Reinventing a DNA sequence reader

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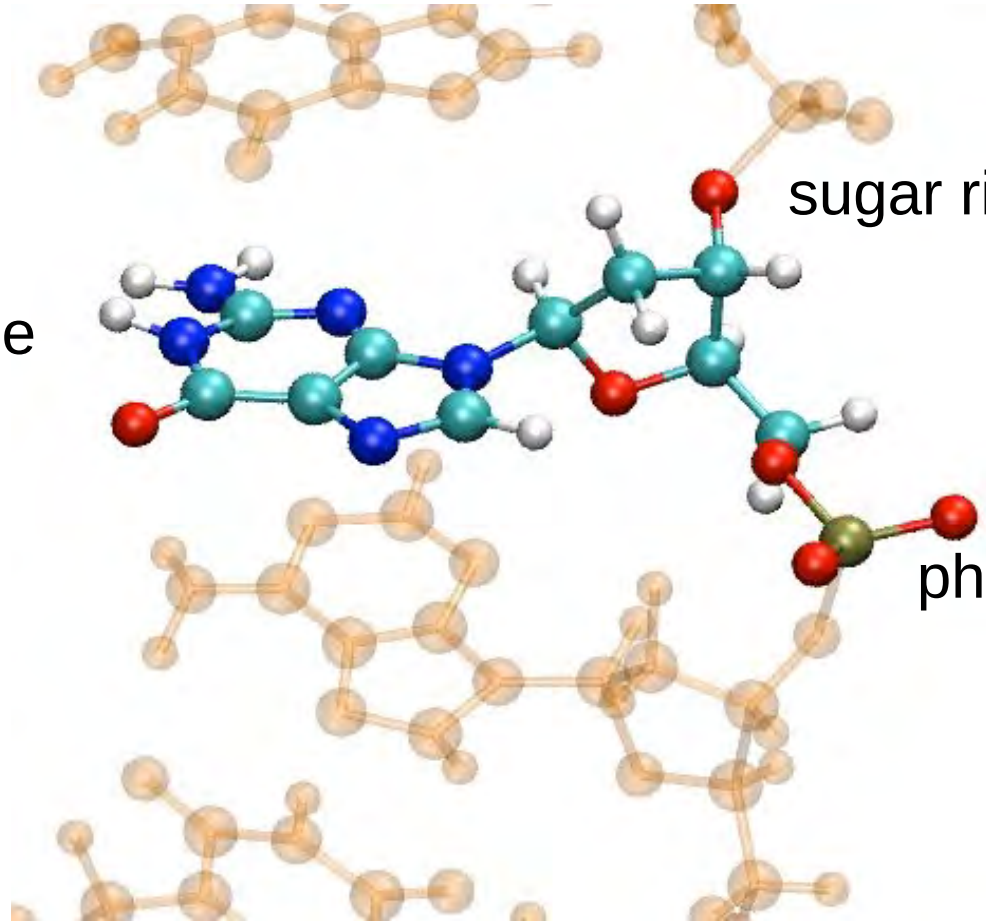
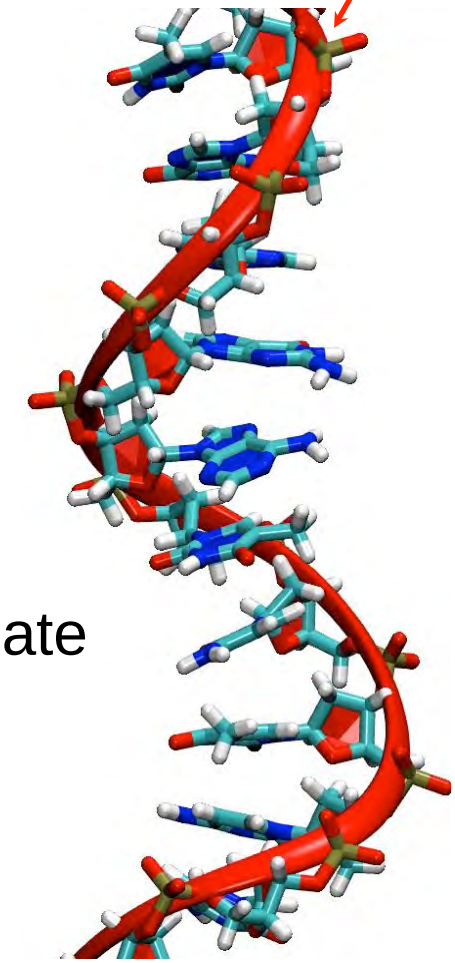
DNA code is written in atoms

Double stranded DNA
(persist. length ~50nm)

Highly charged: 2 electron charges per 0.32nm



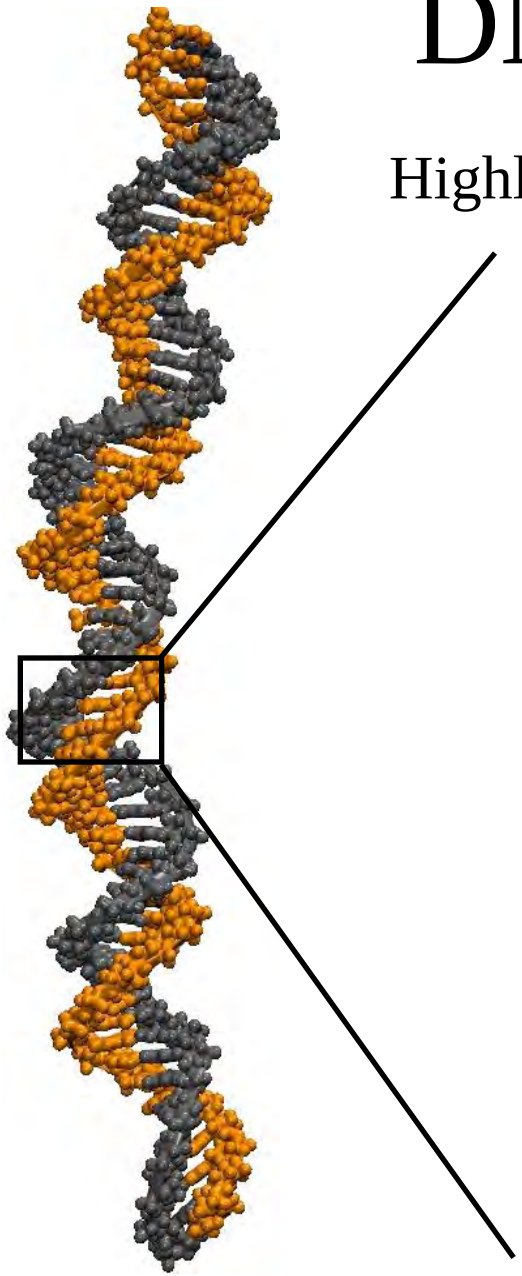
The sequence has direction:
5’-AAGCTGGTTCAG-3’

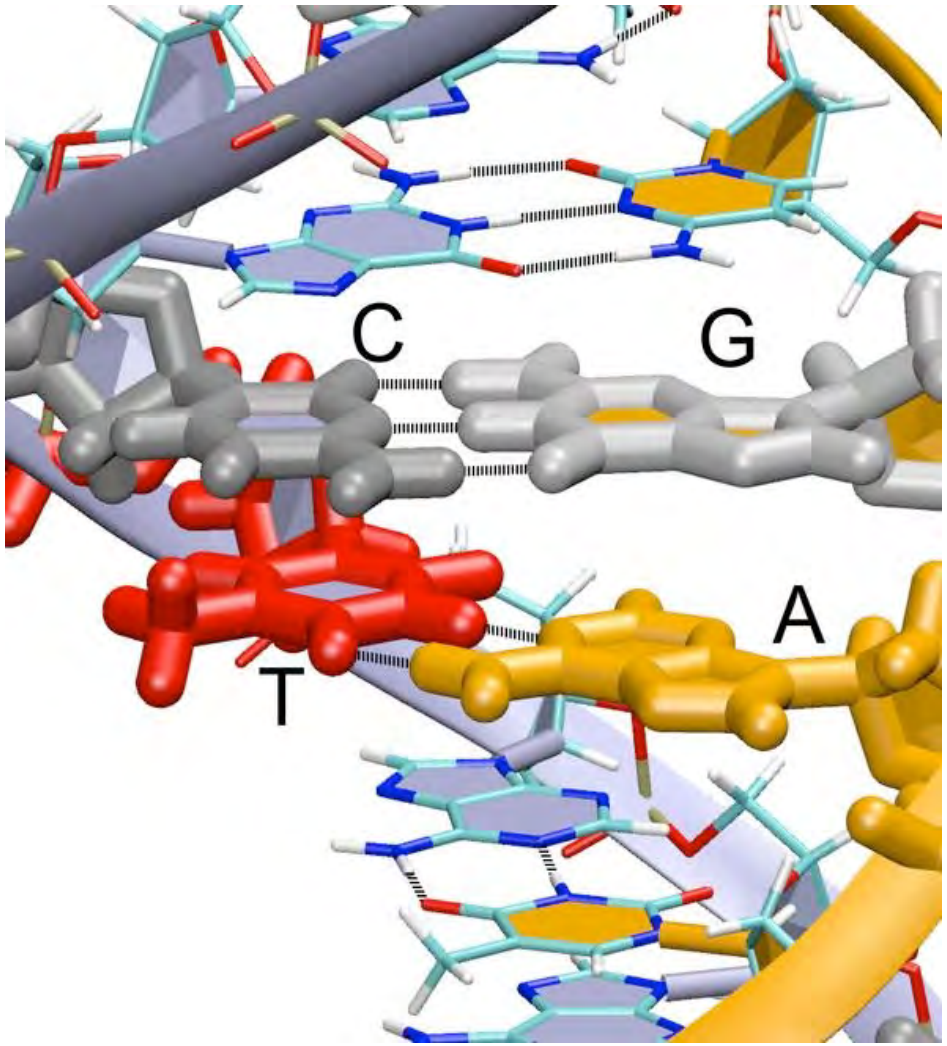


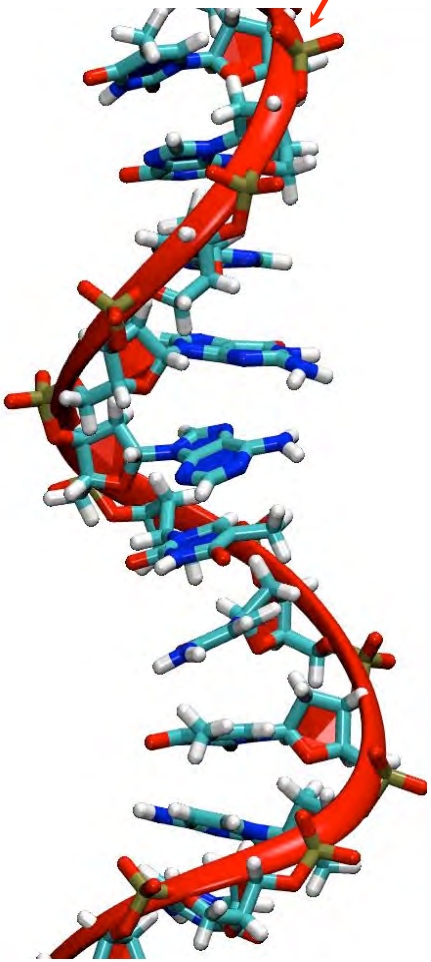
Single stranded DNA
(persist. length ~1.5nm)

DNA code is written in atoms

Highly charged: 2 electron charges per 0.32nm







Double stranded DNA
(persist. length ~50nm)

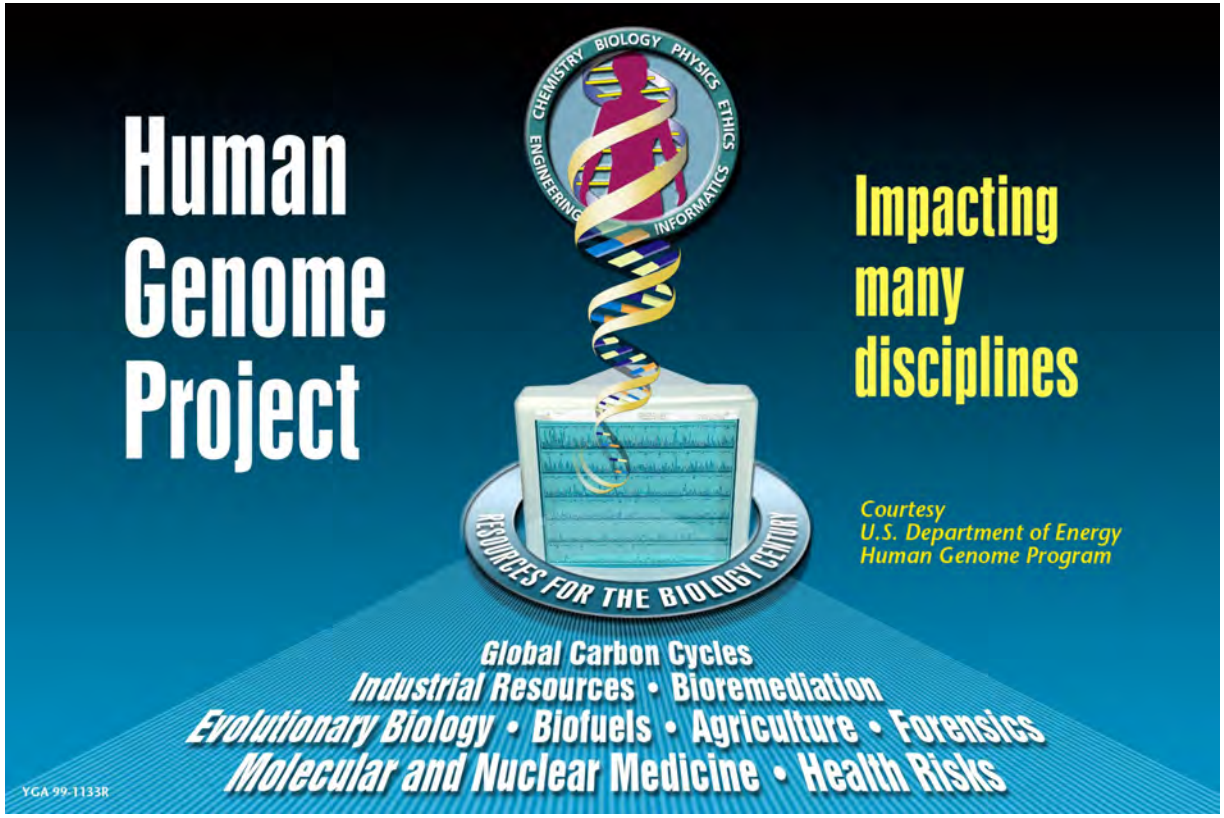
The sequence has direction:
5'-AAGCTGGTTCAG-3'

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

GTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGCGGCAGGTGTTGAAAG
TCGATGTAGTTCGTAGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGT
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GCTACGATCGATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAA
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GTTCGTAGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGACAGGG
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CAGGTGTTGAAAGTCGATGTAGTTCGTAGGTCAGTTGATGTCGATGTGAAAT
GCTGATGCTAGTGGACAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGT
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GTTCGTAGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGACAGGG
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*3*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%)

CAGGTGTTGAAAGTCGATGTAGTTCGTAGGTCAGTTGATGTCGATGTGATC
GATGTAGTTCGTAGGTCAGTTGATGTCGATGTGAAATGCTGATGCTAGTGGA
CAGGGTGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTATTGT
GCTACGATCGATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAA
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TGACTAGTGAATCGATGCTAGCCTAGCTAGTCAGTGGTGCTAGCTACGATC
GATTTCAGGCTGCTGTGGGTGCATAGCTGTGCTGTAAGTGAAGTGAGGCGG

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)

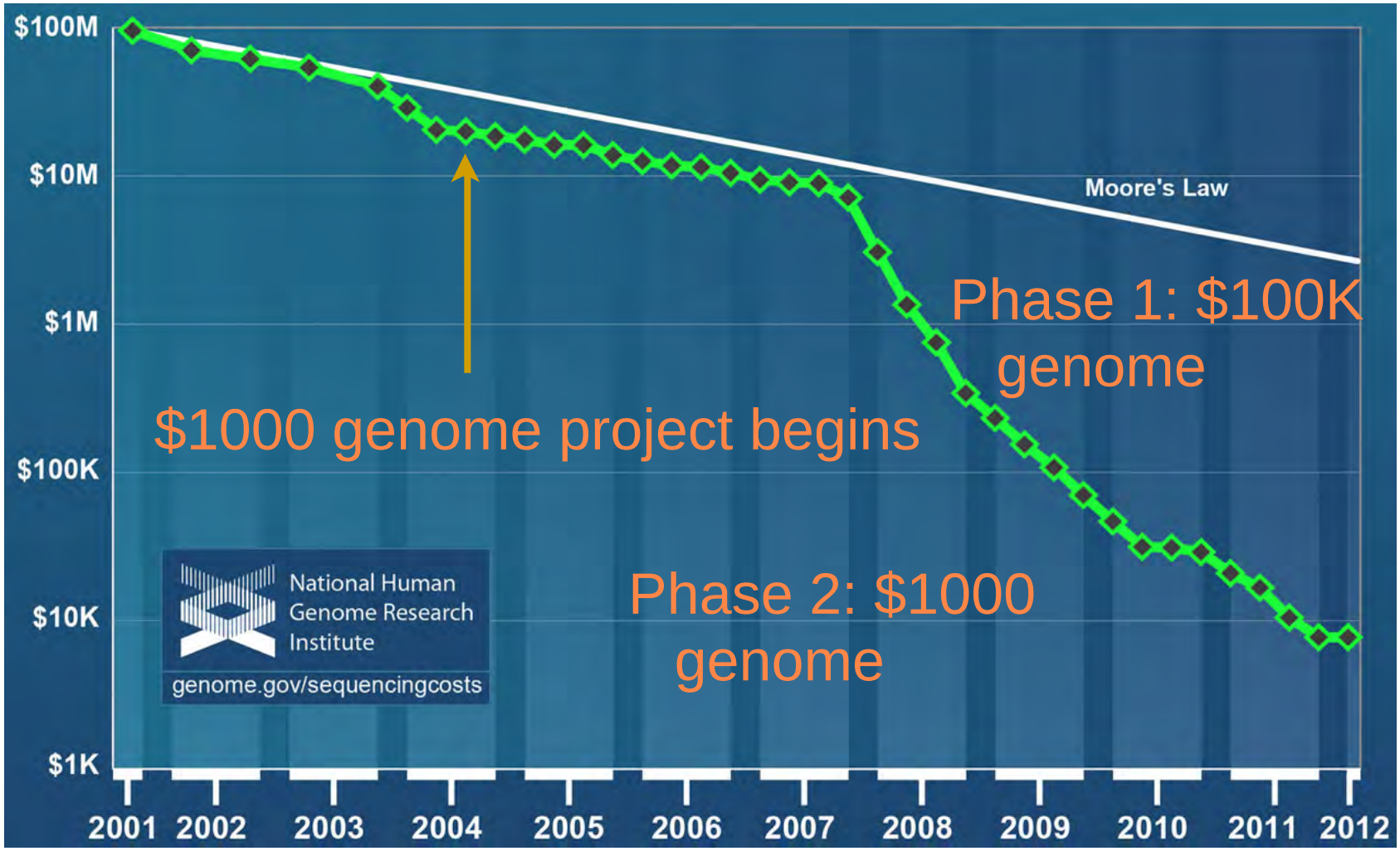
Personal pharmaceutics
(tailor drugs to an individual's genetic make-up)

Cancer: disease of DNA

Prenatal diagnostics

Single cell sequencing

Cost of sequencing a human genome
(logarithmic scale)



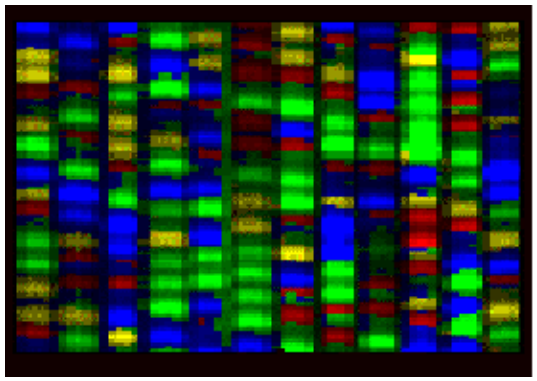
$1,000 genome was claimed to be achieved (Jan 2014)

