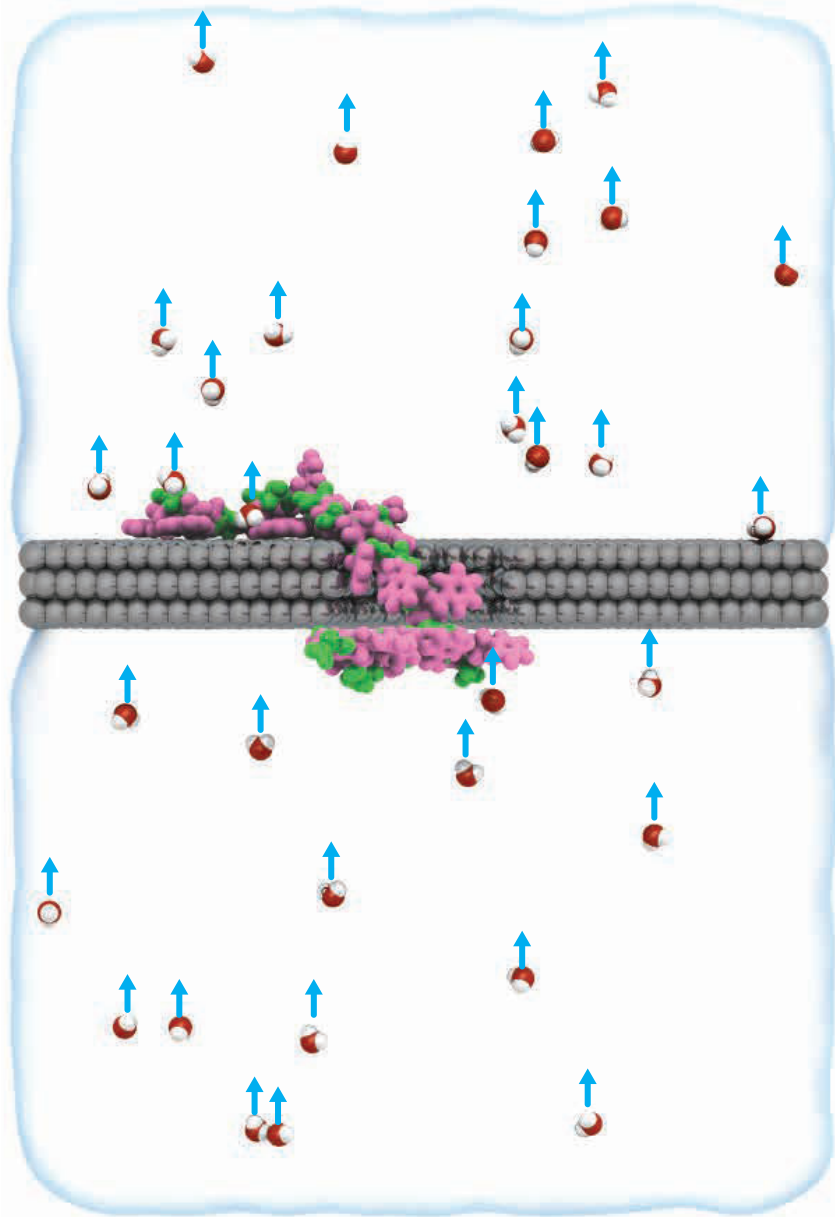


F, White, hydrophobic
D, Red, -1 charge

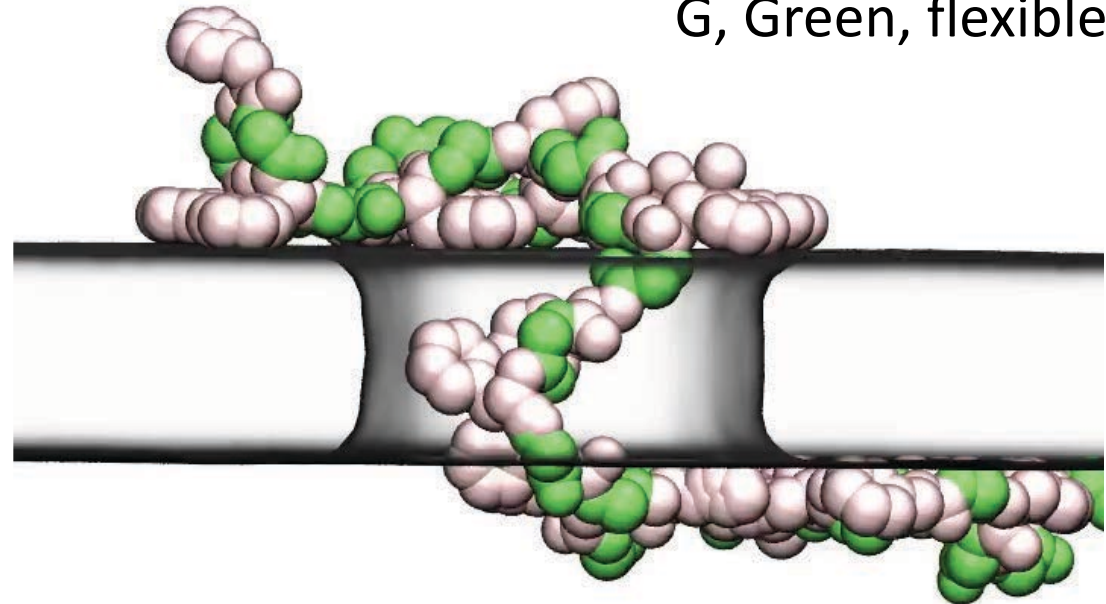
Pauses allow a longer current reading with an unchanging pore

Current readings
are more accurate

Pressure can be used to drive proteins
No charge!