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

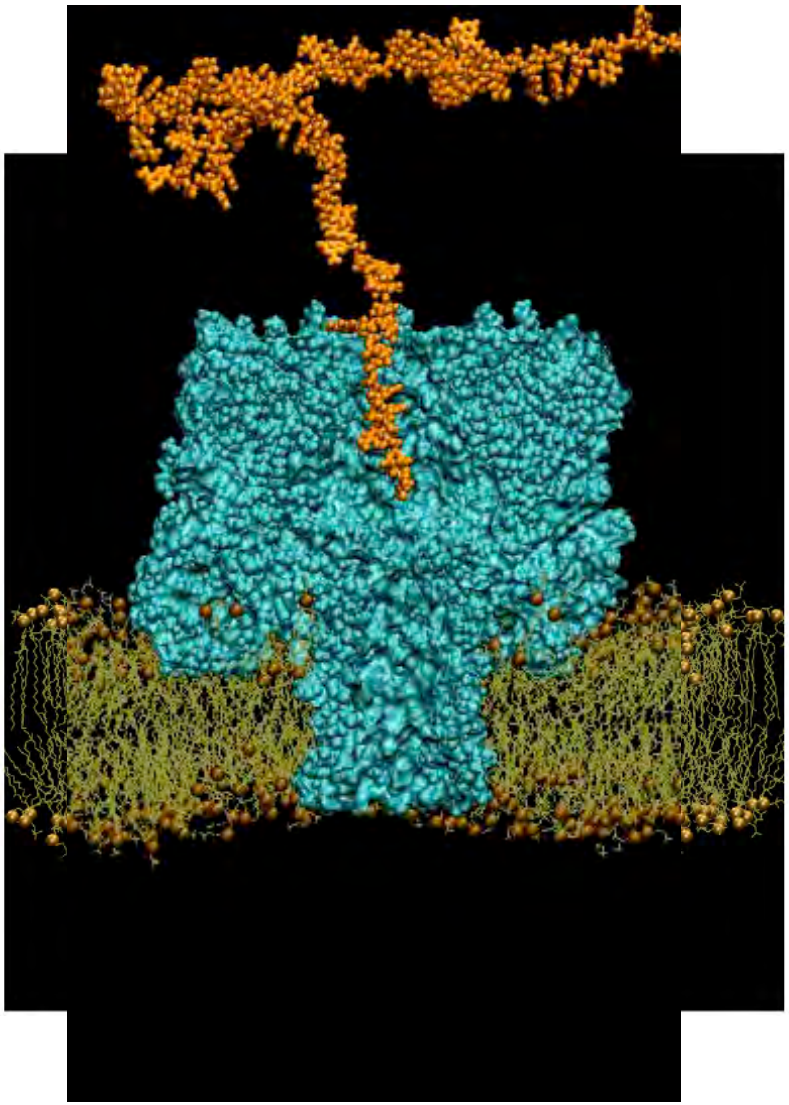
Extremely small pH meeter

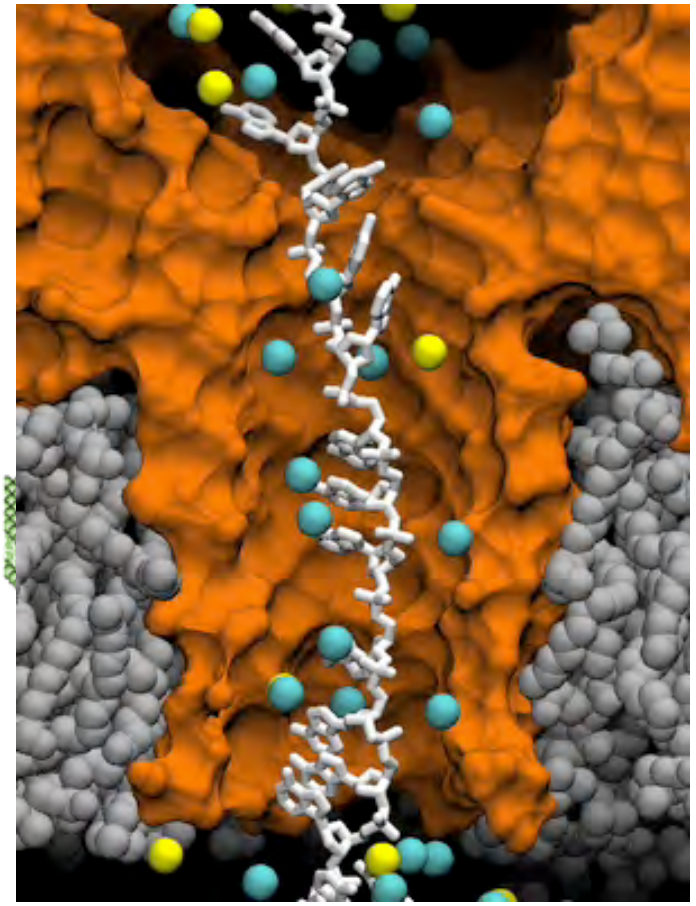
Multiplex optical readout

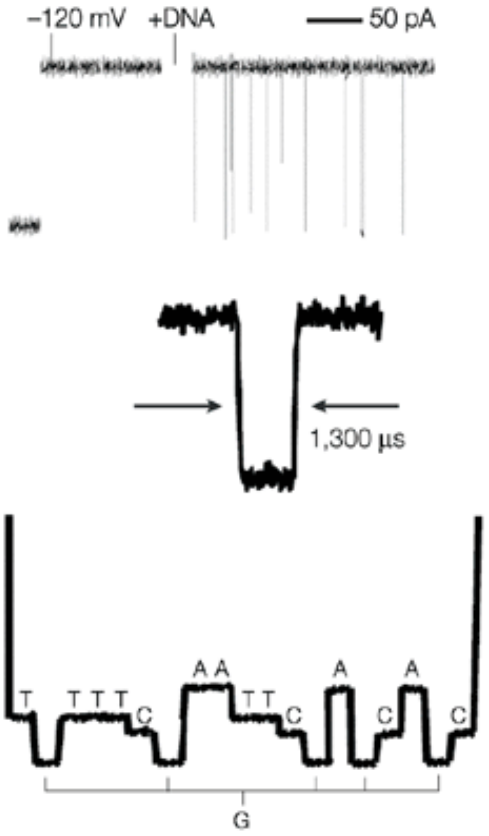
Problem: short reads, amplification, reagent and genome assembly costs

Single molecule optical readout
Problems: costs, accuracy, scalability

Nanopore sequencing of DNA



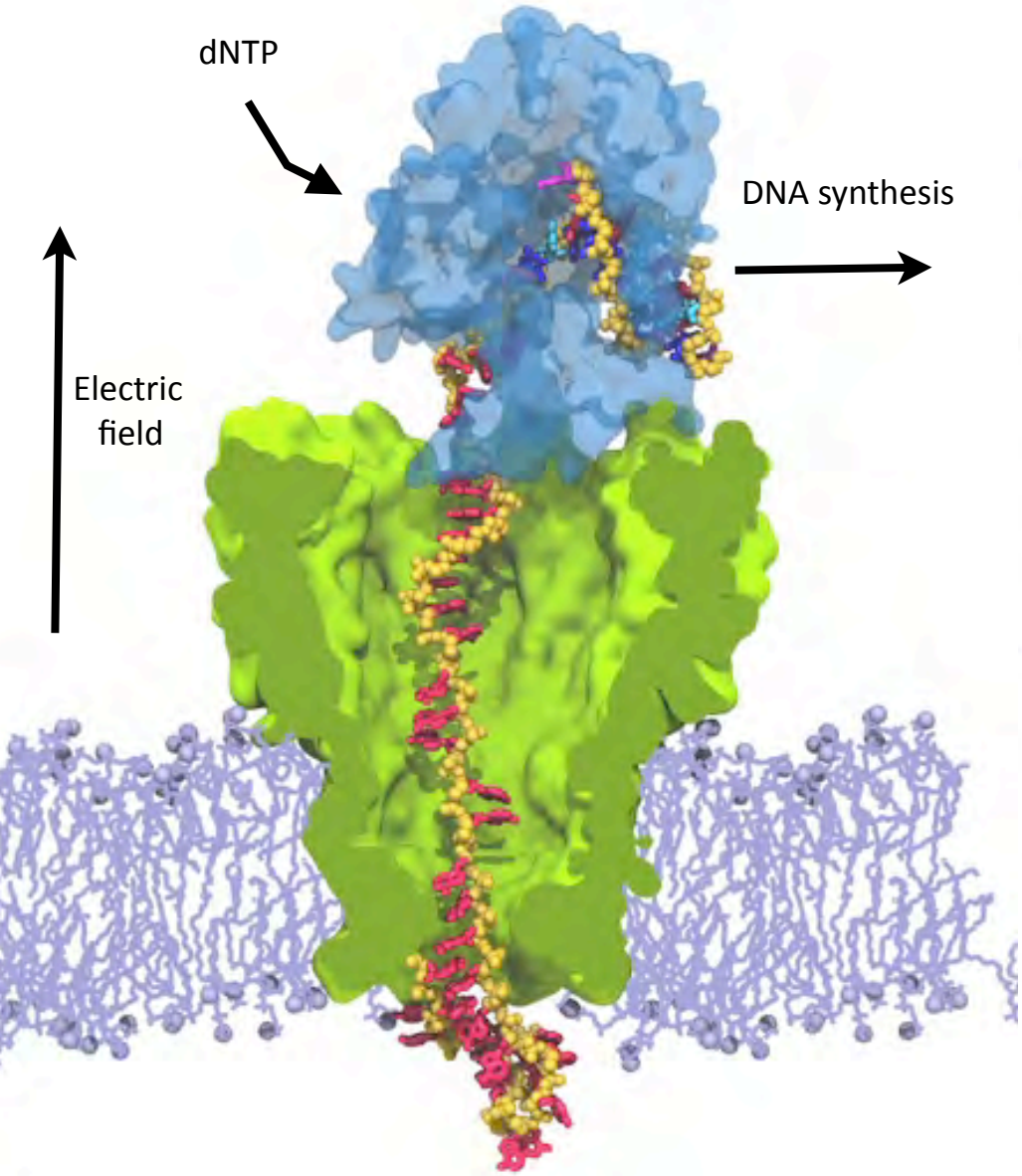




Nature Reviews Drug Discovery 1, 77-84 (January 2002)

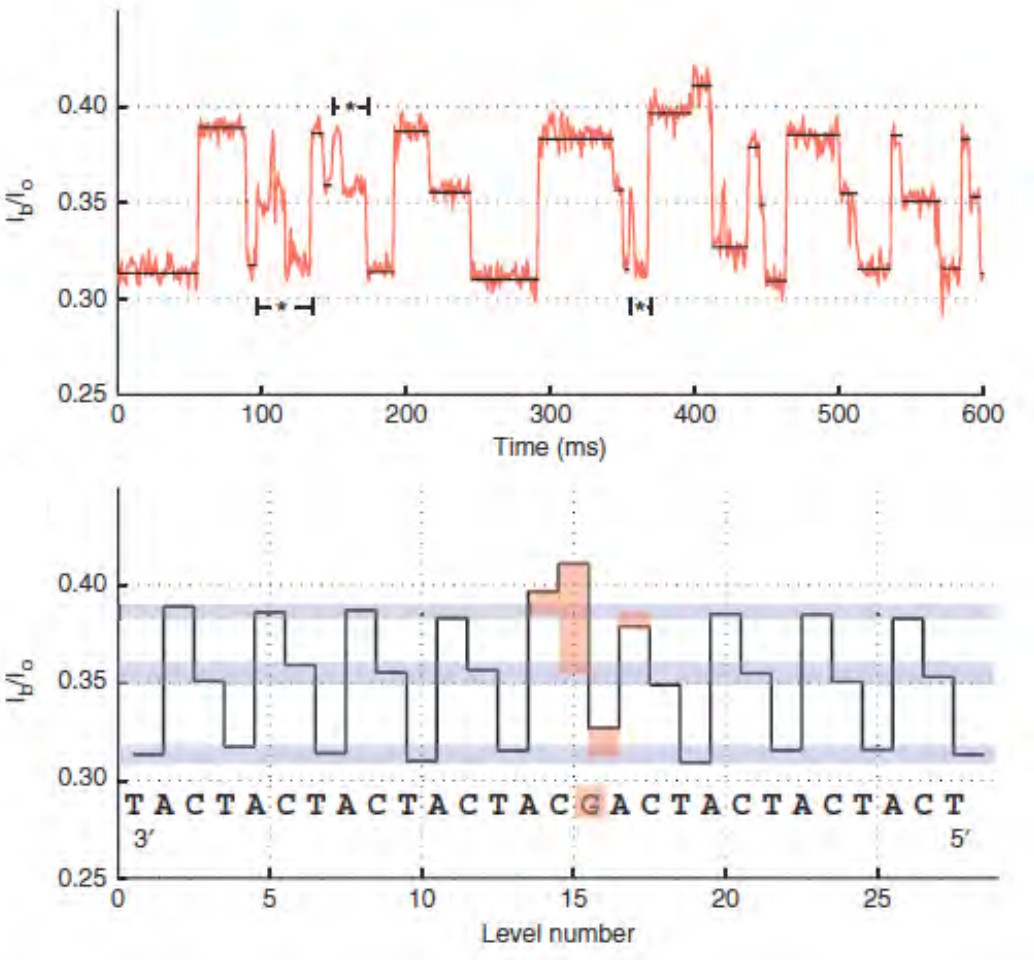
The ionic current blockade reveals the sequence of the confined nucleotides

Sequencing DNA using MspA



MD simulation ssDNA- DNA polymeraze complex

Experimentally measured ionic current blockades



Nature Biotech. 30: 349 - 353 (2012)

Oxford Nanopore Technologies

MiniION: ~800 parallel detection wells

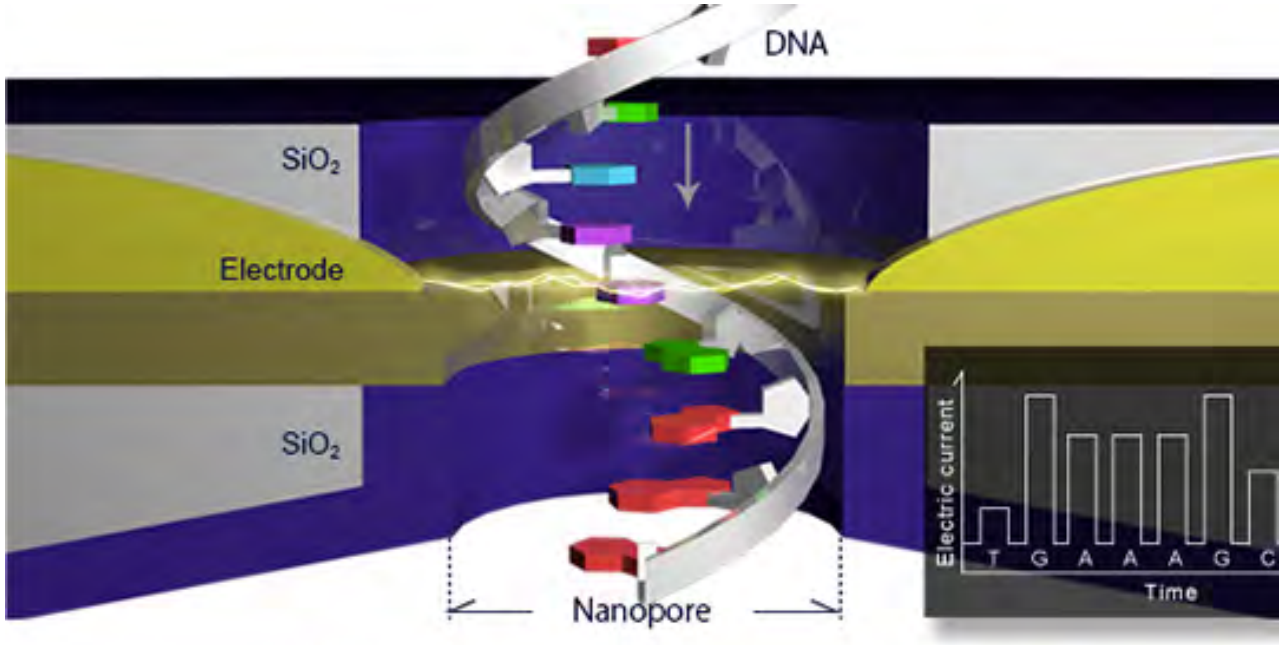
Read length: up to 100,000 nucleotides (2 strands of lambda phage genome)

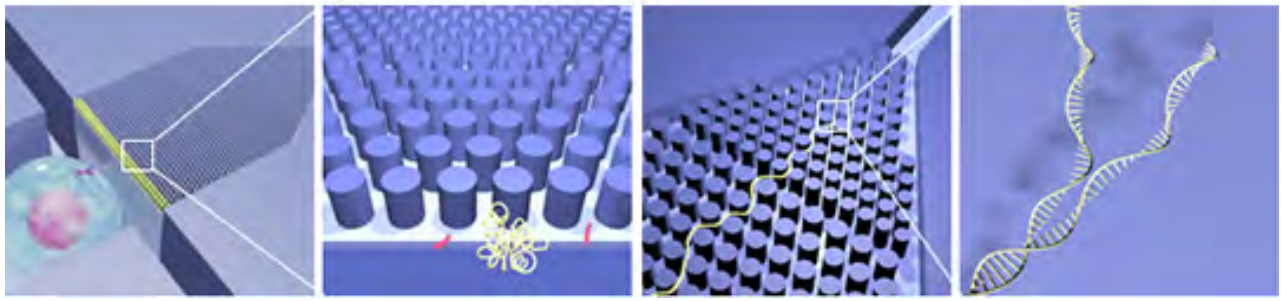
Unknown pore (hemolysin, MspA, other?)

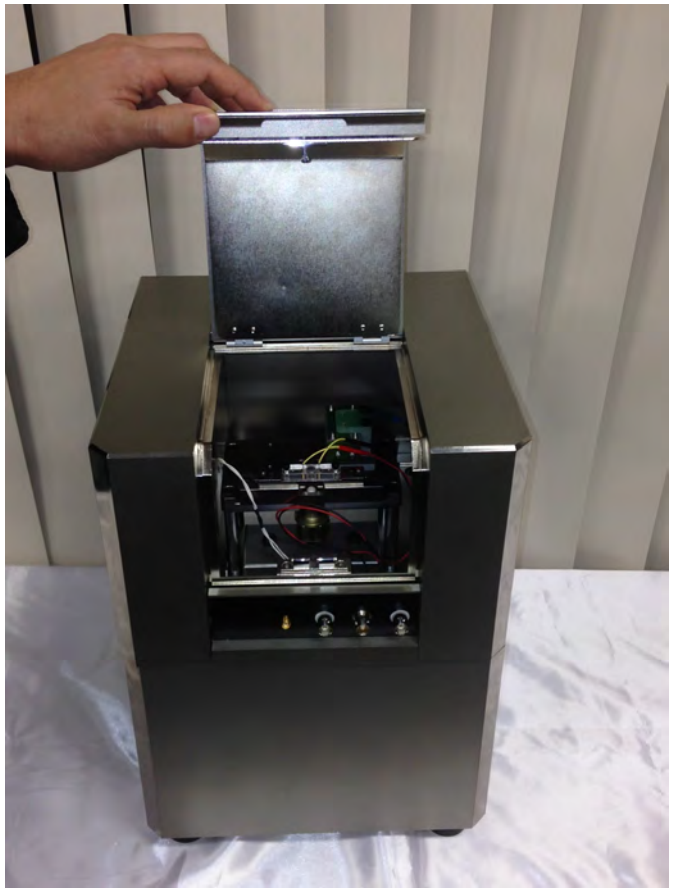
Unknown enzyme (better polymerase? Helicase?)

Accuracy: 96%

Nanopore sequencing: state of the art





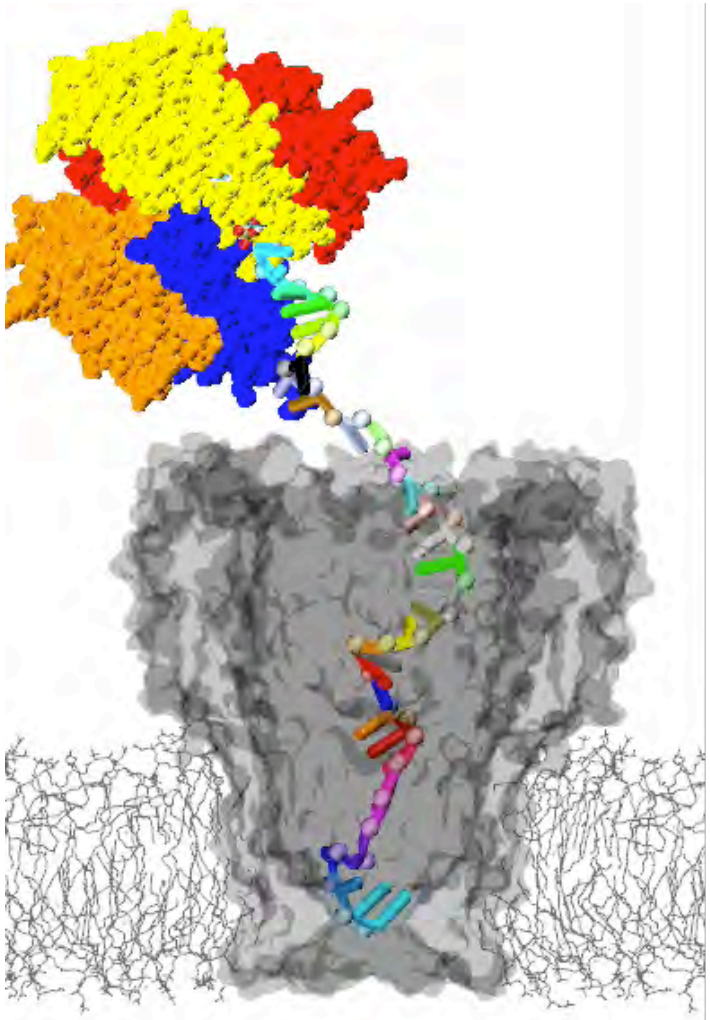


Quantum biosystems

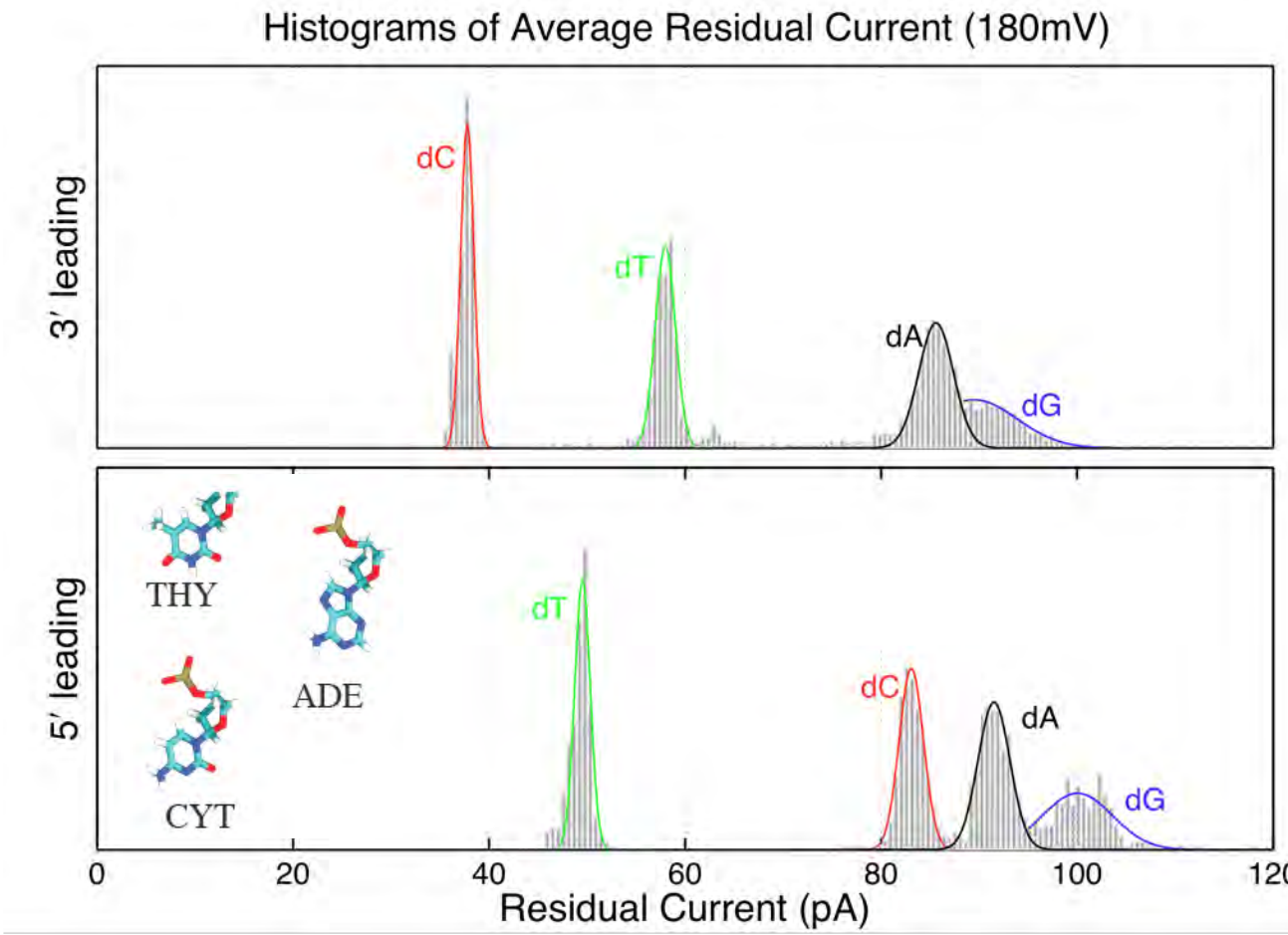
... Genia, Nabsys ...
... Illumina, Roche ...

... 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

RCSB PDB PROTEIN DATA BANK

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An Information Portal to Biological Macromolecular Structures

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Quick Tips :

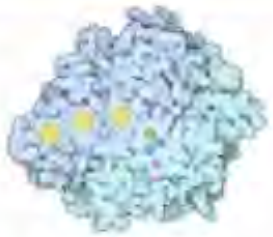
Try the Web Services API

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.

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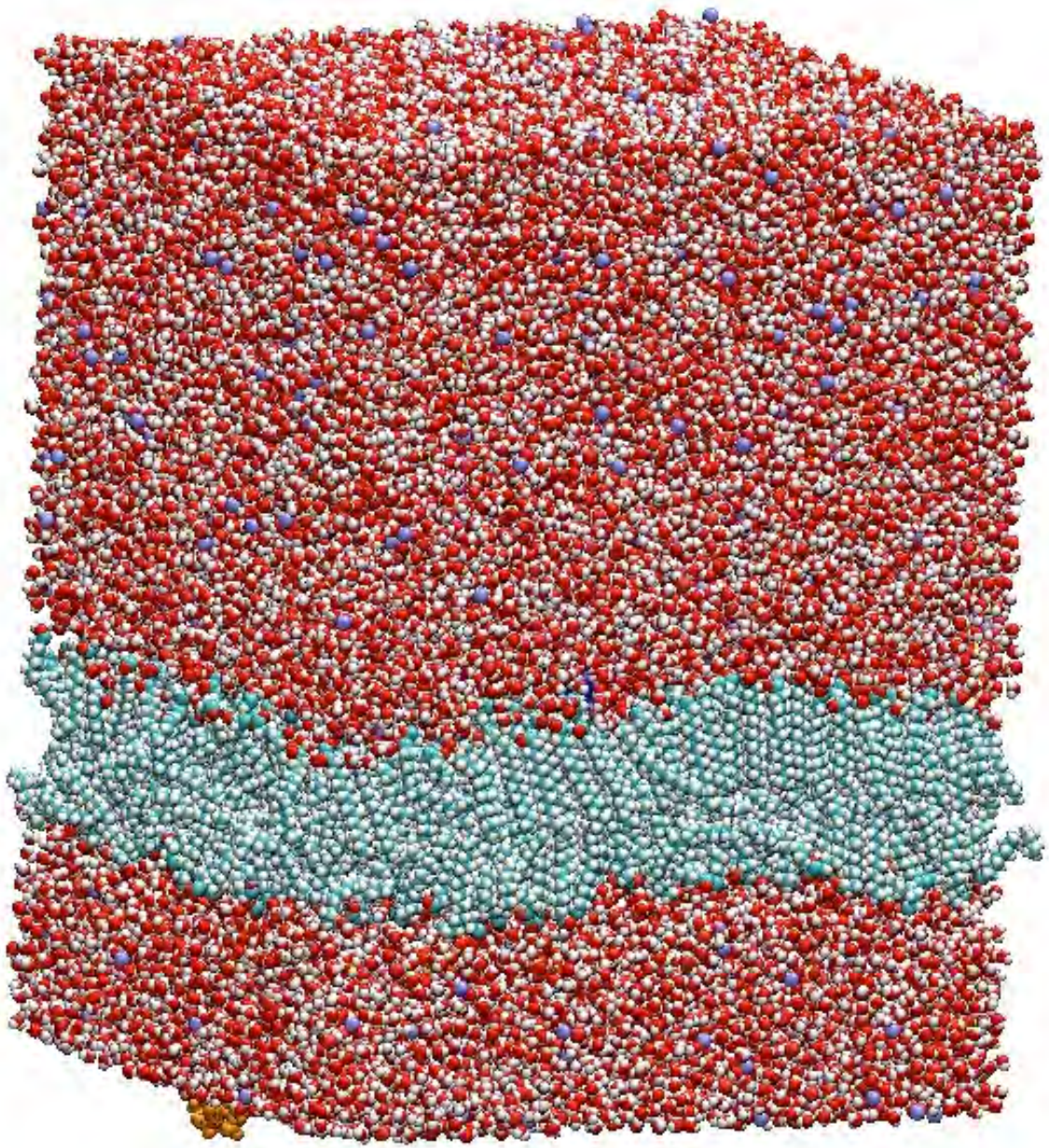
31-March-2009

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

The team from

Setting up a simulation is like cooking



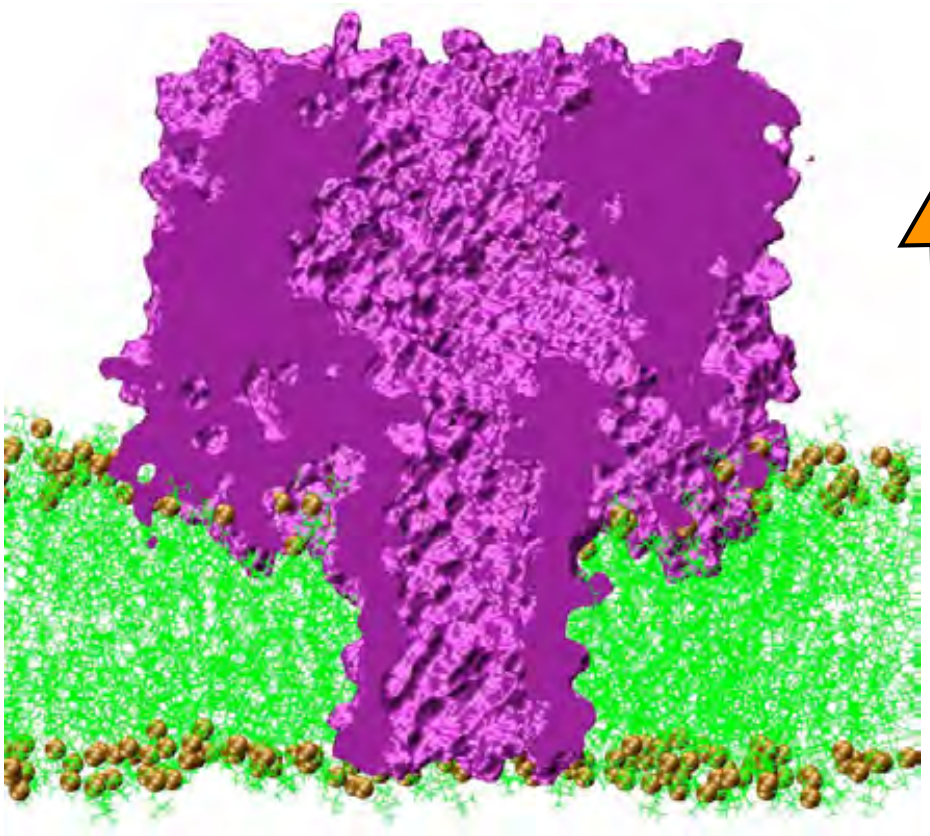
Components

- protein
- DNA
- lipid
- ions
- water

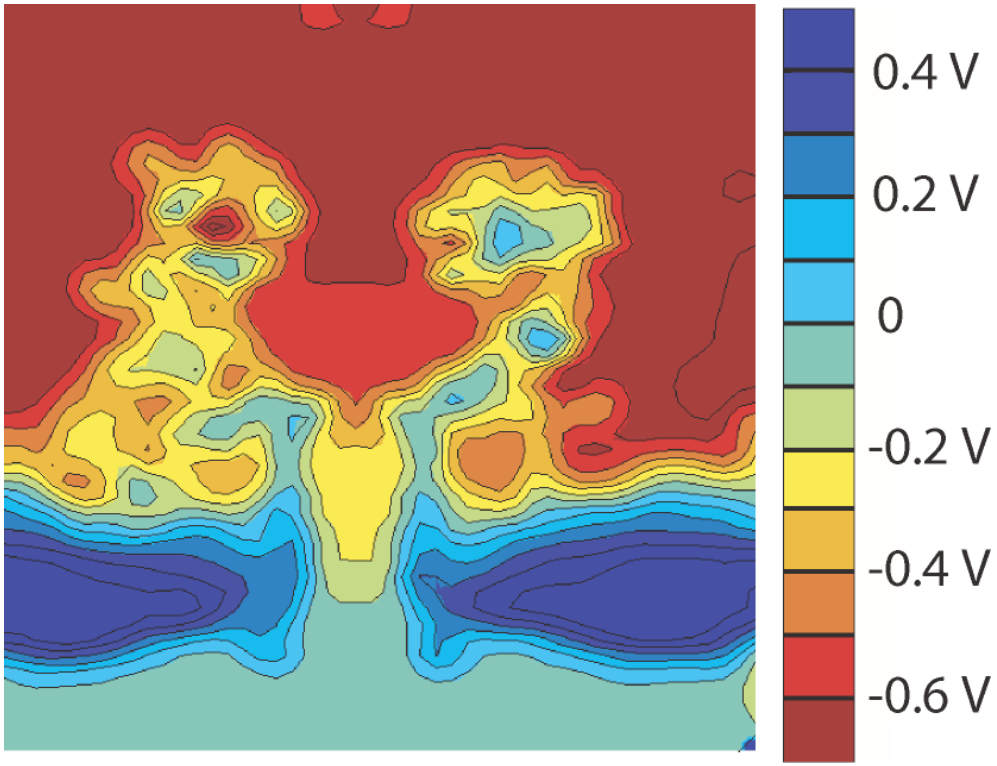
F = ma @ 300 K

Time step = 1 fs

Computing conductance of α-hemolysin with molecular dynamics



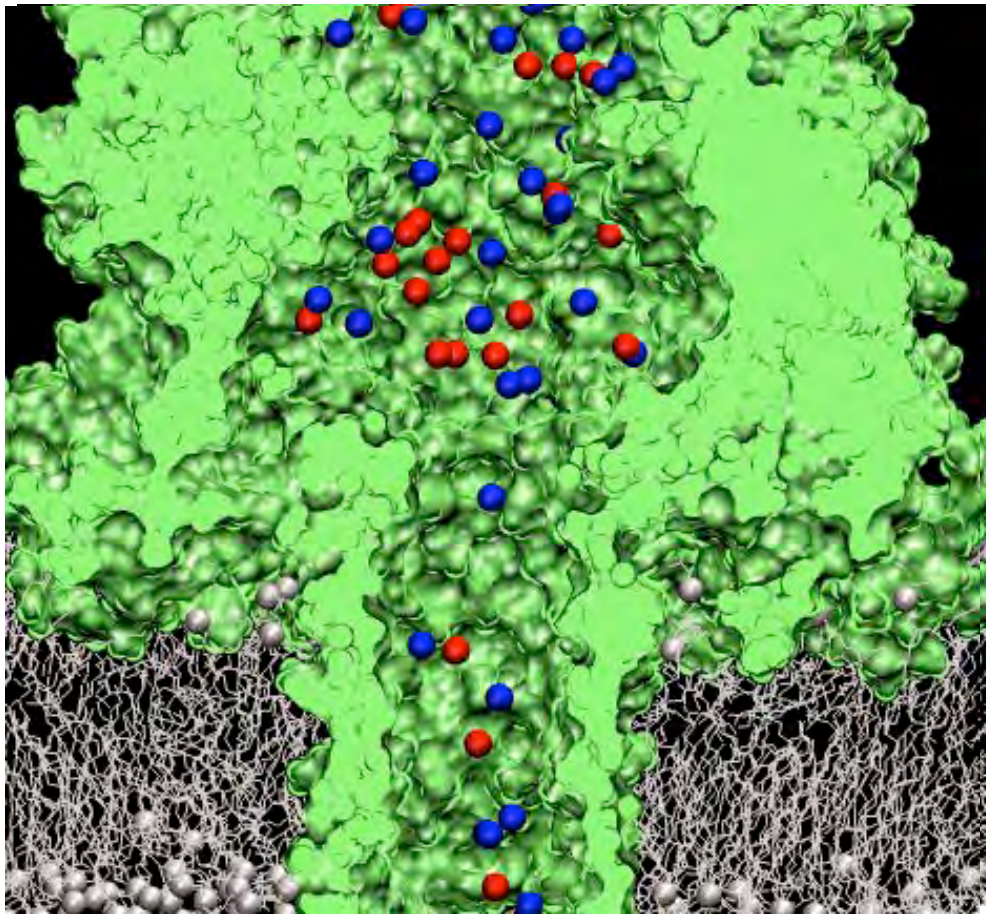
Protein + lipid bilayer membrane + 1M water solution of KCl = ~300,000 atoms

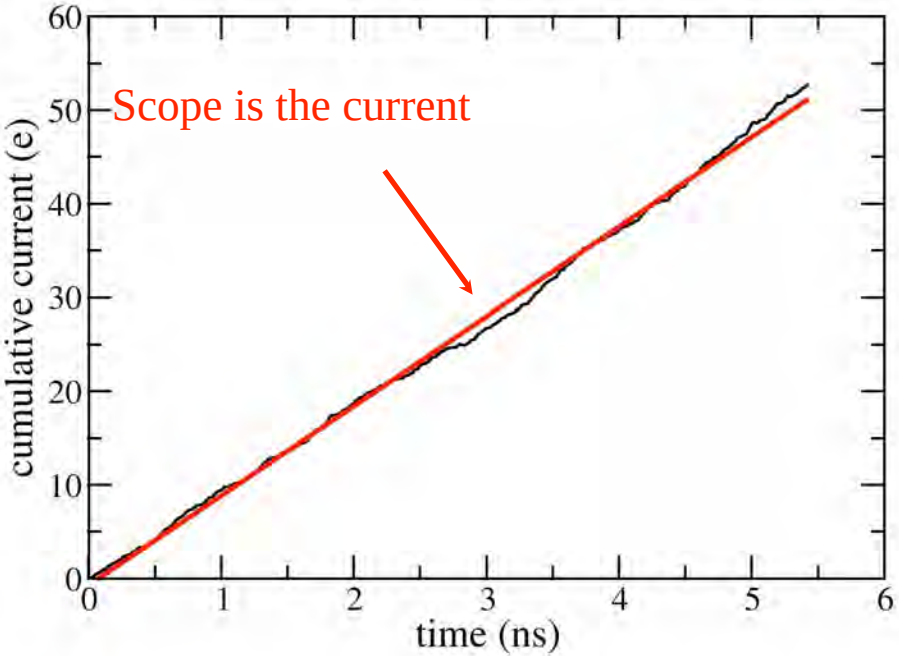


Average electrostatic potential map

Current-voltage curve of α-hemolysin

Biophys. J. 88:3745 (2005)



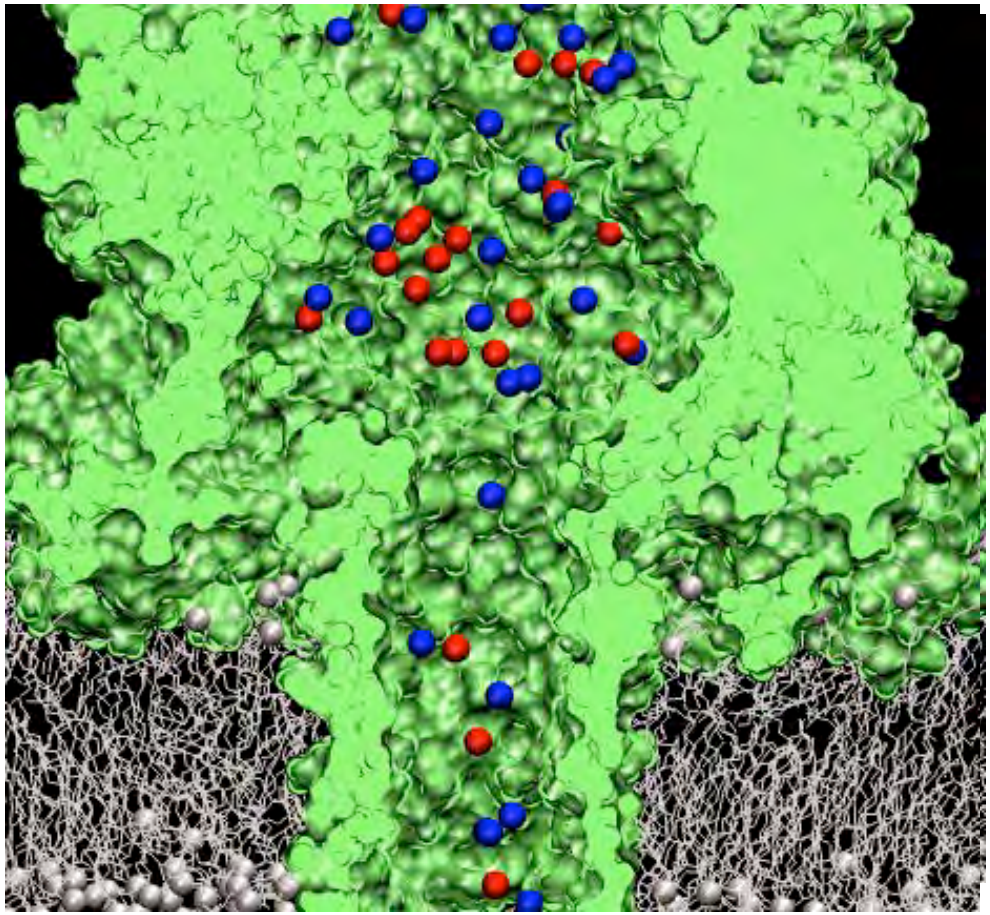


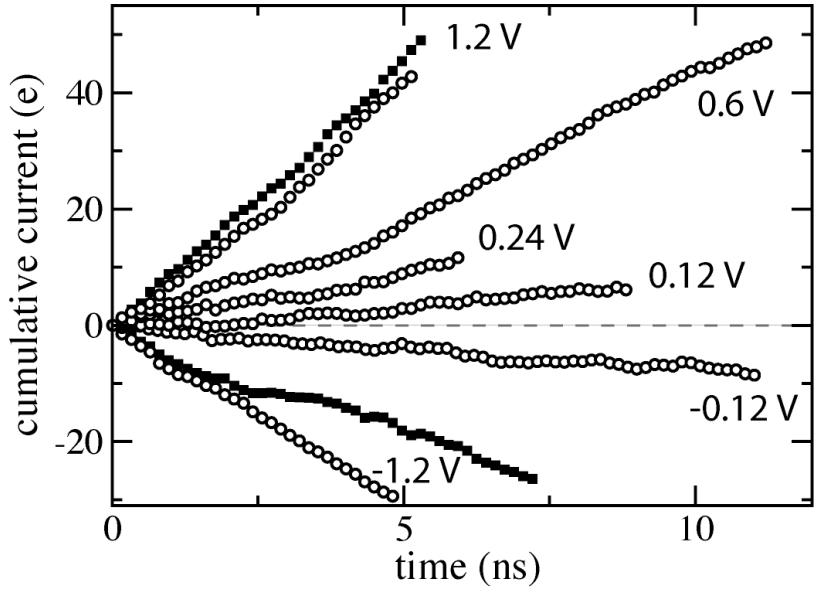
$$I(t) = \frac{1}{\Delta t L_z} \sum_{i=1}^{N} q_i (z_i(t + \Delta t) - z_i(t))$$