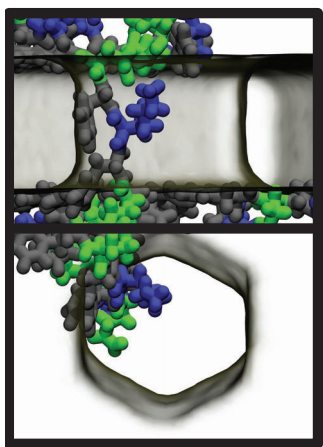
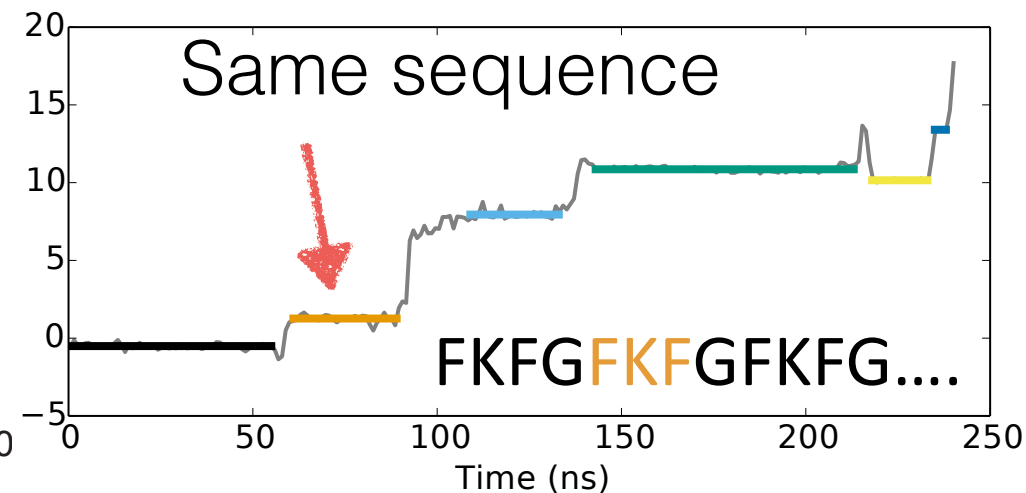
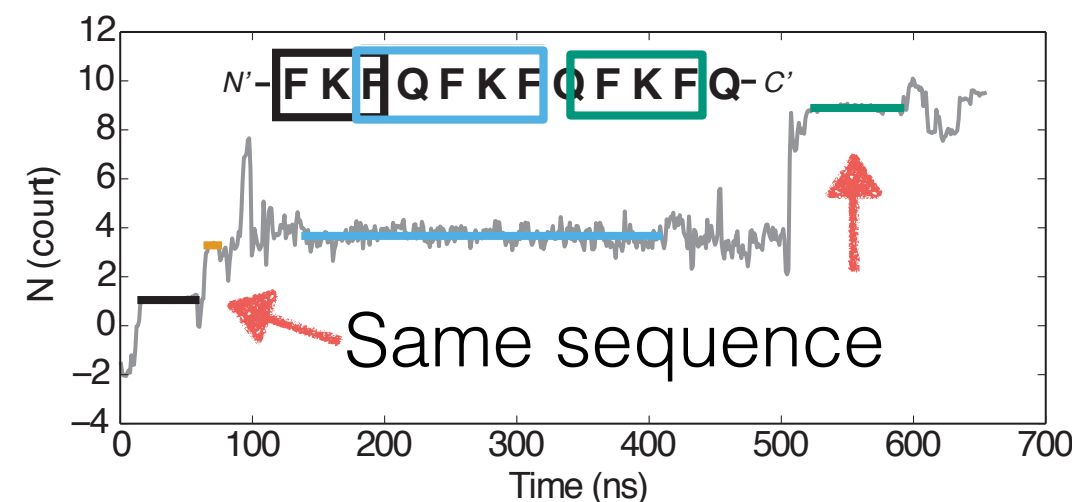
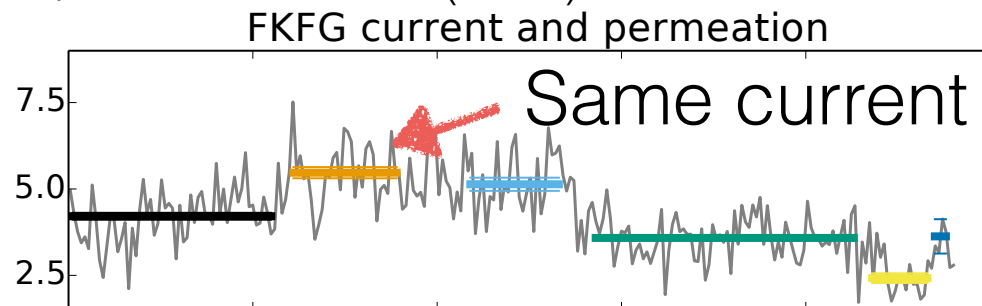
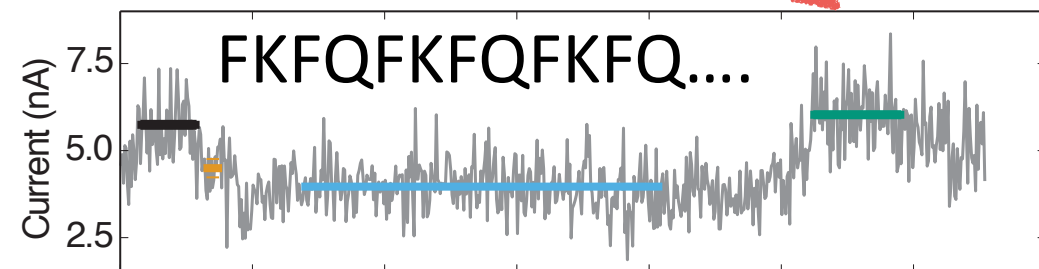
200 ns F, White, hydrophobic
G, Green, flexible



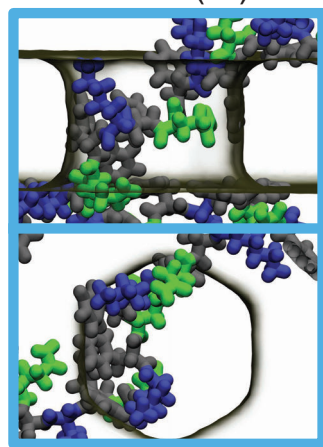
FG

Same current Current Signature

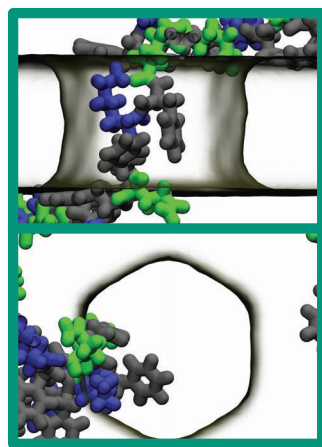
Wilson et al., Adv. Func. Mat. 10.1002/adfm.201601272 (2016)



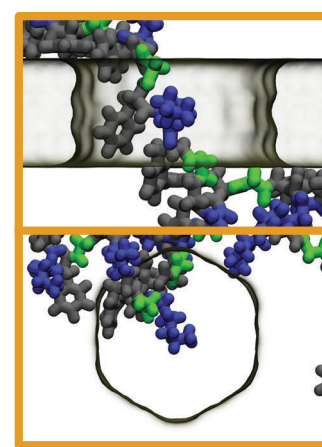
40 ns



250 ns



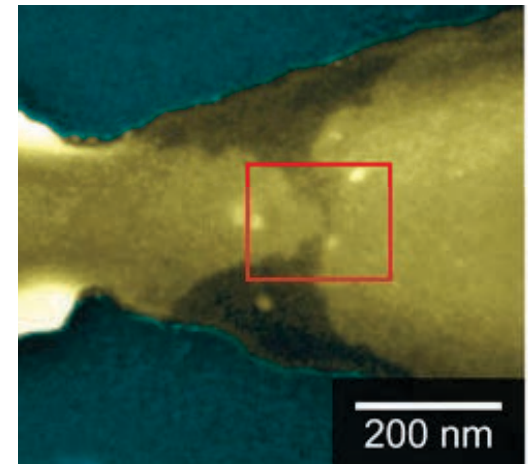
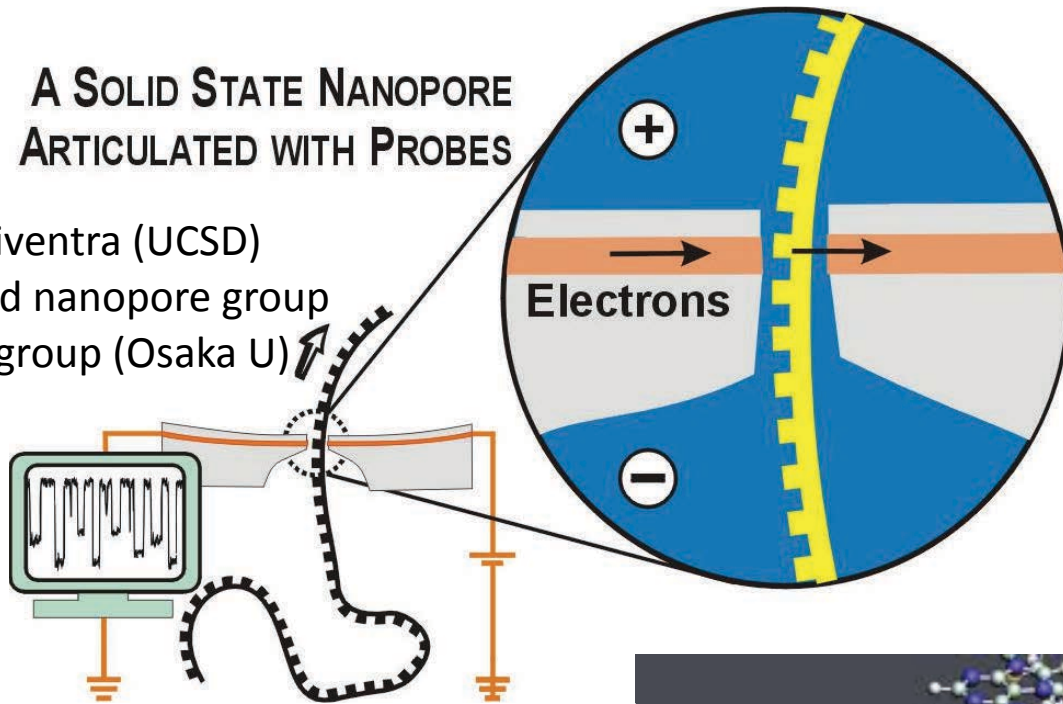
545 ns



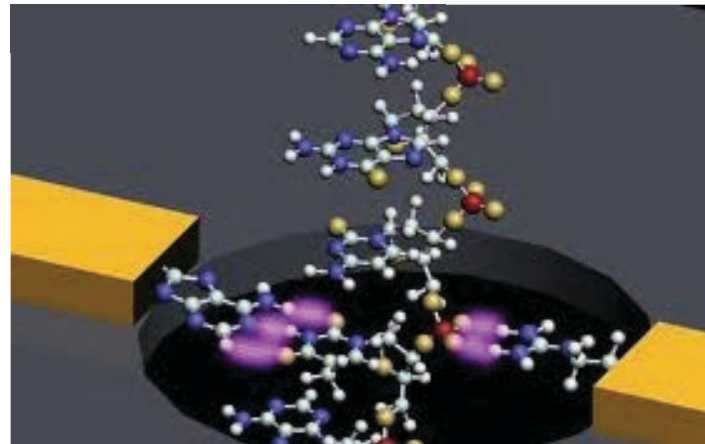
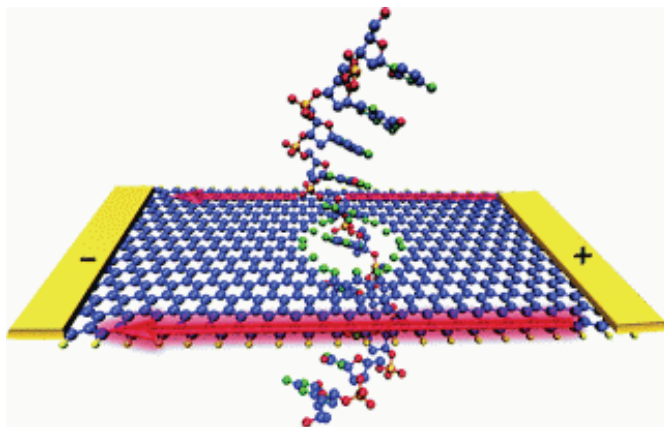
Sequencing by transverse current

A SOLID STATE NANOPORE
ARTICULATED WITH PROBES

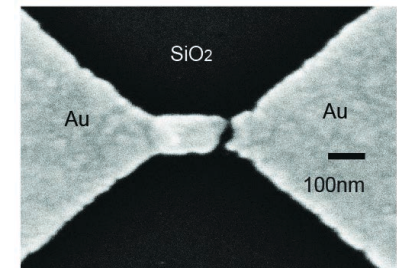
Max Diventra (UCSD)
Harvard nanopore group
Kawai group (Osaka U)



Scientific Reports 1:46



Stuart Lindsay (ASU)



Temperature effects in nanopores

Slowing DNA transport:

Meller et al. Phys. Rev. Lett. 2001

Wanunu et al. Nat. Nanotech (2010)

Regulating transport in :

aHL: Movileanu et al. J. Am. Chem. Soc. 2006

solid-state pores:

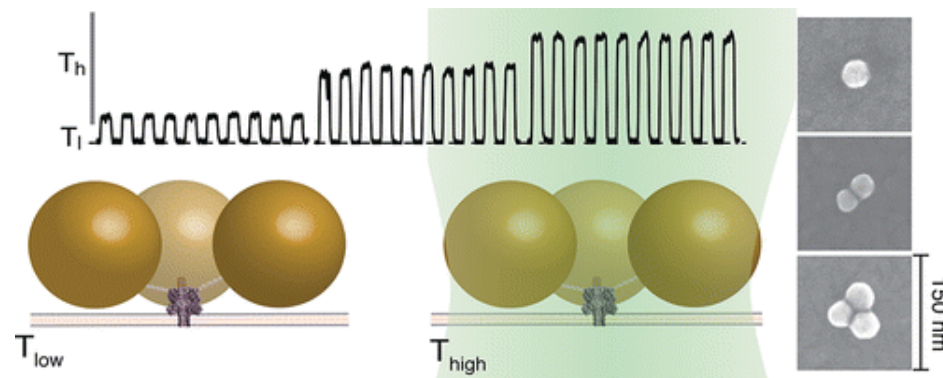
ChemPhysChem 639 2010, 11, 859

Nanotechnology 2012, 23, 225502

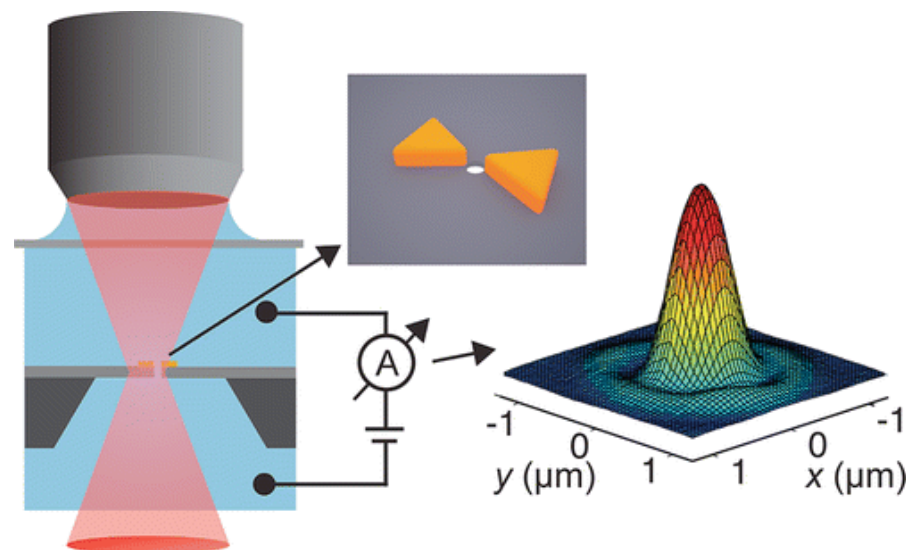
Finding the pore:

Keyser et al. Nano Lett. 2005, 5, 2253

Plasmonic heating:



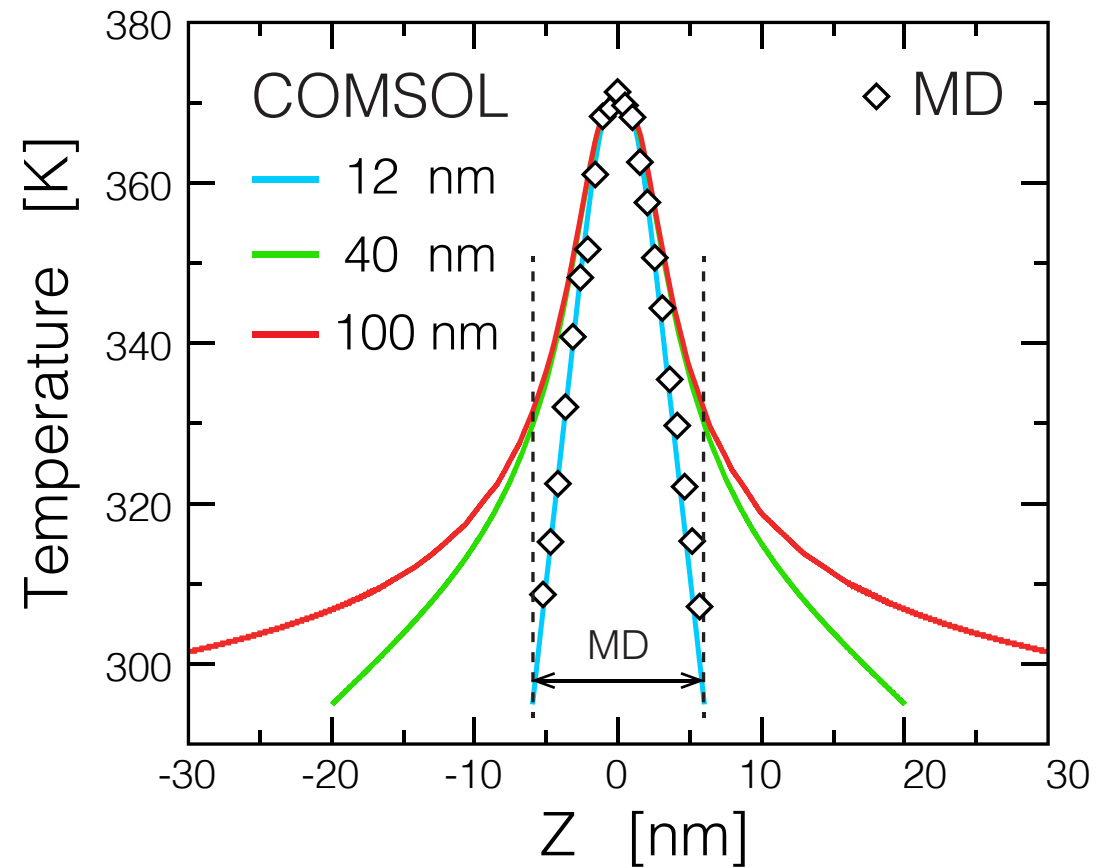
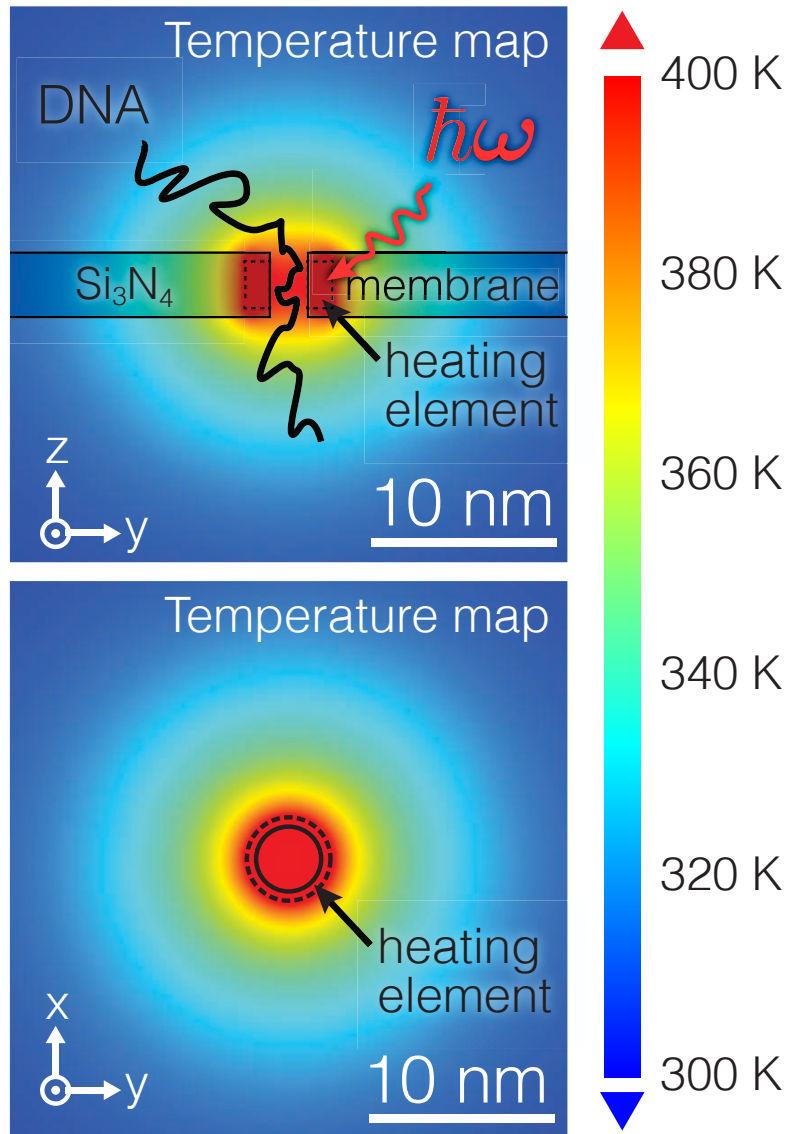
JACS 135: 3087 (2013)