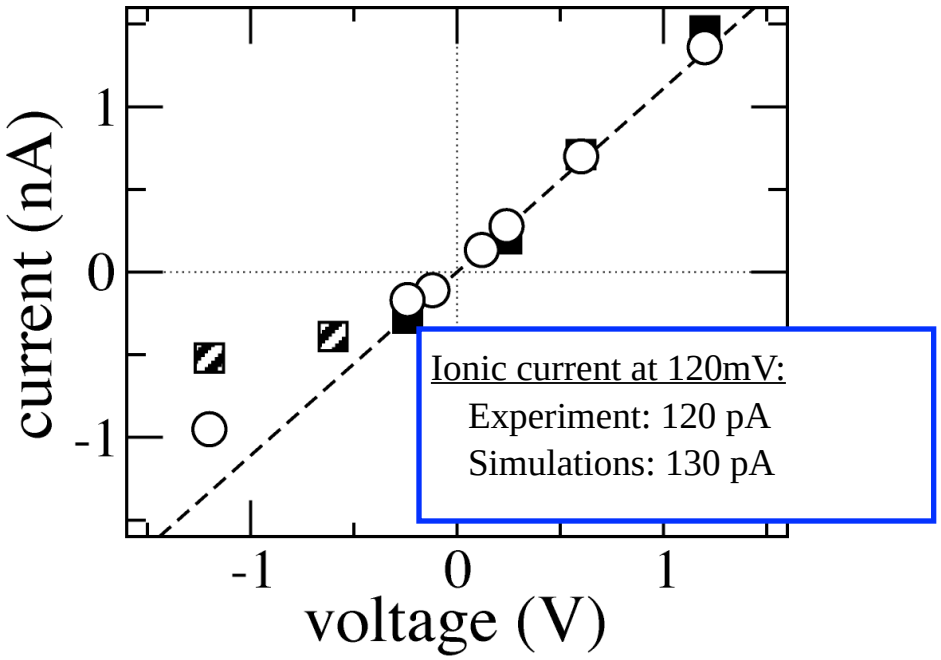
Instantaneous current

Current-voltage curve of α-hemolysin

Biophys. J. 88:3745 (2005)



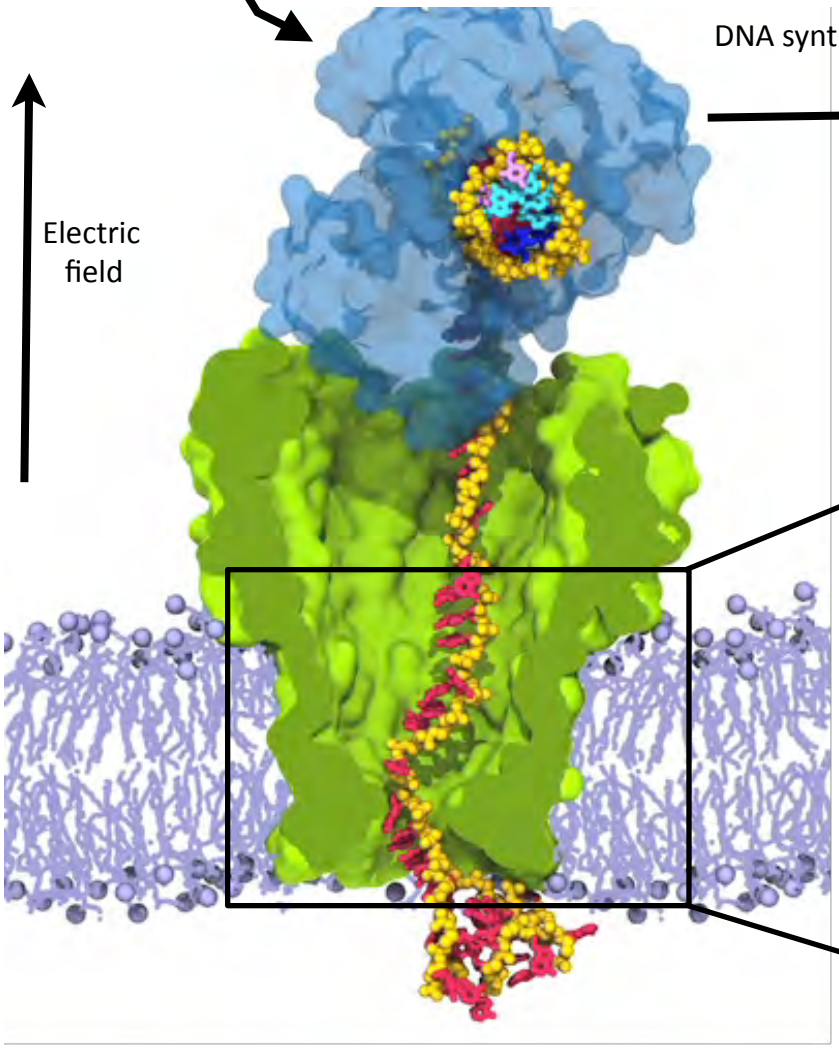


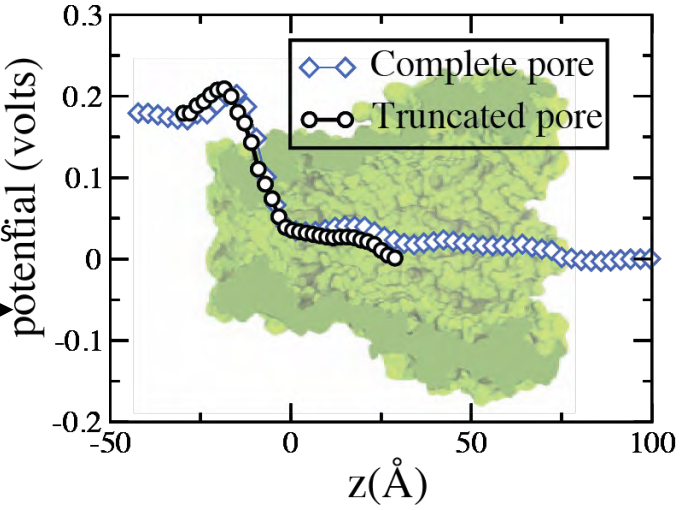


$$I(t) = \frac{1}{\Delta t L_z} \sum_{i=1}^{N} q_i (z_i(t + \Delta t) - z_i(t))$$

Instantaneous current

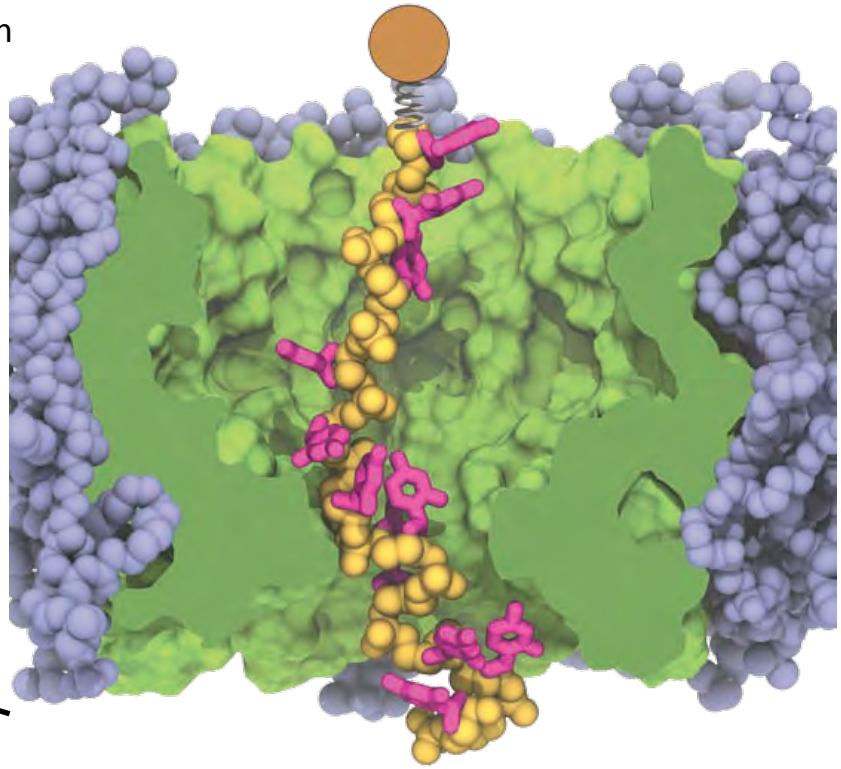
MD simulations of current blockades in MspA





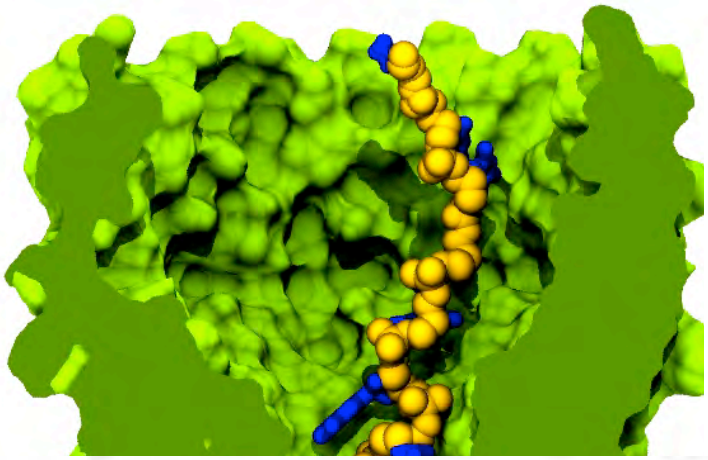
DE Shaw's Anton

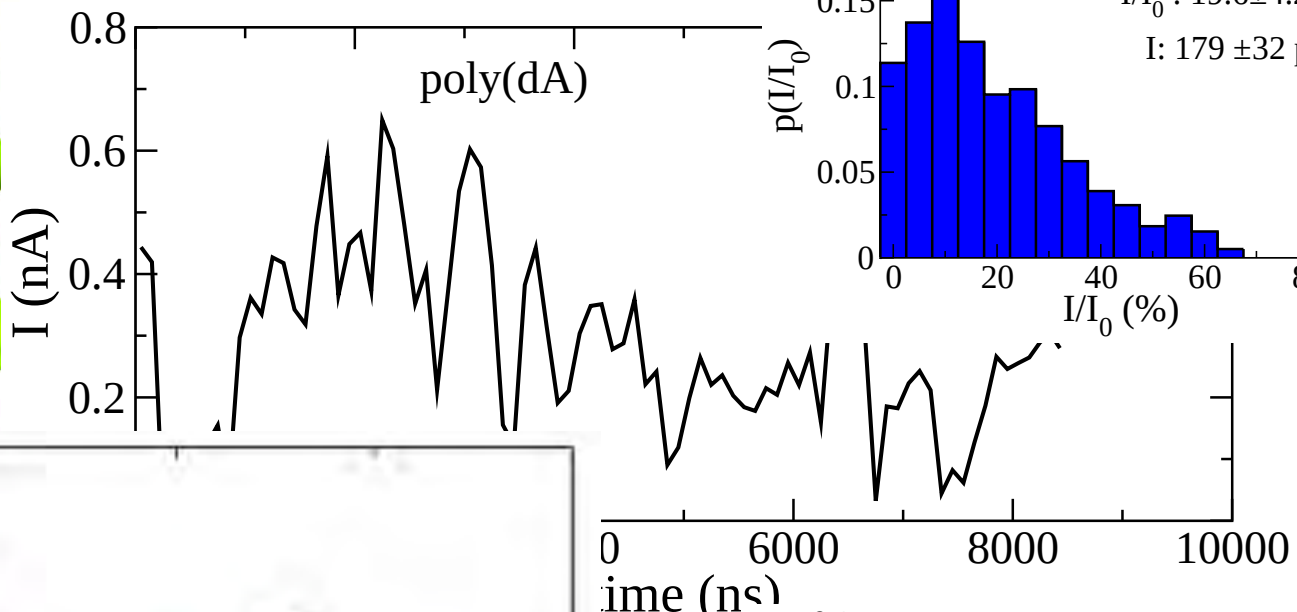
Swati Bhattacharya



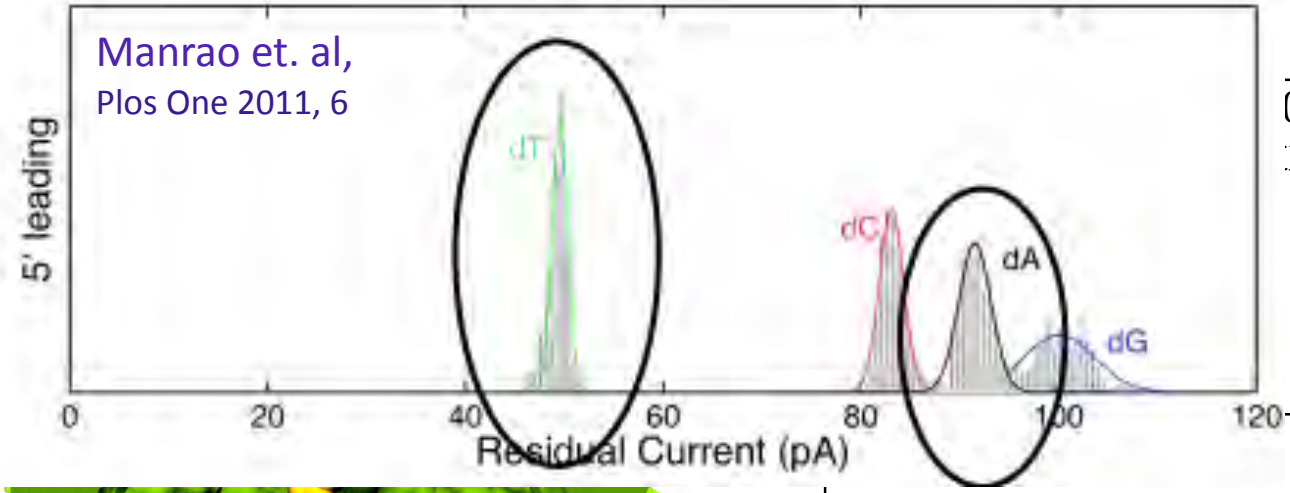
MD simulation ssDNA- DNA polymerase complex
(350,000 atoms, 150 ns)

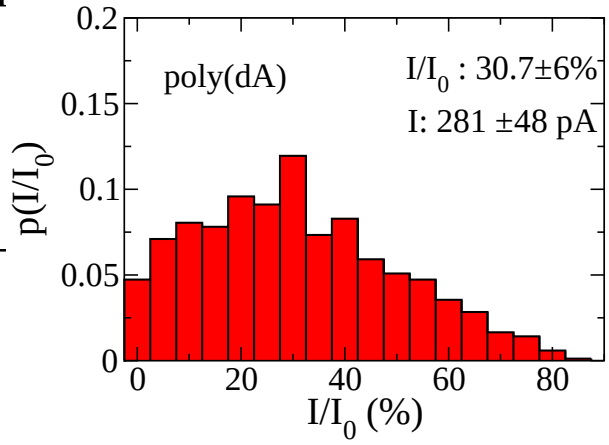
Reduced system (28,000 atoms)

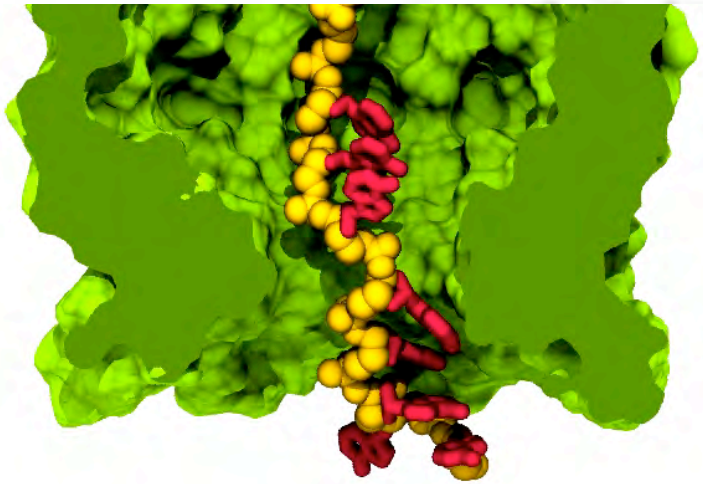


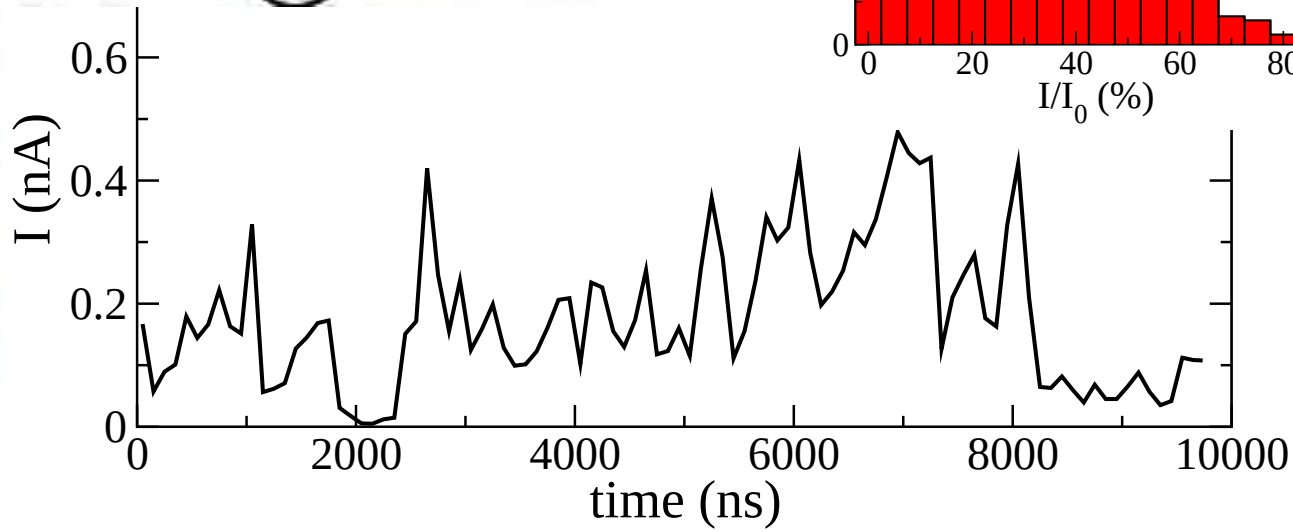

poly(dA)
I (nA)
0.8
0.6
0.4
0.2
0
6000
8000
10000
ime (ns)

poly(dT)
I/I0 : 19.6±4.2%
I: 179 ±32 pA
p(I/I0)
0.2
0.15
0.1
0.05
0
0
20
40
60
80
I/I0 (%)

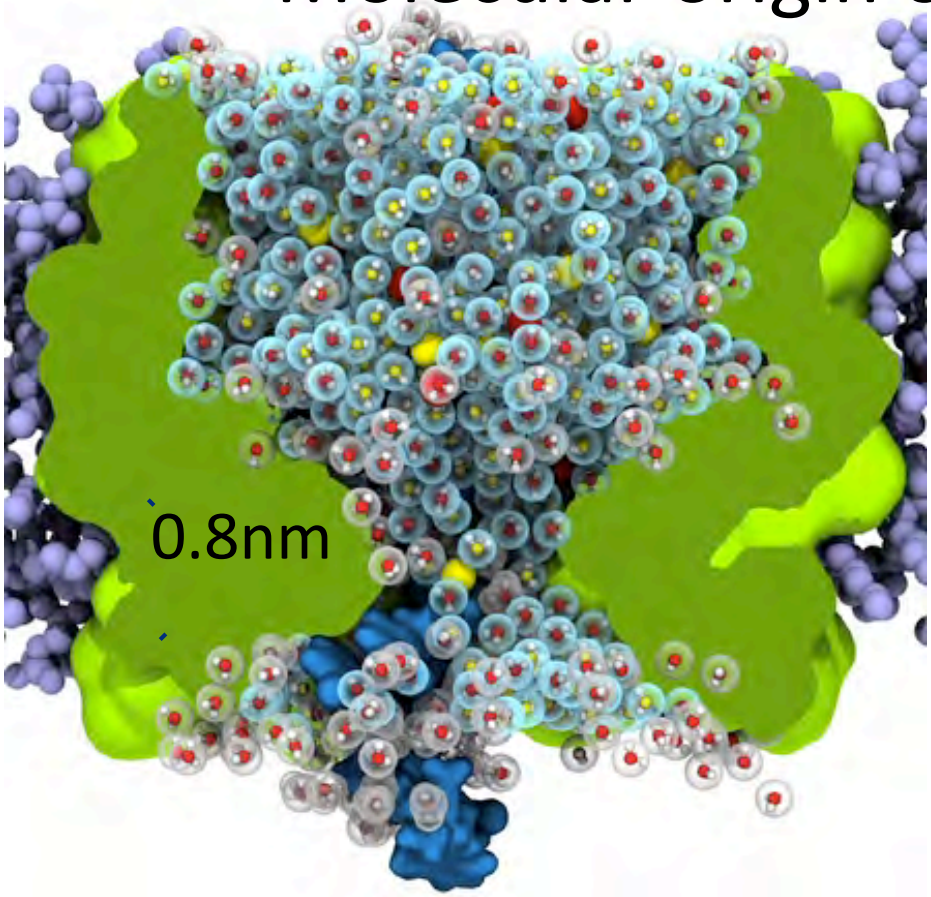

Manrao et. al,
Plos One 2011, 6
5' leading
dT
dC
dA
dG
0
20
40
60
80
100
120
Residual Current (pA)


poly(dA)
I/I0 : 30.7±6%
I: 281 ±48 pA
p(I/I0)
0.2
0.15
0.1
0.05
0
0
20
40
60
80
I/I0 (%)