Nano Letters 13: 1029 (2013)

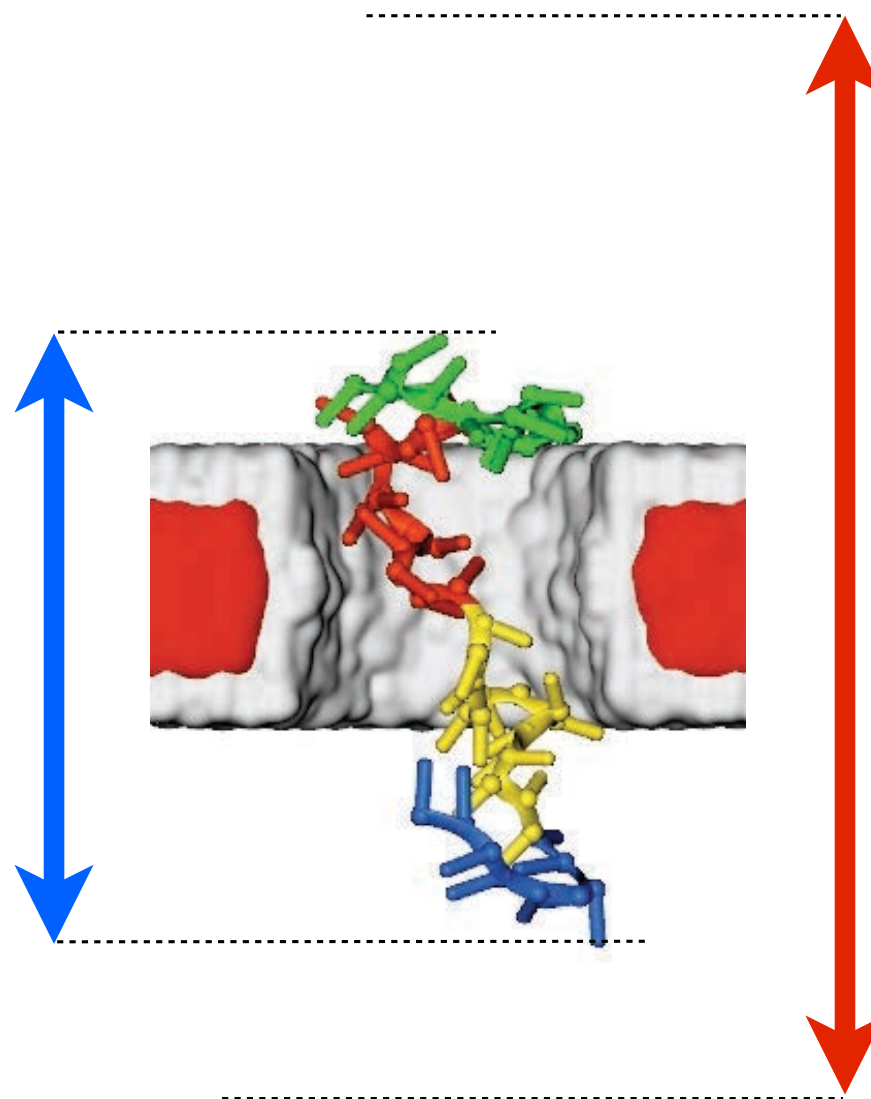
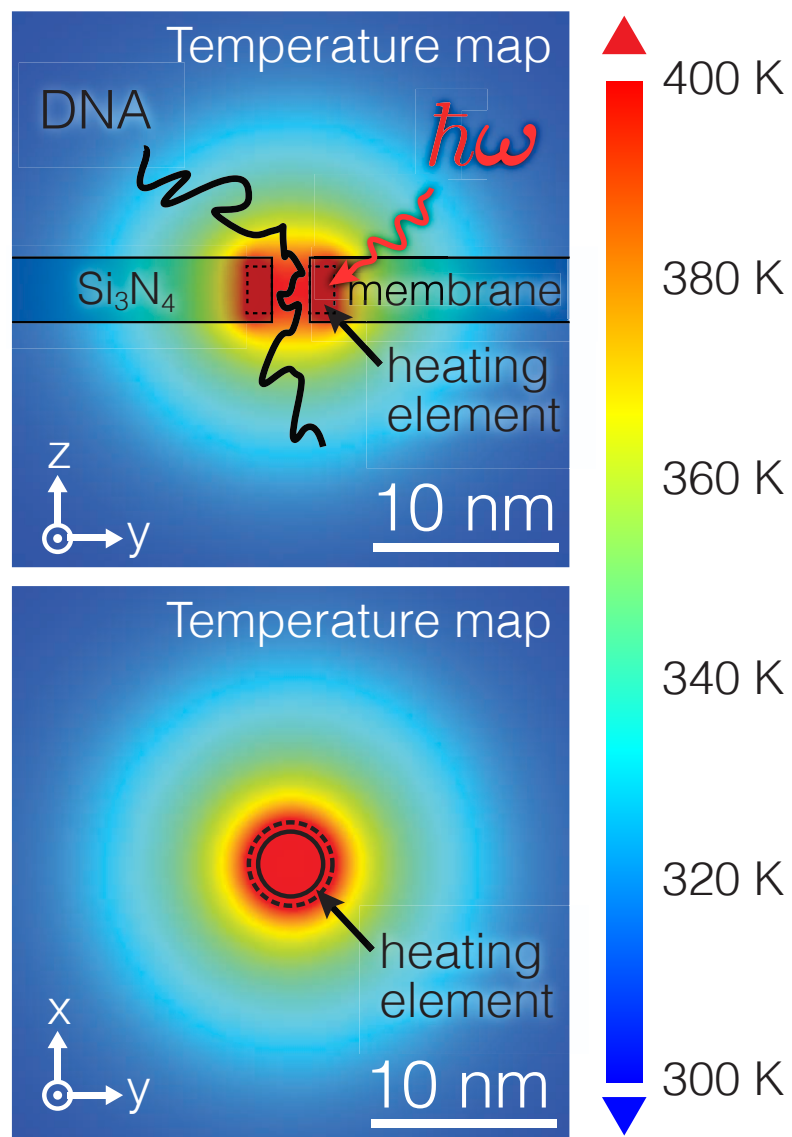
Local plasmonic heating stretches ssDNA

M Belkin et al. ACS Nano 7:6816 (2013)

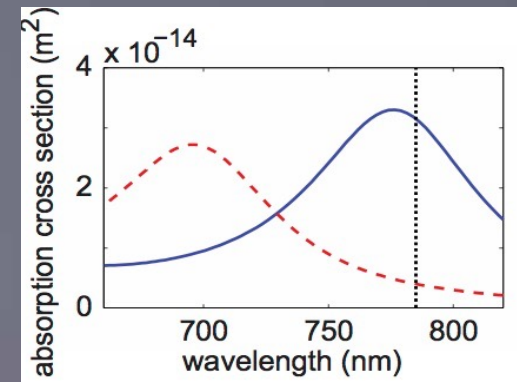
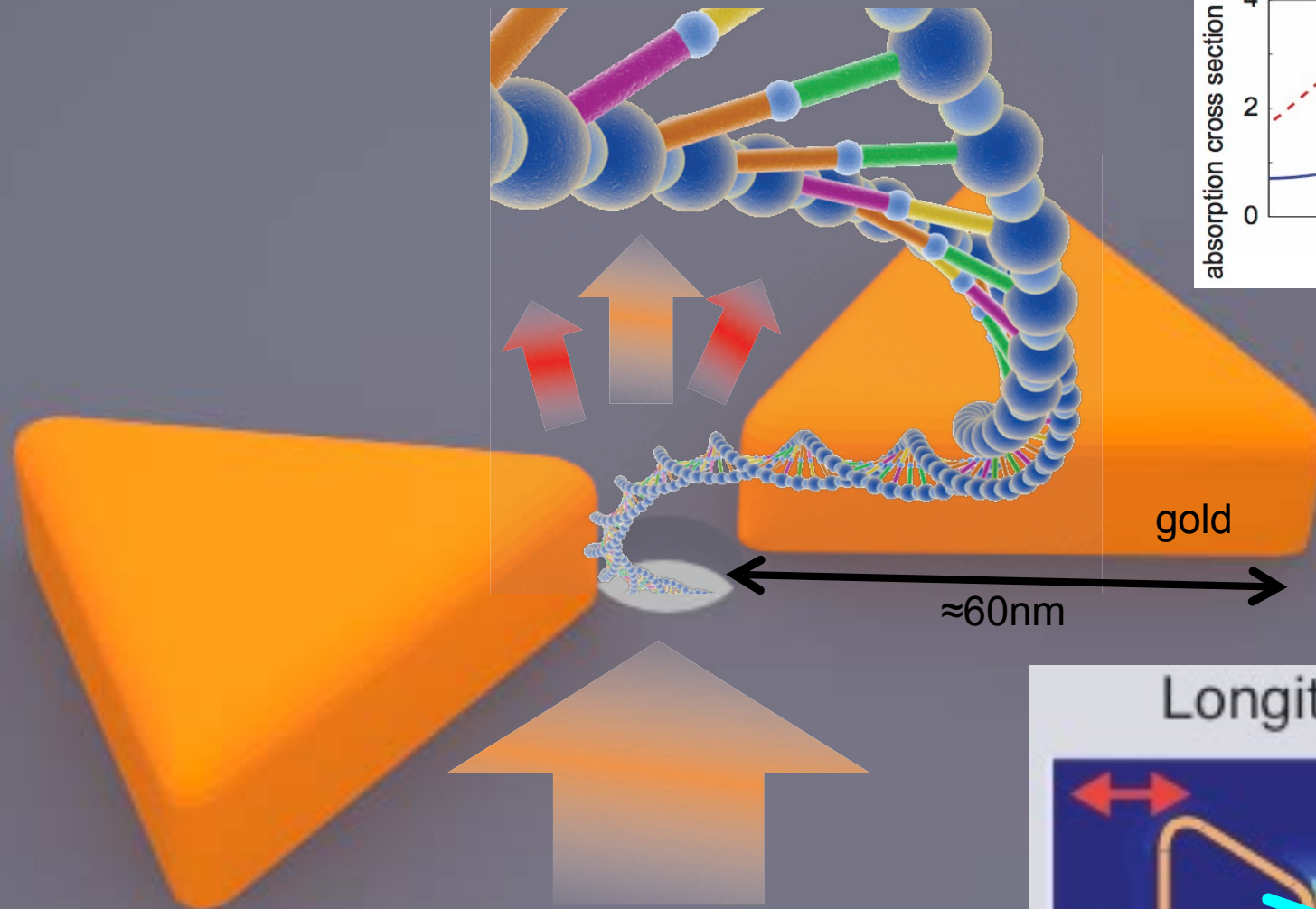


Local heating in nanopore systems

M Belkin et al. ACS Nano 7:6816 (2013)