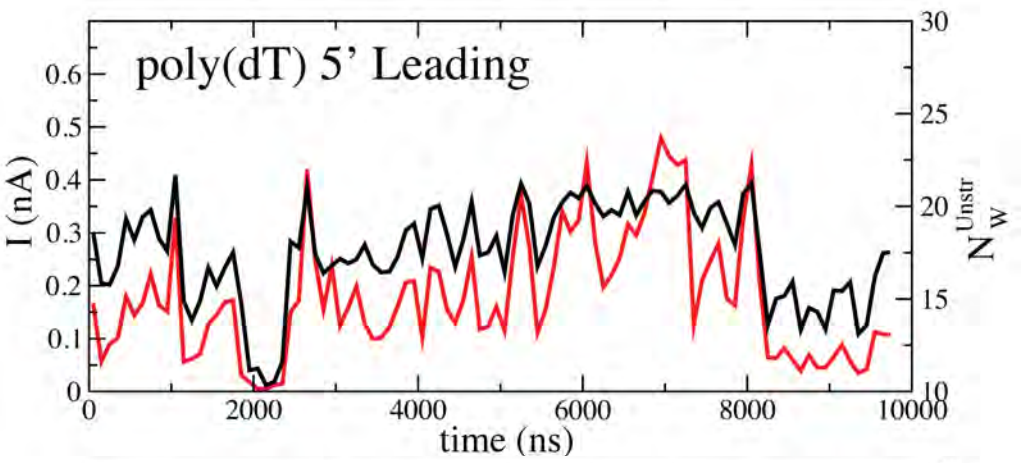

I (nA)
0.6
0.4
0.2
0
0
2000
4000
6000
8000
10000
time (ns)

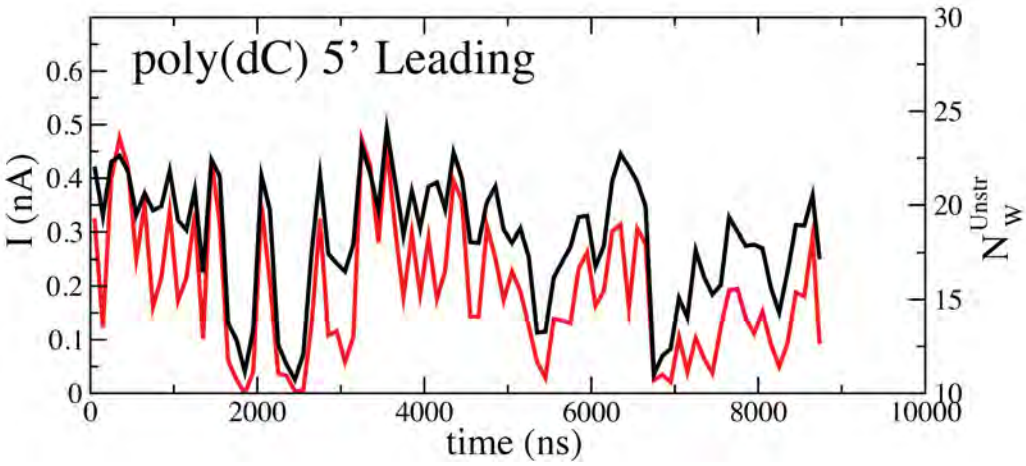
Molecular origin of the current blockade

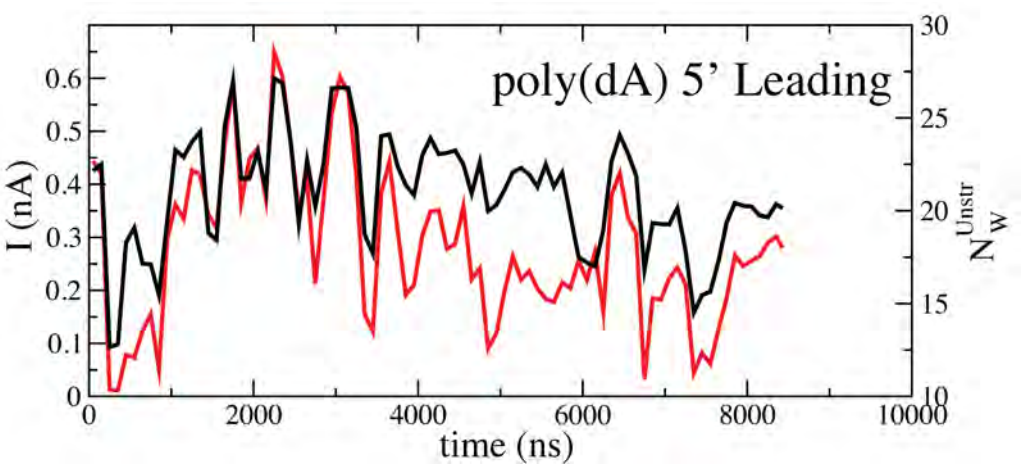


Unstructured (bulk-like) water: more than 2.5A away from protein or DNA

Correlation between Current and Water:
Pearson Coefficient
Poly(dT): 0.86
Poly(dC): 0.90
Poly(dA): 0.85



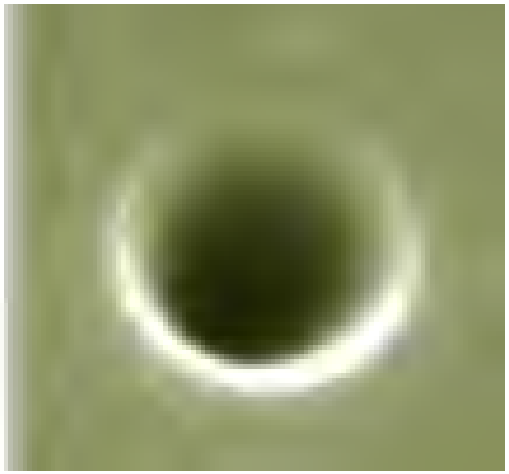




Nanopore efforts around the world

Polymer

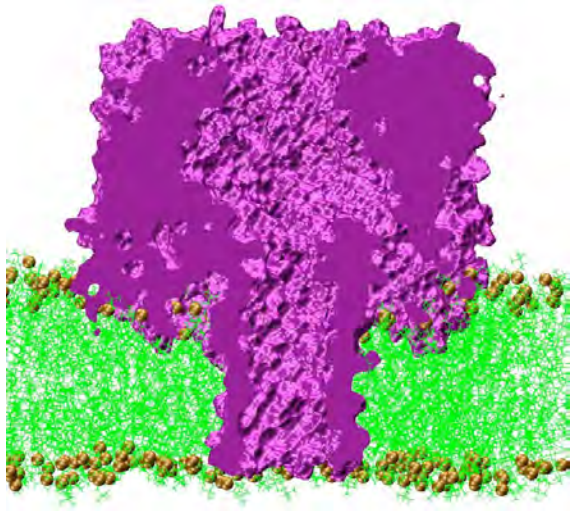
Darmstadt,UND,
UC Irvine, UF,
…



Ion track echted
Thick layers (~µm)
Robust
Fixed charge
Unknown dimensions
Surface modifications
High speed, low field
Indi address difficult

Proteins

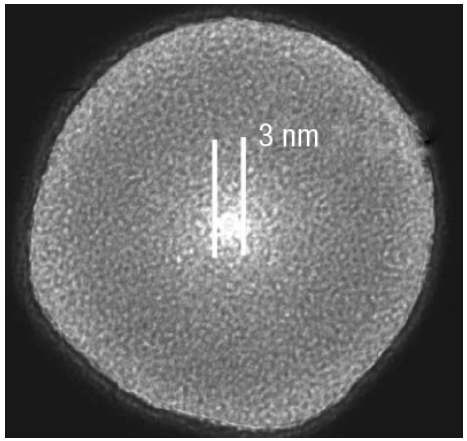
NIST, UCSC, Harvard, UBC,
Oxford, Evry, BU, U Wash.,
Syracuse, …



Self-assembled
Lipid membranes (~4nm)
Fragile
Fixed charge
Atomically precise
Can be engineered
Low speed, high field
Indi address difficult

Nitride/oxide

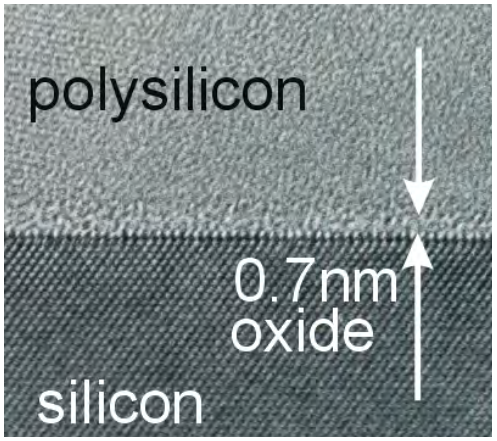
Harvard, UBC, BU,
UIUC, Delft, Arkansas,
Brown, UNC, NE(!),
...



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

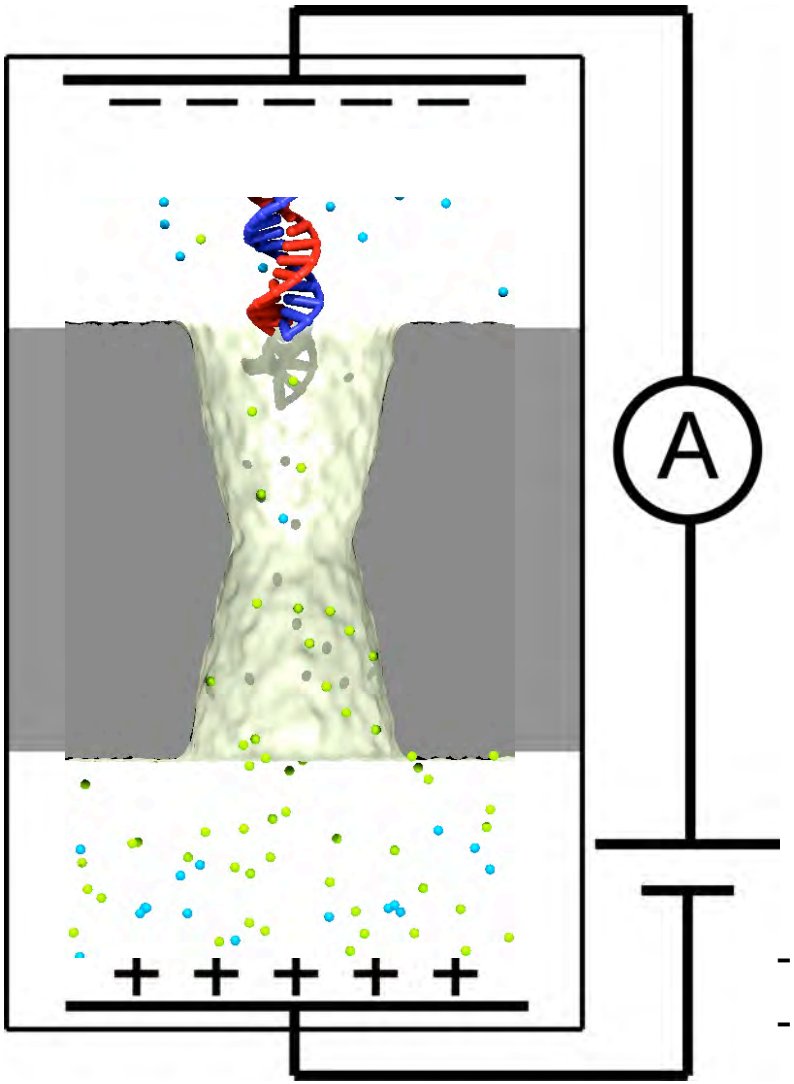
Active hetero structures

IBM, UIUC,
Lausanne,...

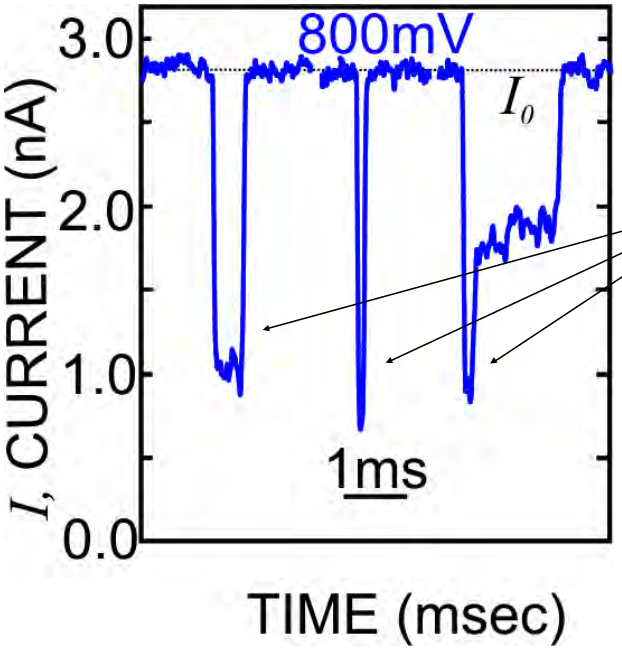


Fabricated
<1 nm
Robust
Field-effect adjustment
Sub-nm
Surface modifications
High speed, high field
Indi addressed

DNA transport through solid-state nanopore



Ionic current through pore measured



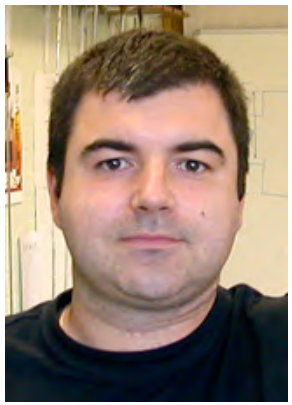
current transients associated with passage of dsDNA

- 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!

+

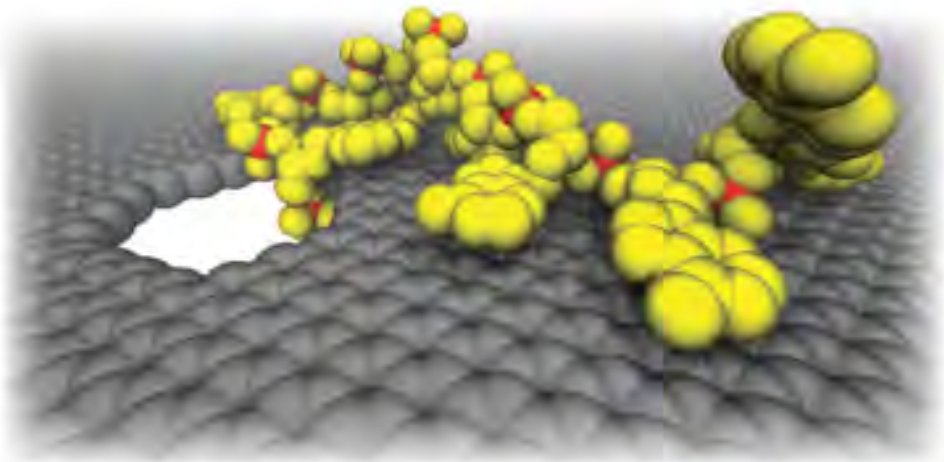
+

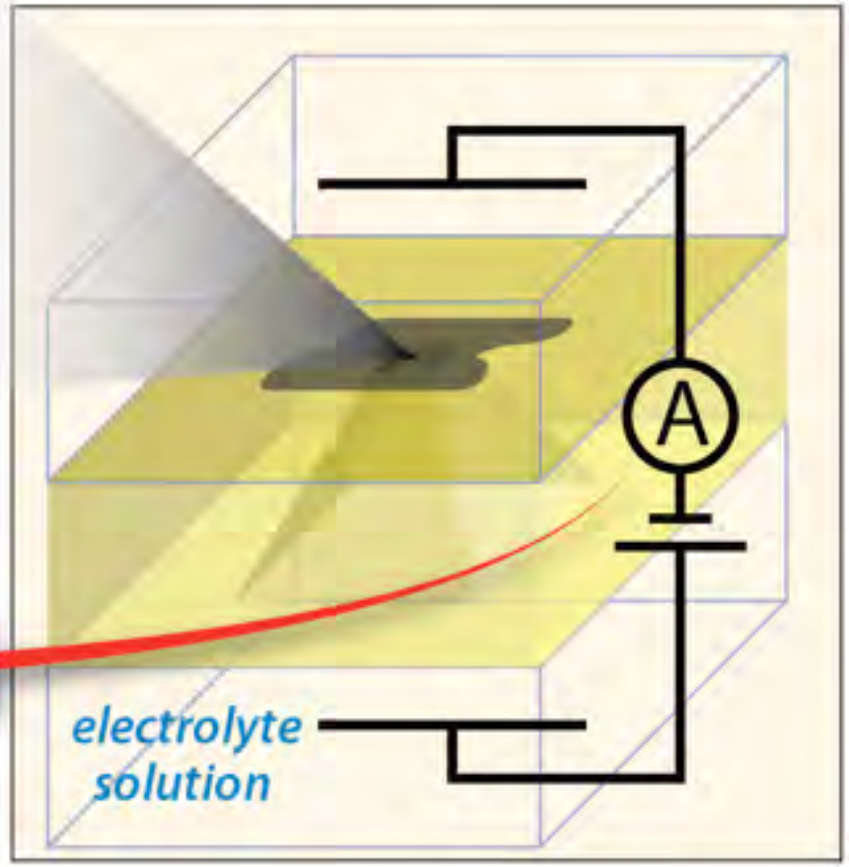


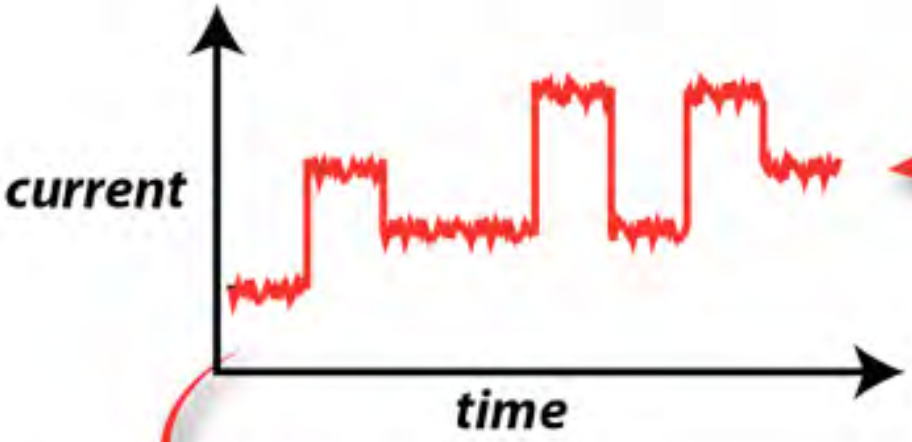
Andre Geim Konstantin Novoselov

=

Graphene Nanopores



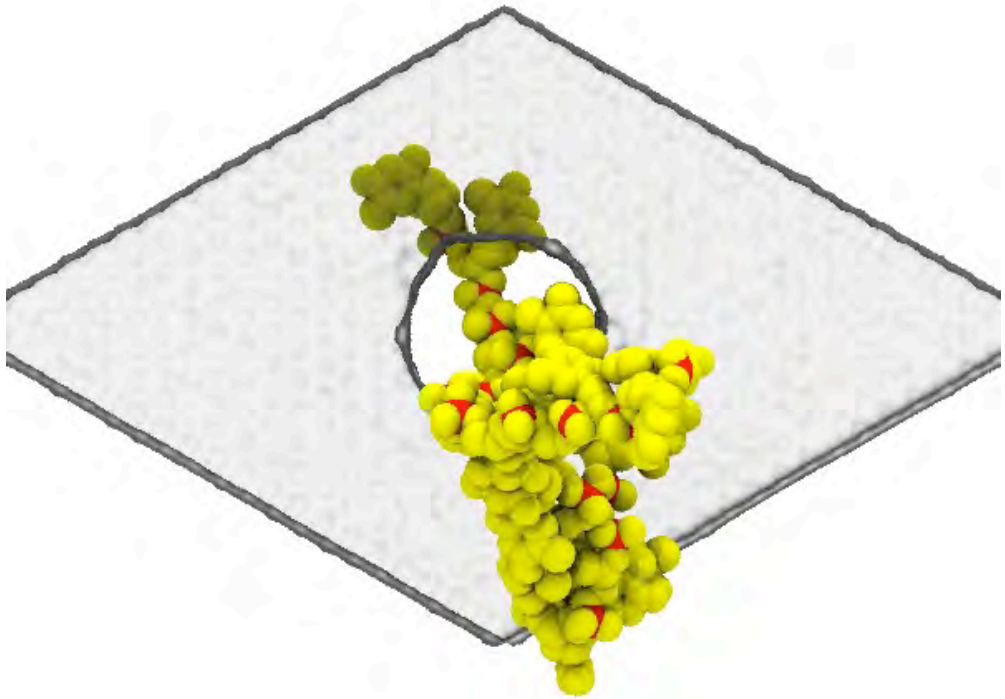


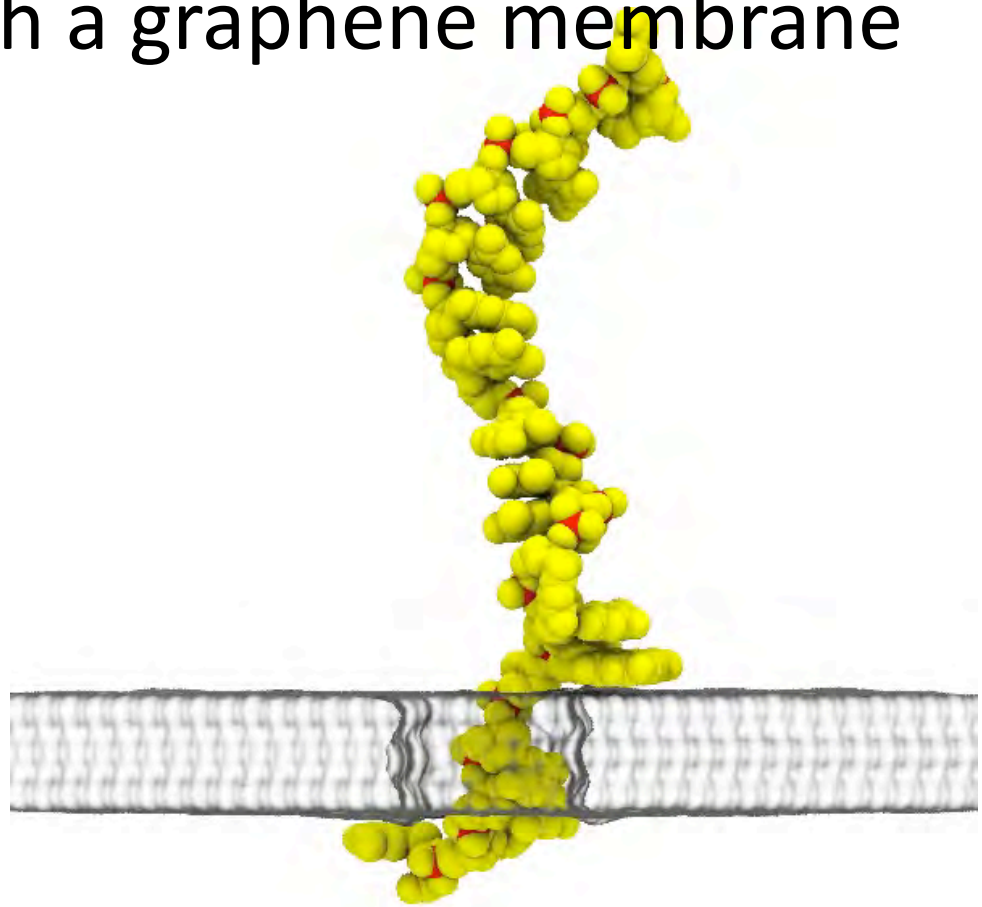


ACGGTGTCGATTA

Interaction of ssDNA with a graphene membrane

Top view



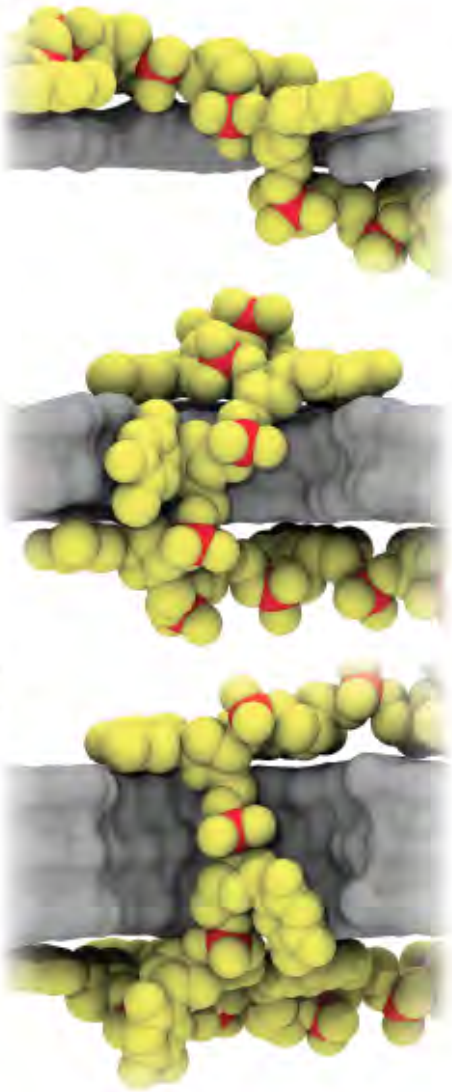


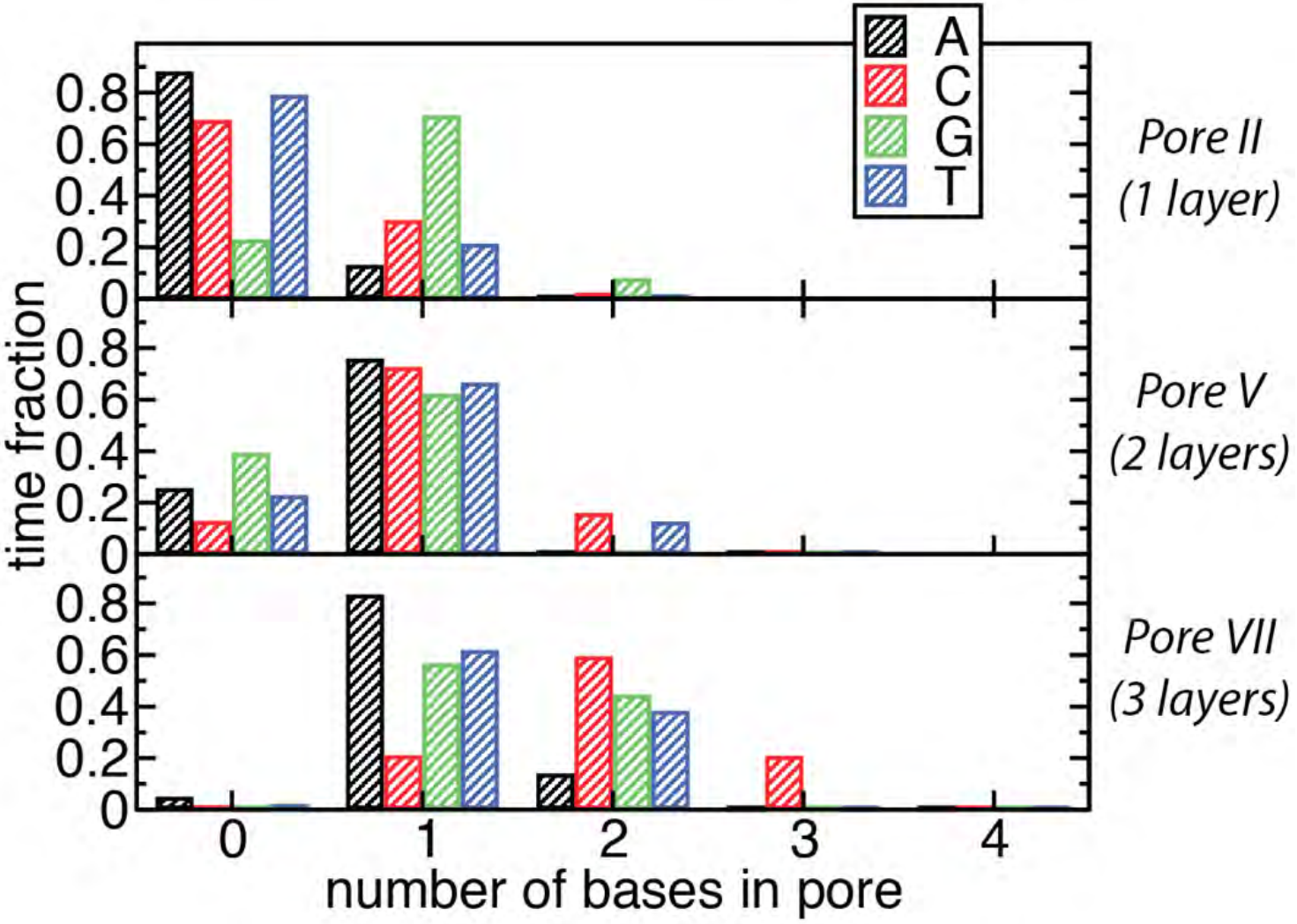
Side view

14-A diameter pore (surface-to surface);
3-layer graphite;
poly$(dT)_{20}$; 500 mV bias

Nano Letters 12:4117 (2012)

The thinner the better?

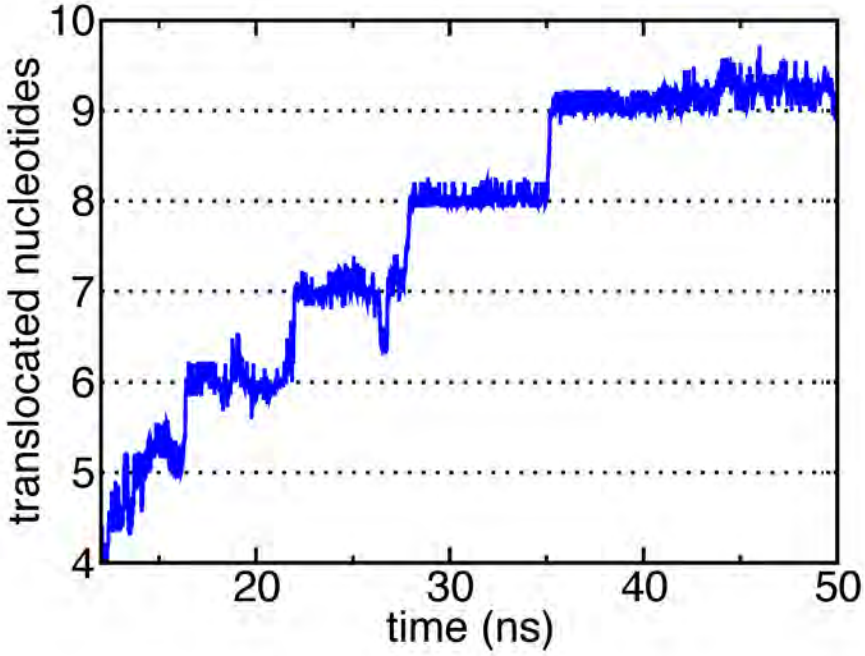




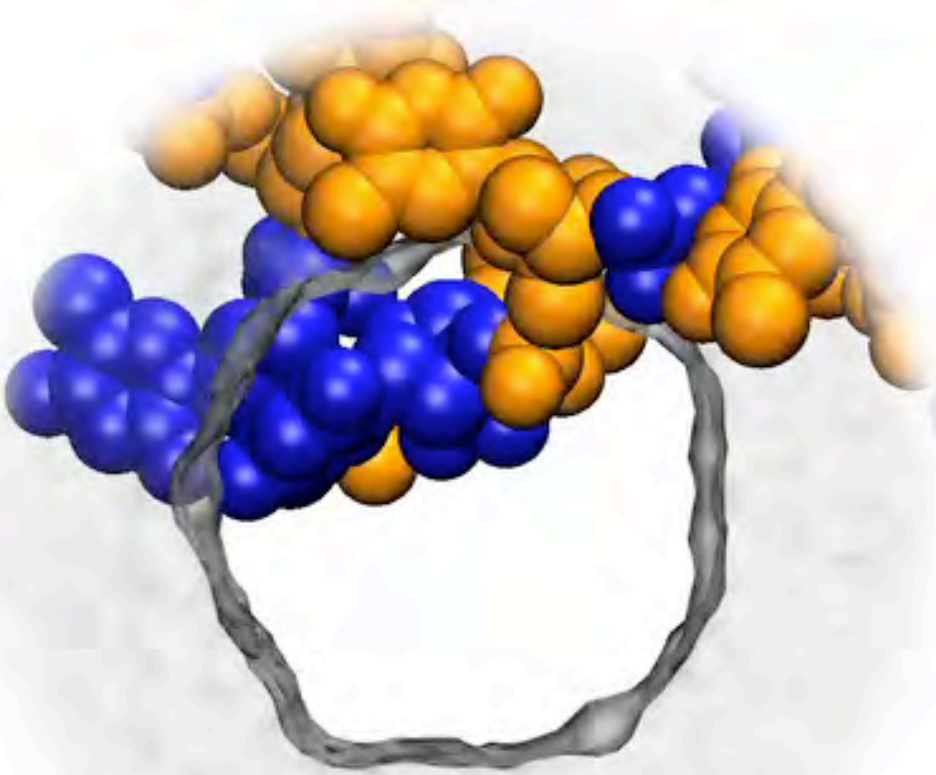
Nano Letters 12:4117 (2012)

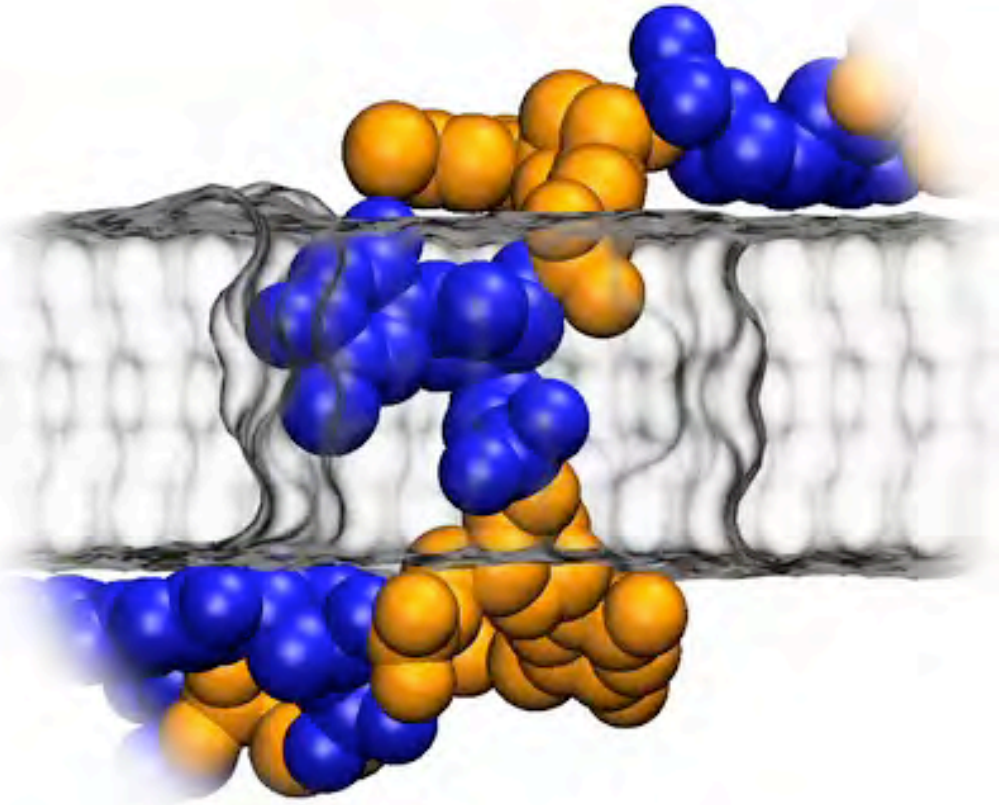
Stepwise transport of ssDNA through graphene nanopore

14-A diameter pore (surface-to surface);
3-layer graphite;
poly$(dT)_{20}$; 500 mV bias



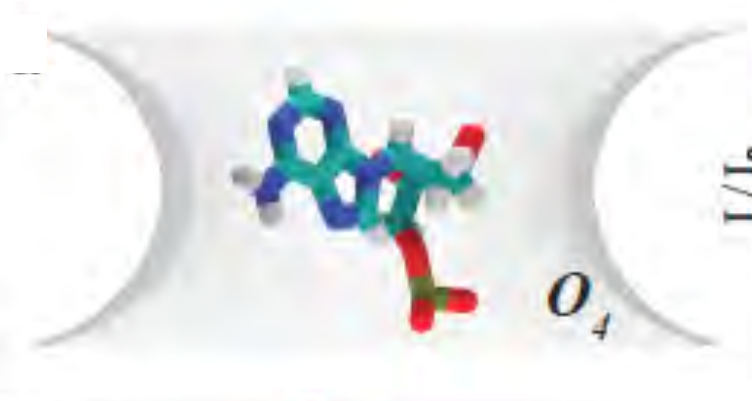
Acts like a polymerase!

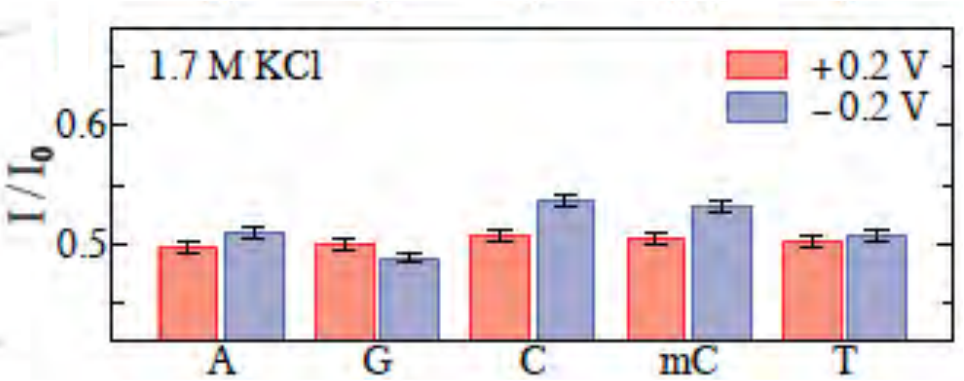


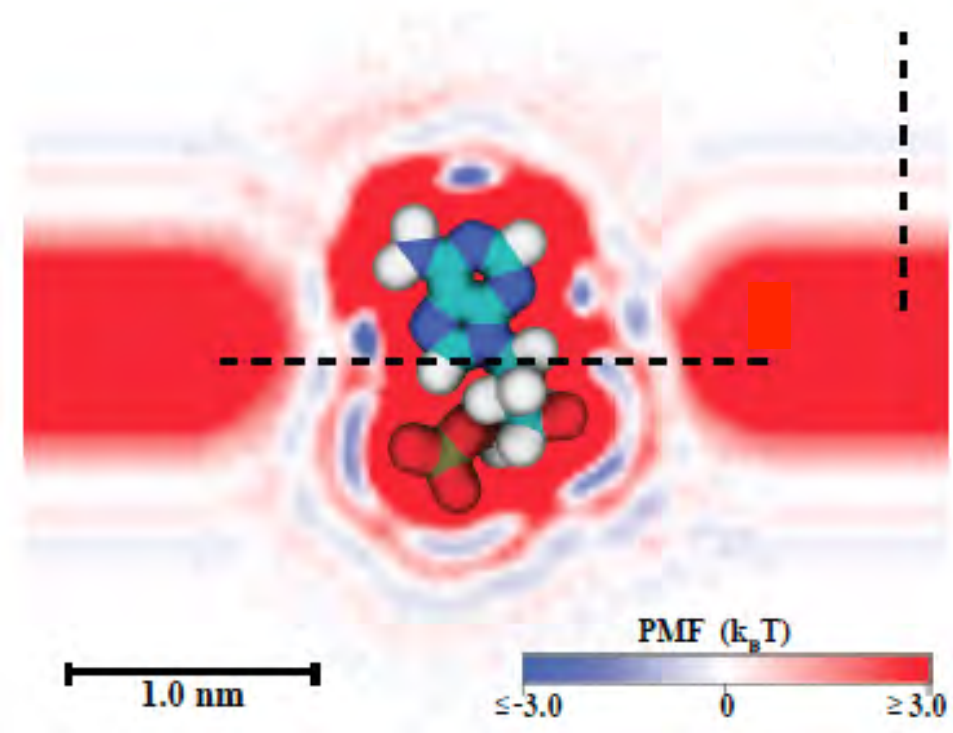


Nano Letters 12:4117 (2012)