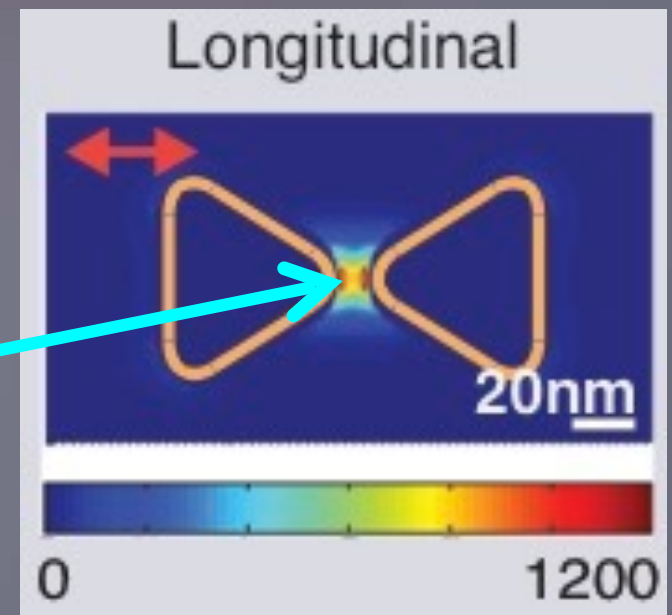
Plasmonic nanopores



PLASMONIC HOT SPOT

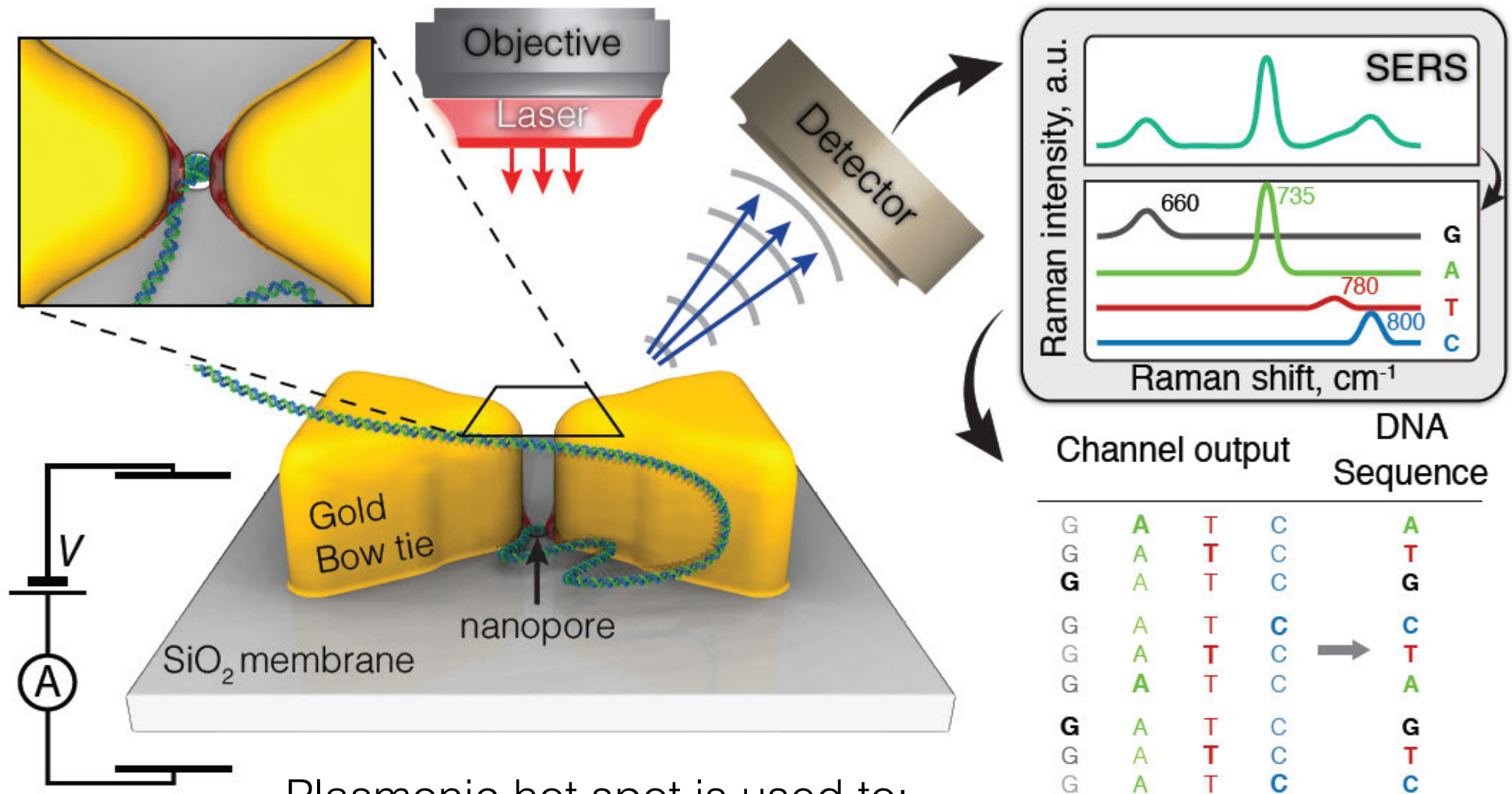
**High field gradients
optical forces**

Laser



DNA sequencing using a plasmonic nanopore

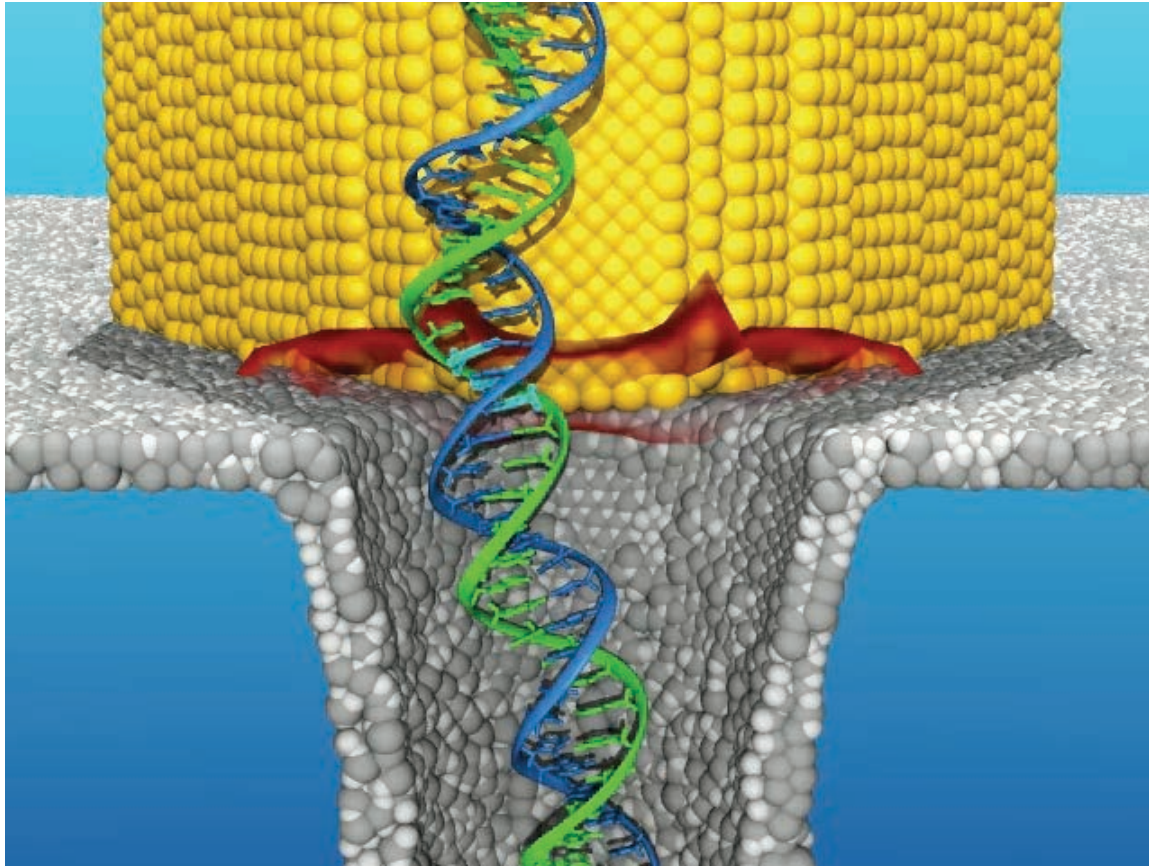
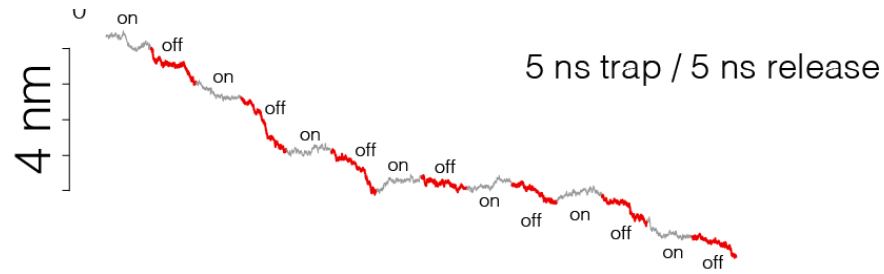
Belkin et al, ACS Nano 9: 10598 (2015)



Plasmonic hot spot is used to:

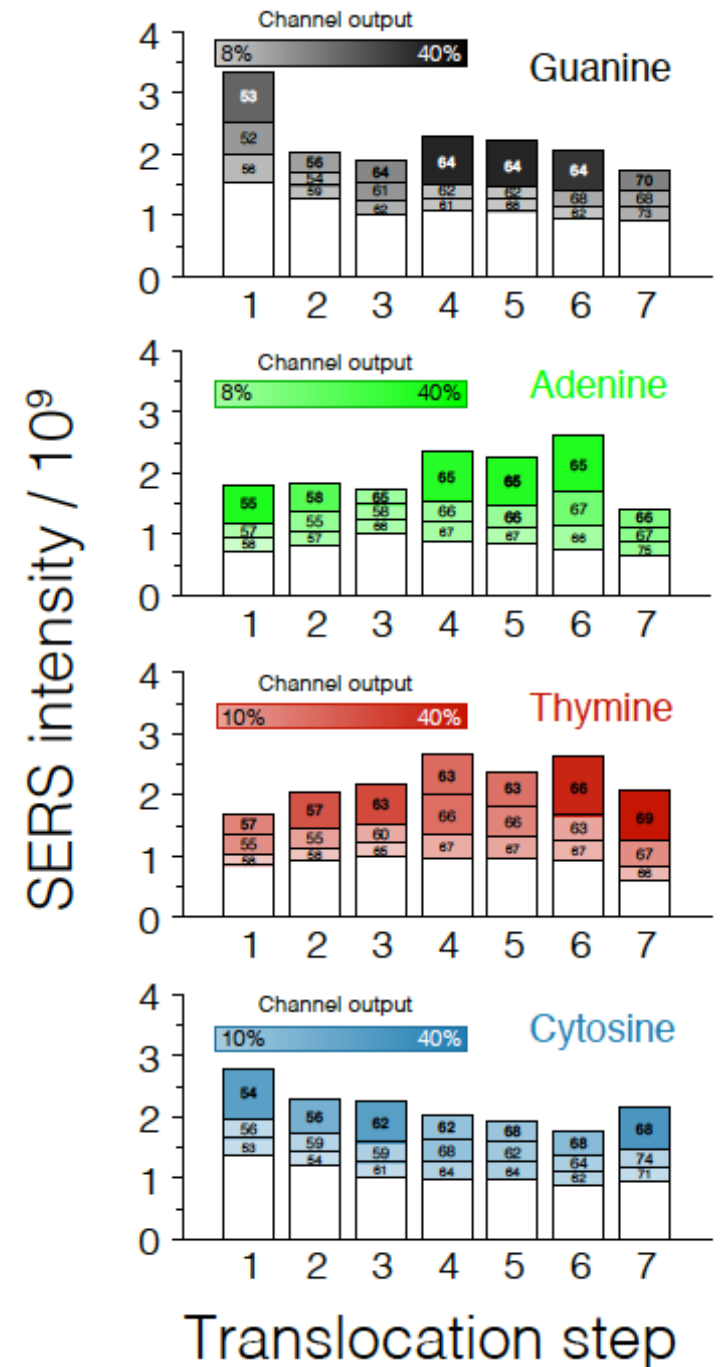
- control DNA motion
- stimulate Raman emission

Raman signatures of random-sequence DNA

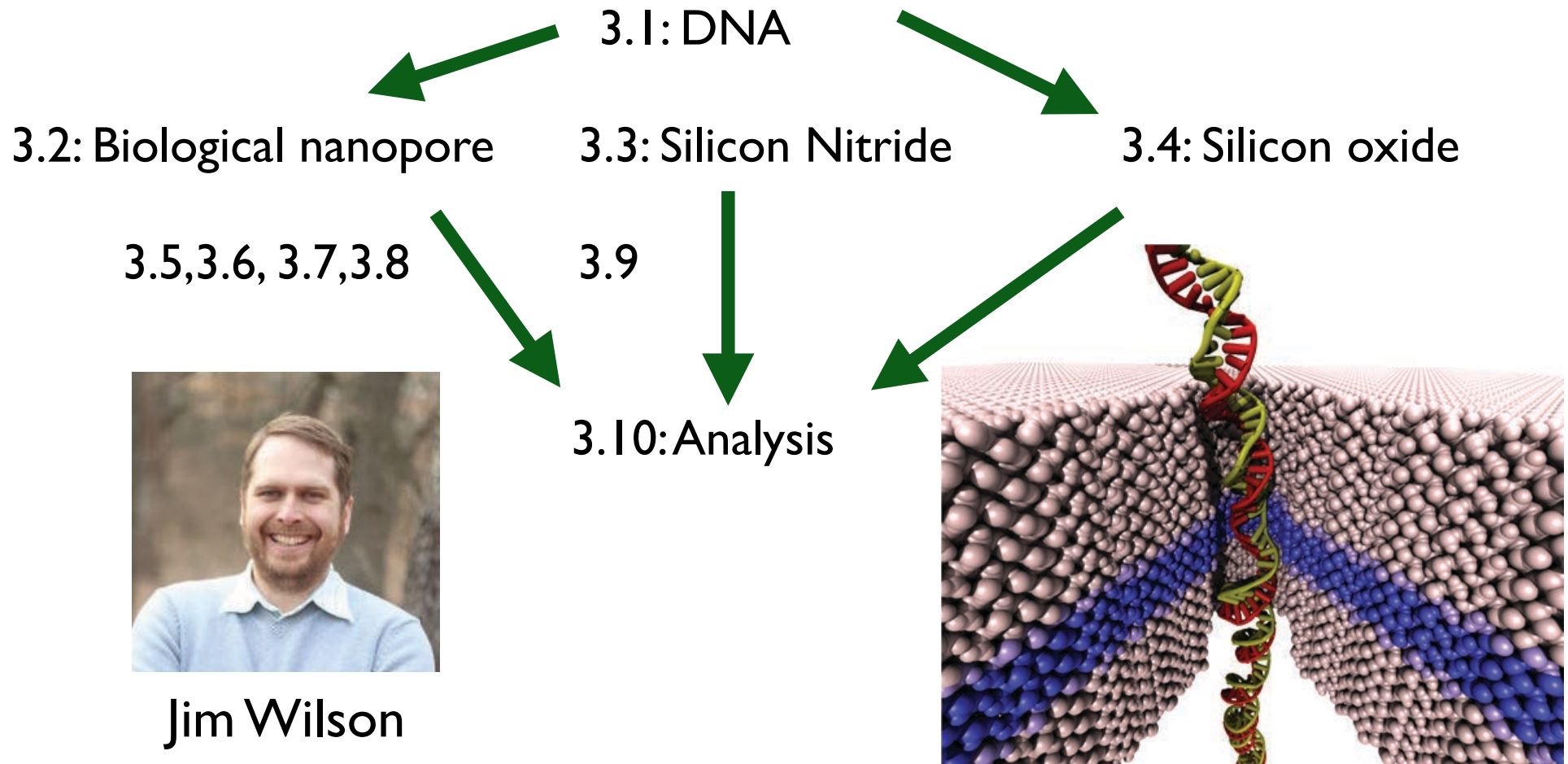


Single-spot trapping

Belkin et al, ACS Nano 9: 10598 (2015)



Tutorial: Modeling Nanopores for Sequencing DNA



<http://bionano.physics.illinois.edu/tutorials/modeling-nanopores-sequencing-dna>

Acknowledgements

Jeff Comer
Maxim Belkin
Rogan Carr
David Wells
Manish Shankla
Swati Bhattacharya
Jejoong Yoo
Chen-Yu Li
Chris Maffeo
Shu-Han Chao
Derek Vandamme



Swati Bhattacharya



Jejoong Yoo



Maxim Belkin



David Wells



Jeff Comer



Chris Maffeo



VMD and NAMD