Ionic current blockades can reveal the DNA sequence



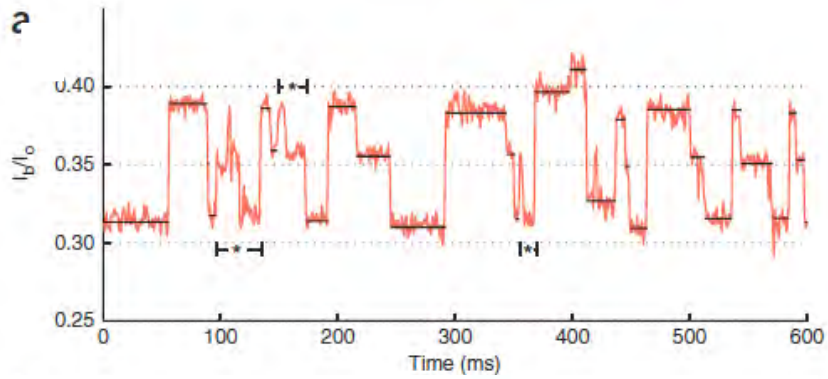


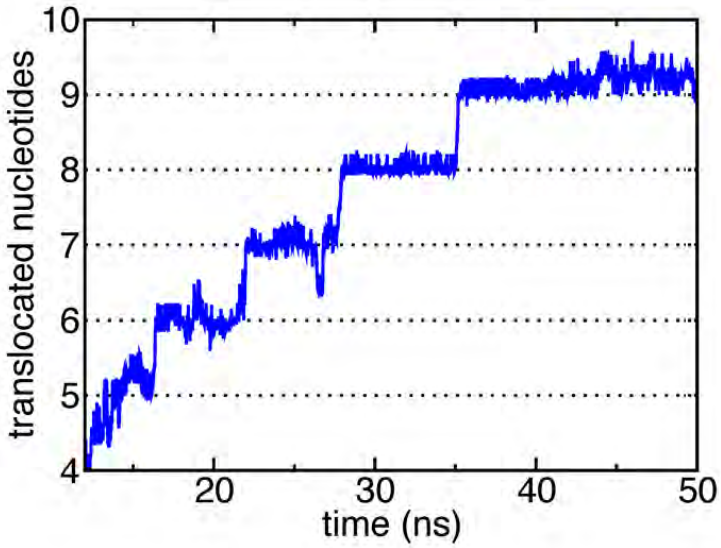


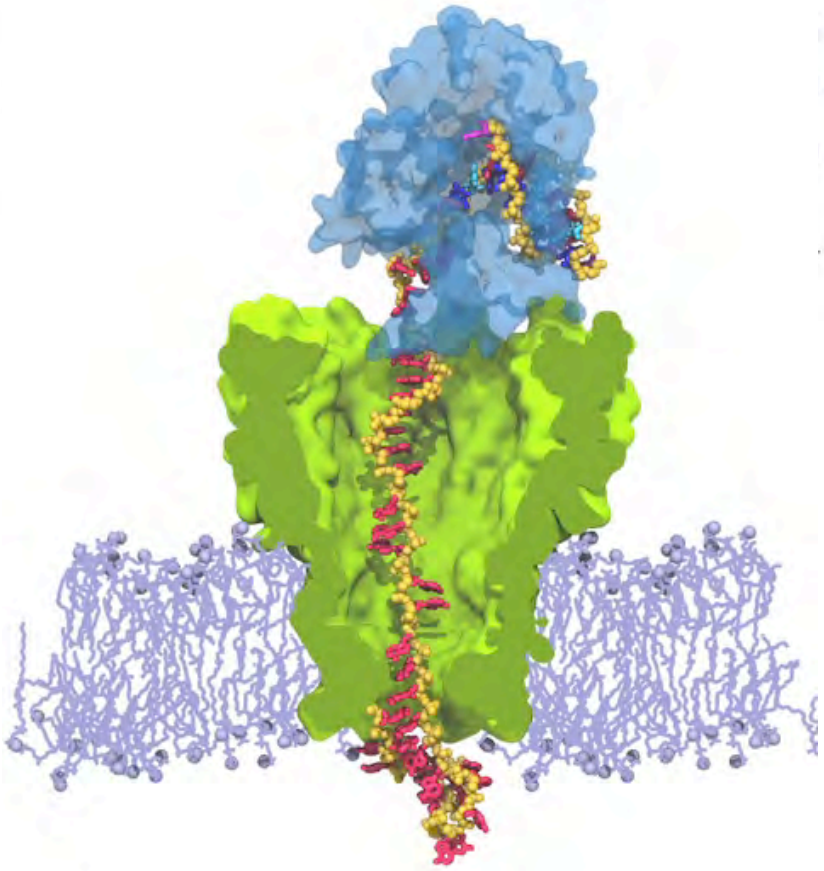
Atomic-Resolution Brownian Dynamics simulations of ionic current blockades in graphene nanopores

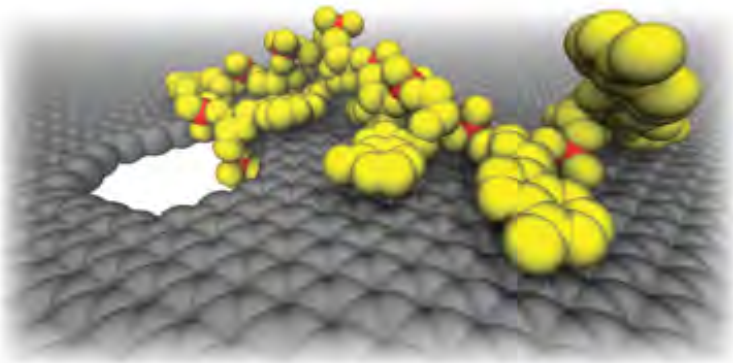
Wells, Belkin, Comer, Aksimentiev, Nano Letters 12:4117 (2012)

Just like polymerase: transport is stochastic

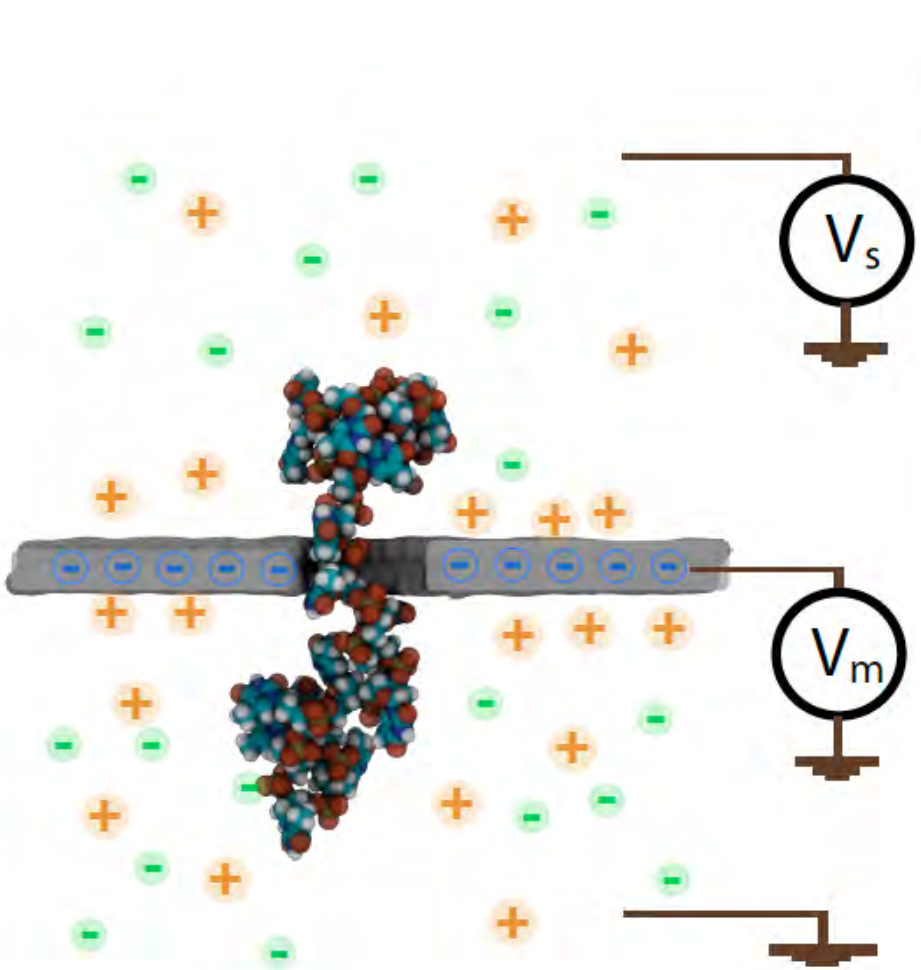


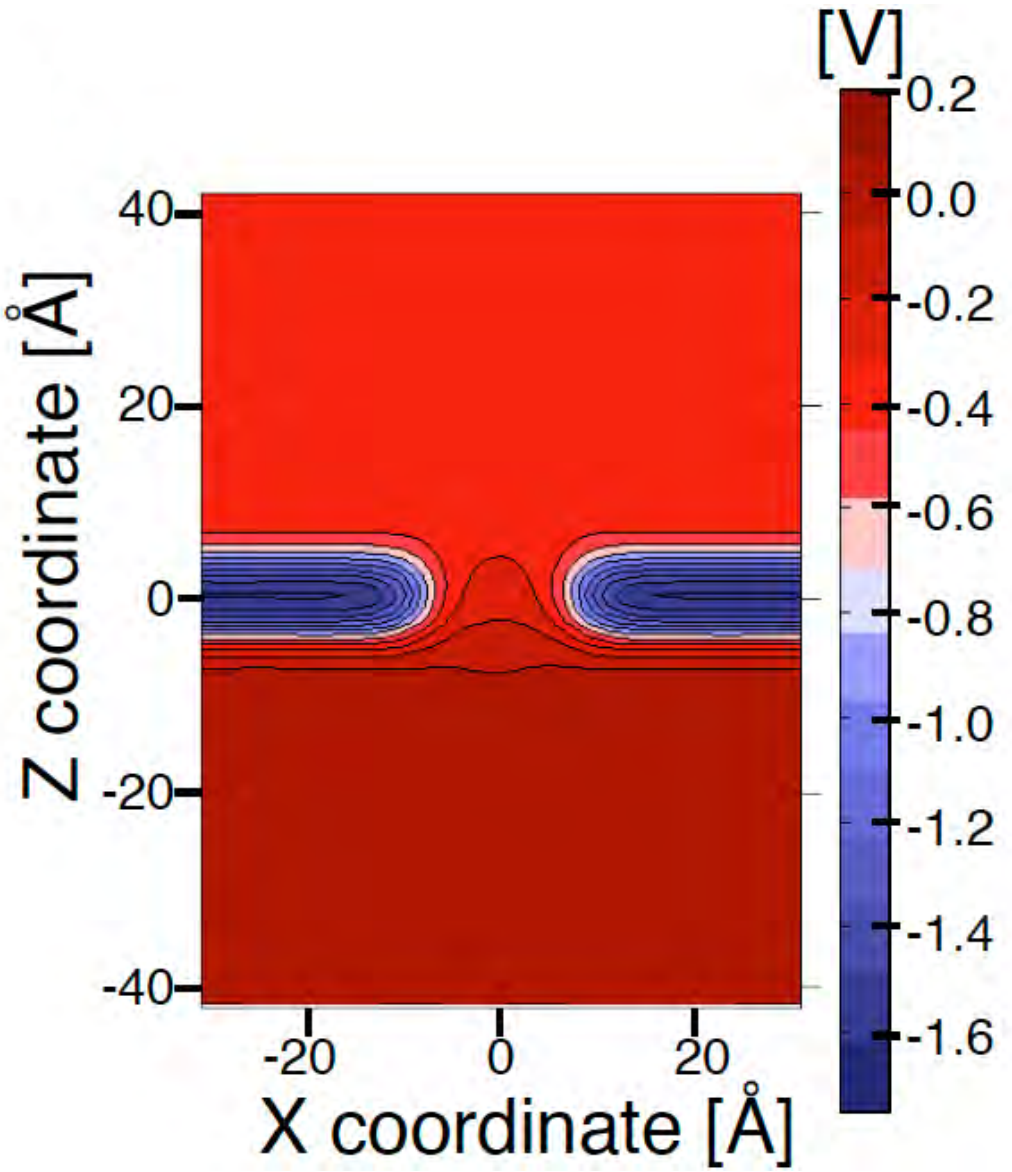




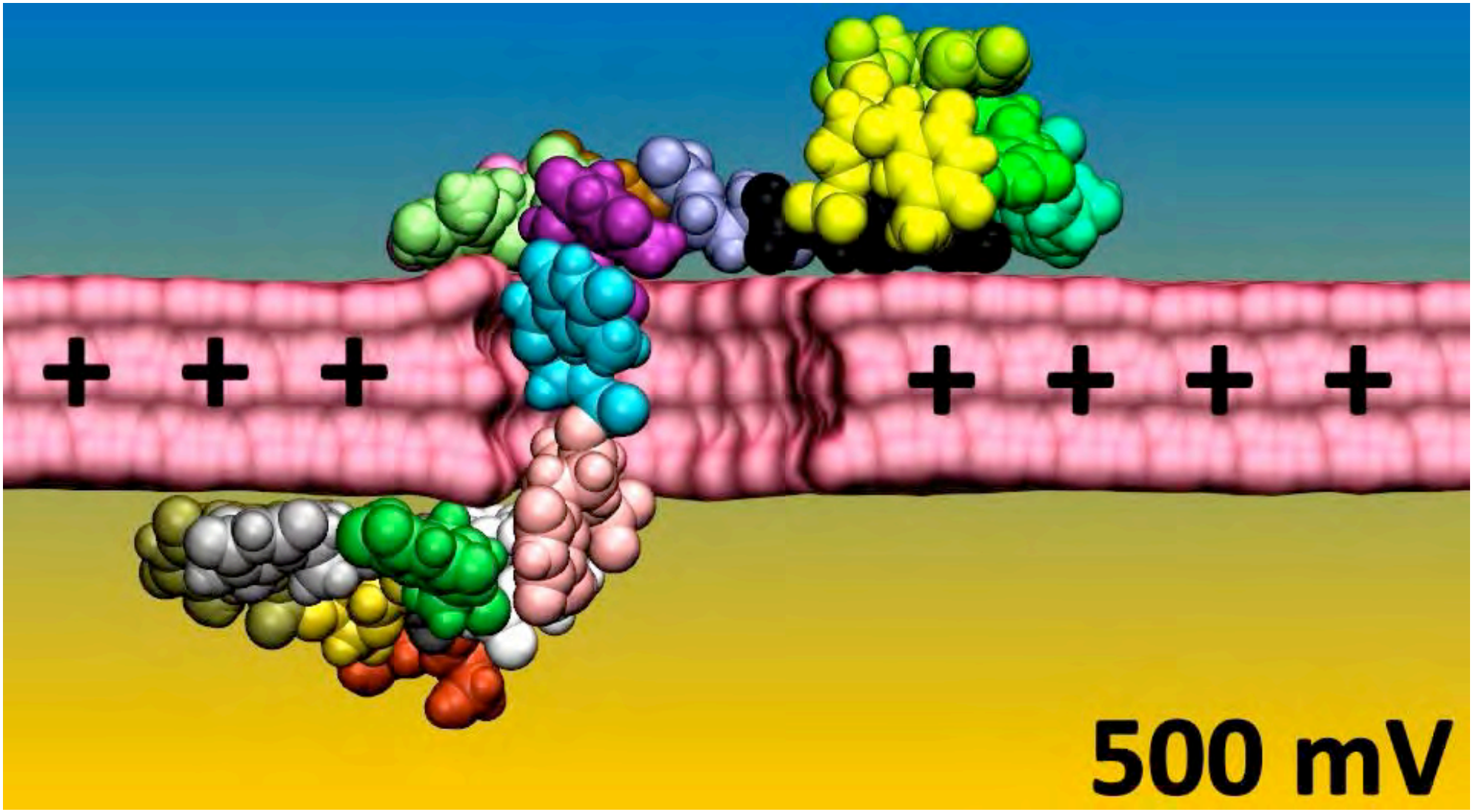


Charge modulates velocity of ssDNA translocation



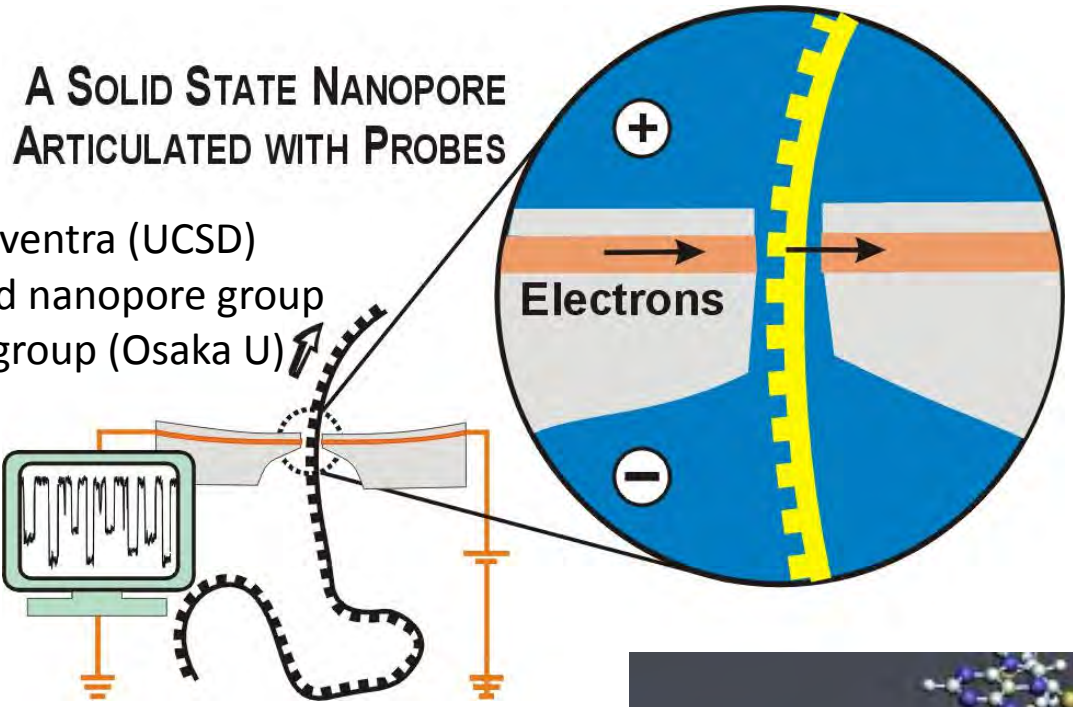


Charge modulates velocity of ssDNA translocation

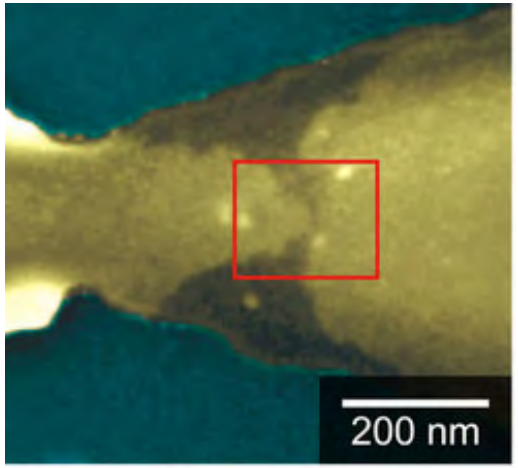


Manish Shankla et al. (to be published)

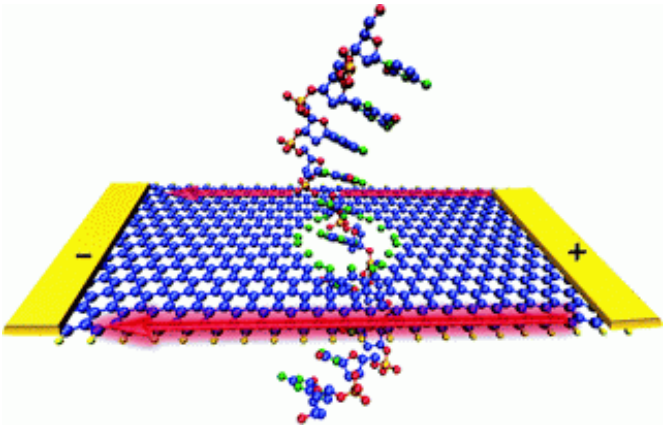
Sequencing by transverse current

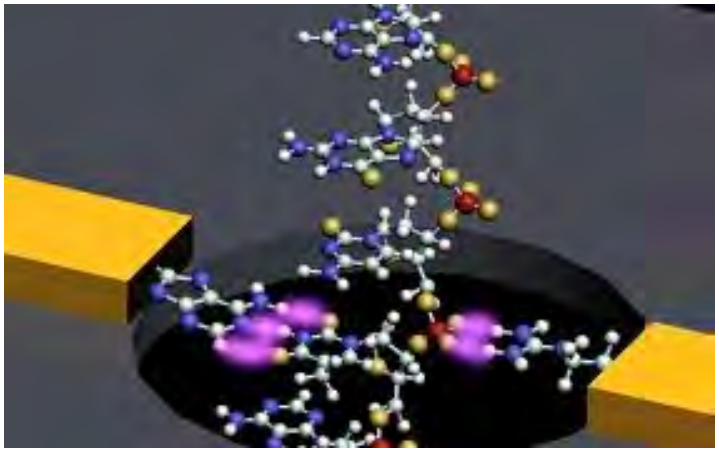


Max Diventra (UCSD)
Harvard nanopore group
Kawai group (Osaka U)

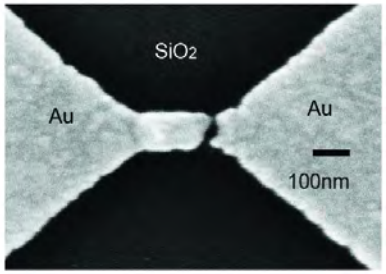


Scientific Reports 1:46





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 at al. J. Am. Chem. Soc. 2006

solid-state pores:

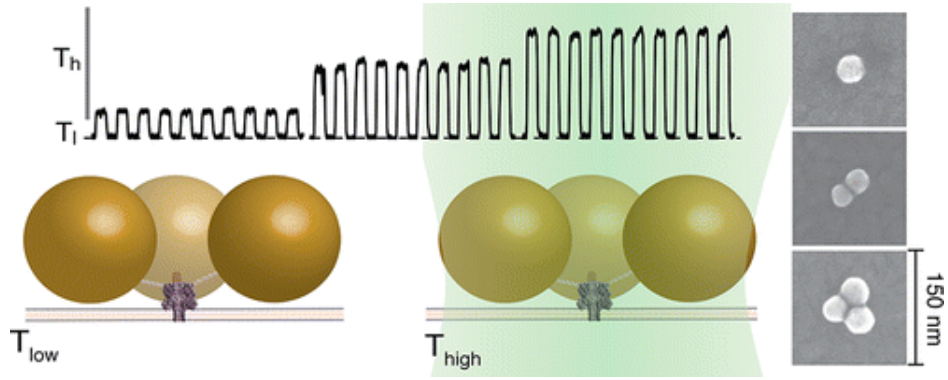
ChemPhysChem 639 2010, 11, 859

Nanotechnology 2012, 23, 225502

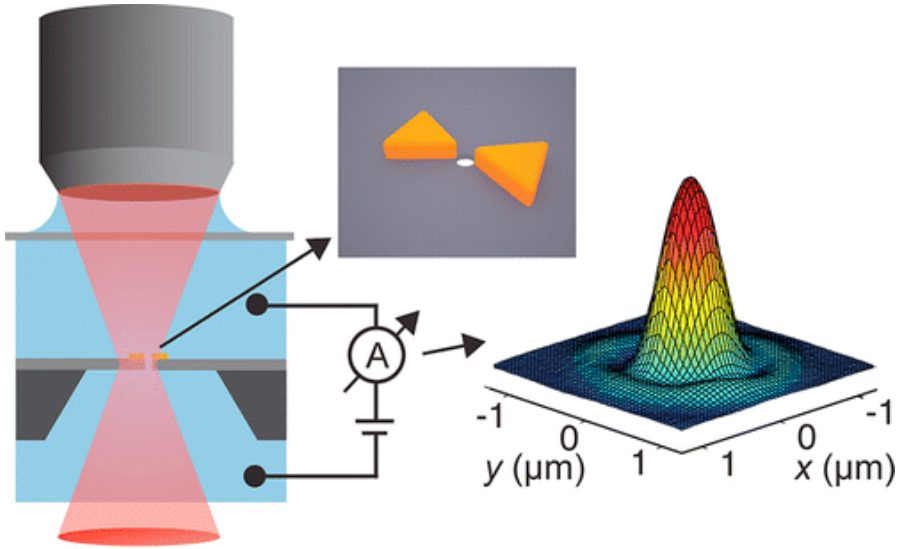
Finding the pore:

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

Plasmonic heating:



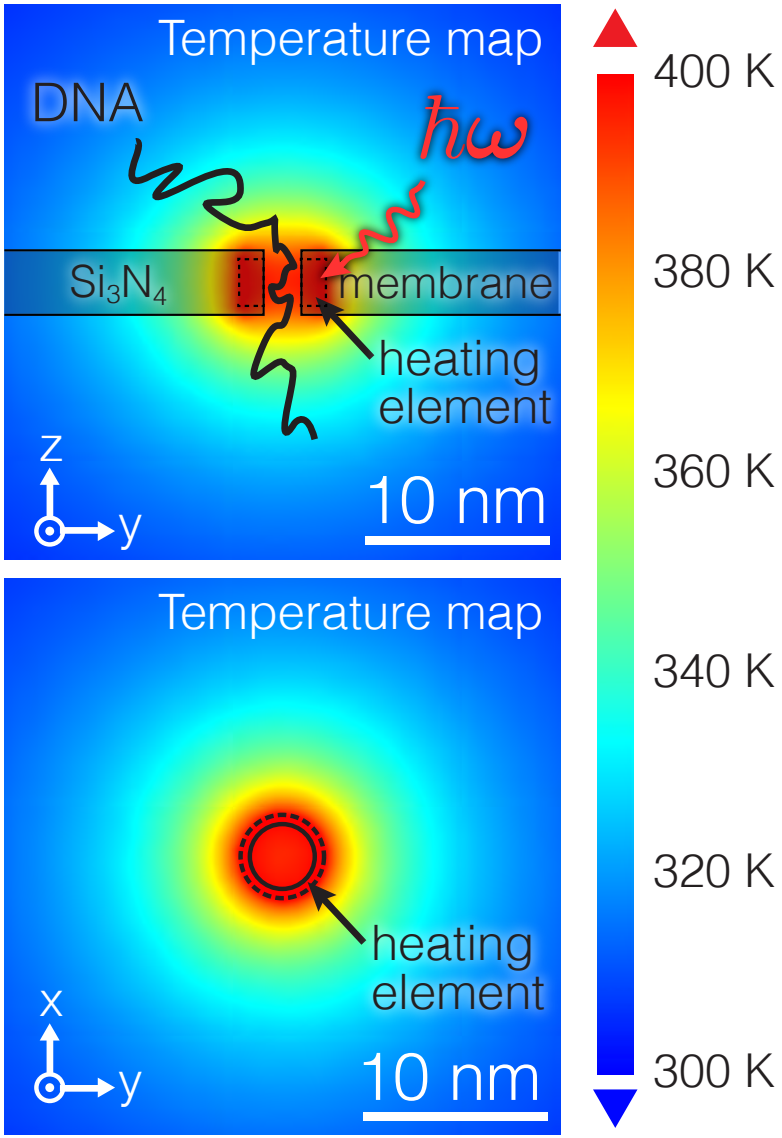
JACS 135: 3087 (2013)

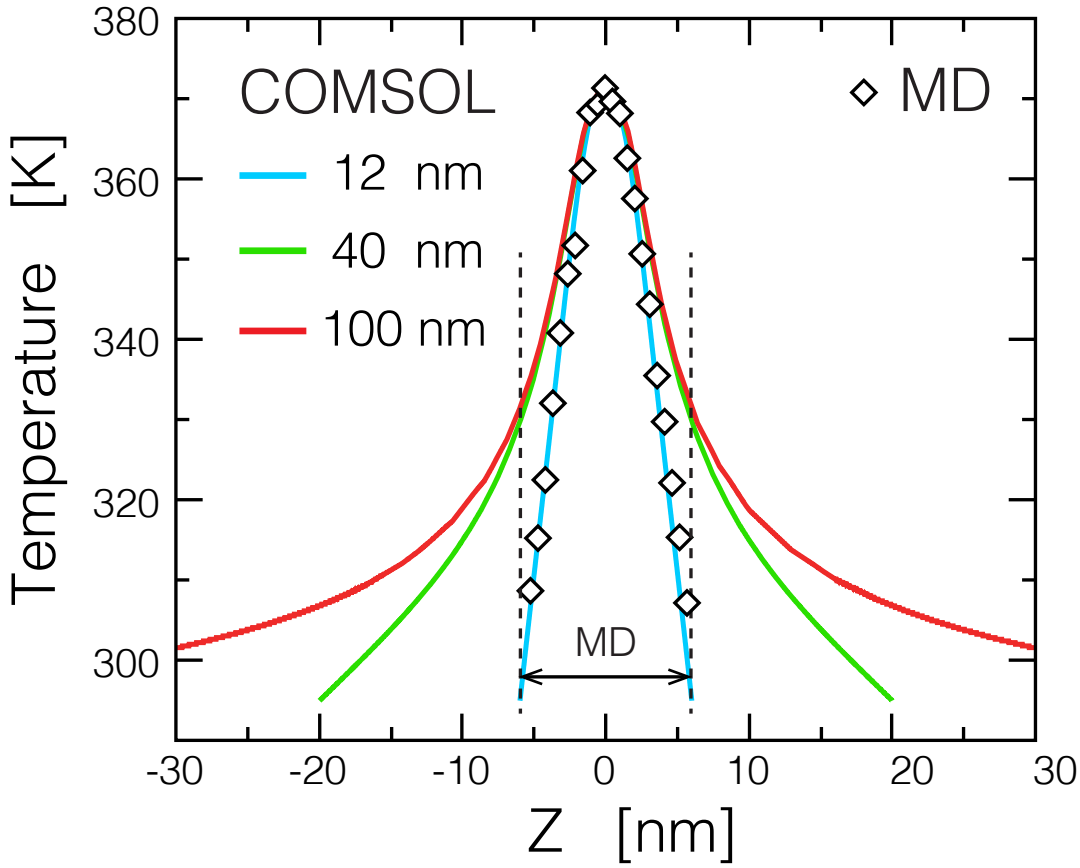


Nano Letters 13: 1029 (2013)

Local plasmonic heating stretches ssDNA

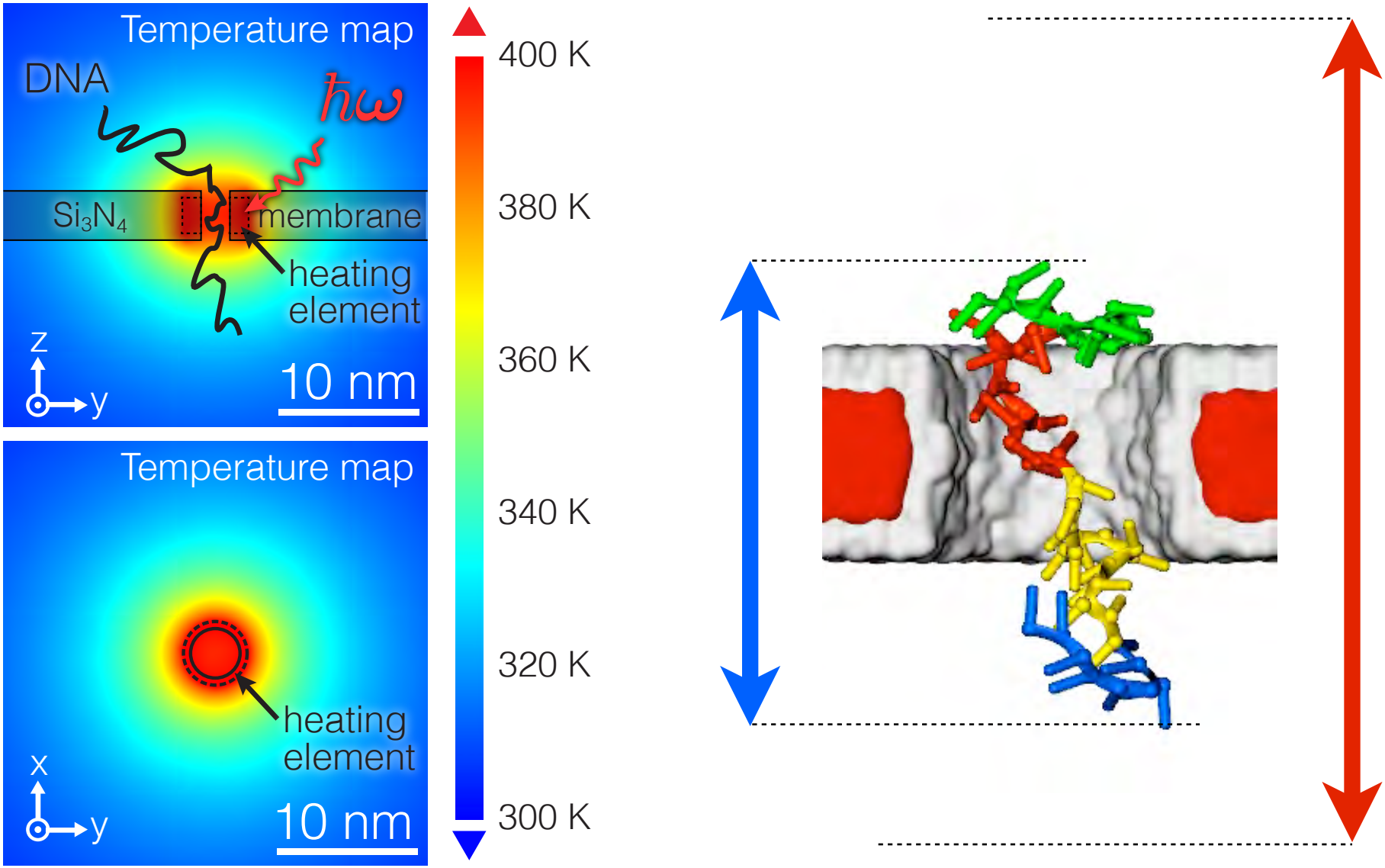
M Belkin et al. ACS Nano 7:6816 (2013)





Local heating in nanopore systems

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



Thermophoresis

Non-convective mass transport along temperature gradients

First reported in electrolyte solutions

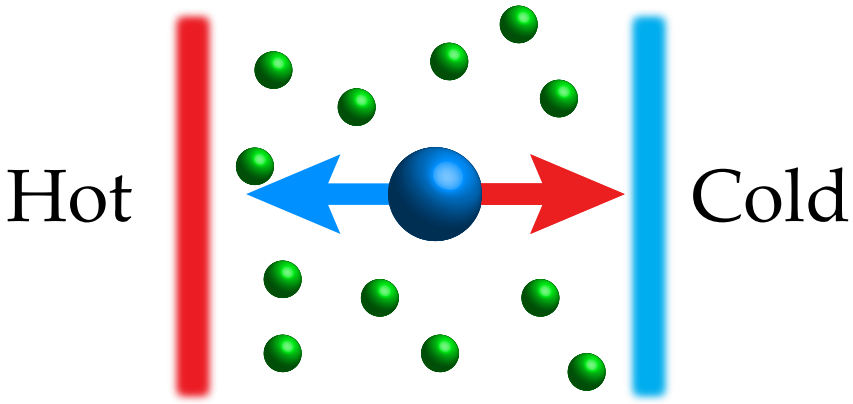
1856 - Carl Ludwig

1879 - Charles Soret

Carl Ludwig

Charles Soret

positive thermophoresis



negative thermophoresis

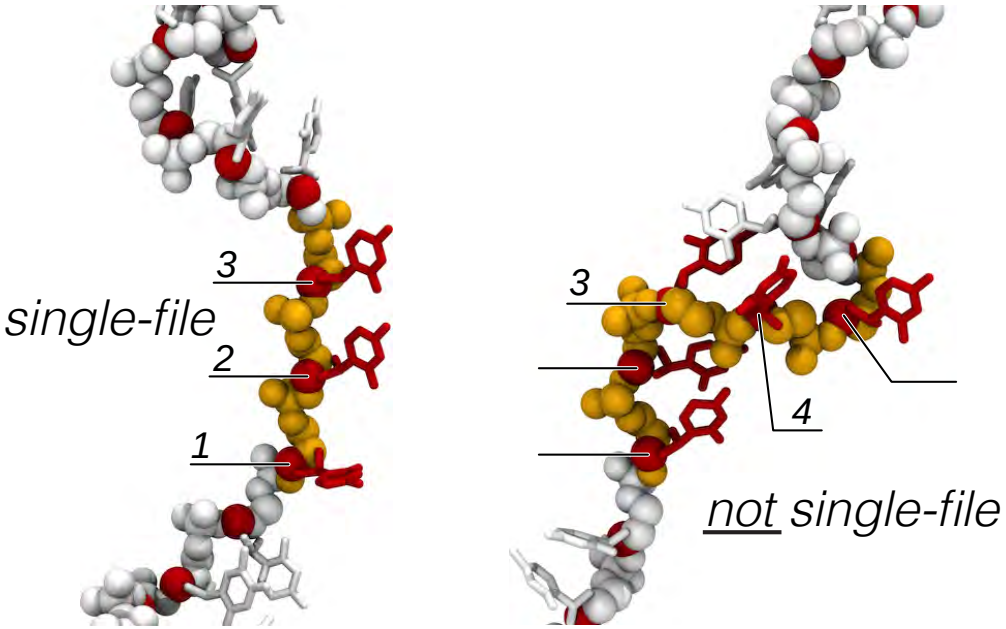
Magnitude and direction depend on:

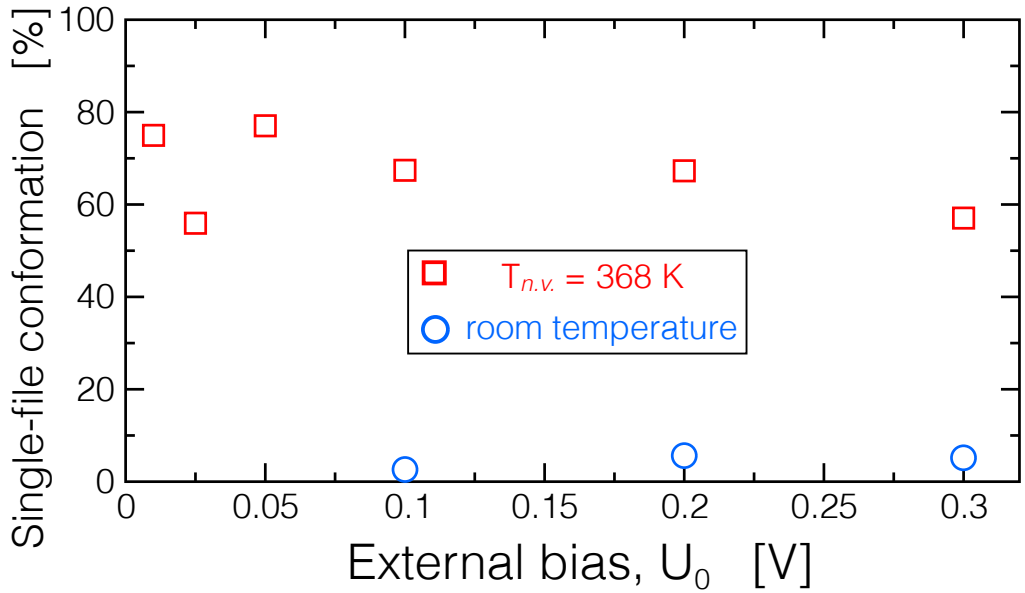
- Temperature
- Temperature gradient
- Concentration
- Charge
- Size of species ...

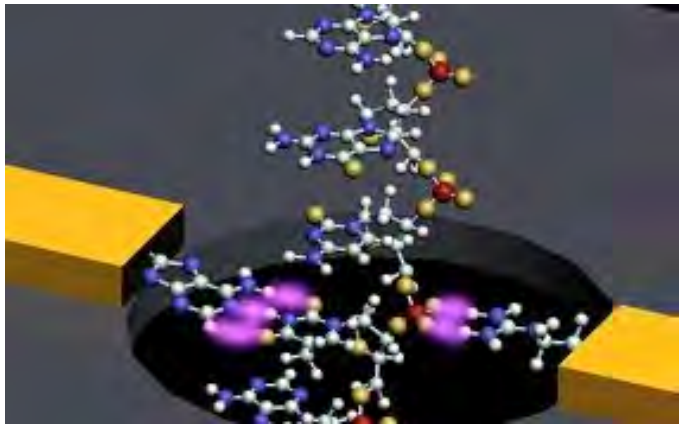
Found in: electrolyte solutions, gas mixtures, polymer solutions, plasma,...

Local heating promotes single-file translocation

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







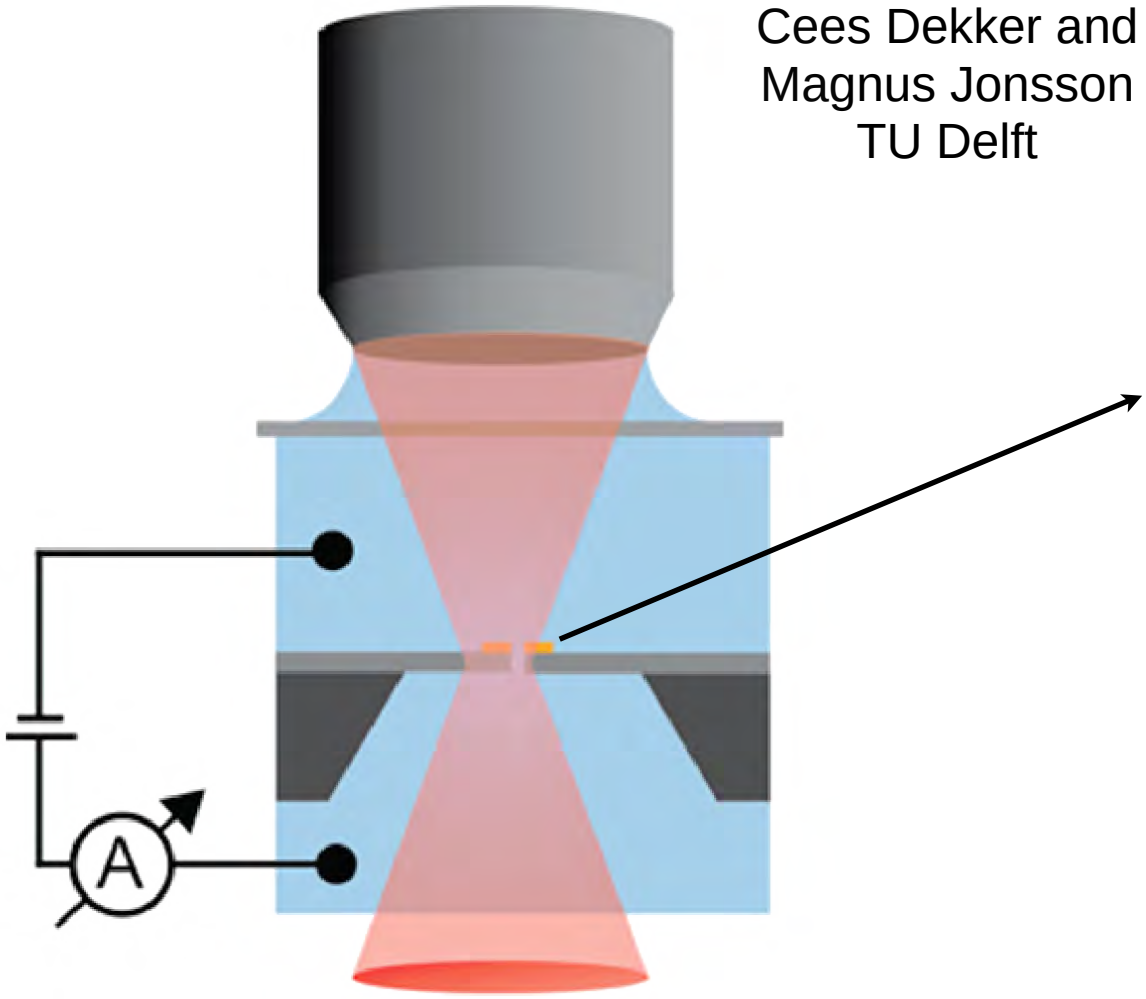
Local heating:

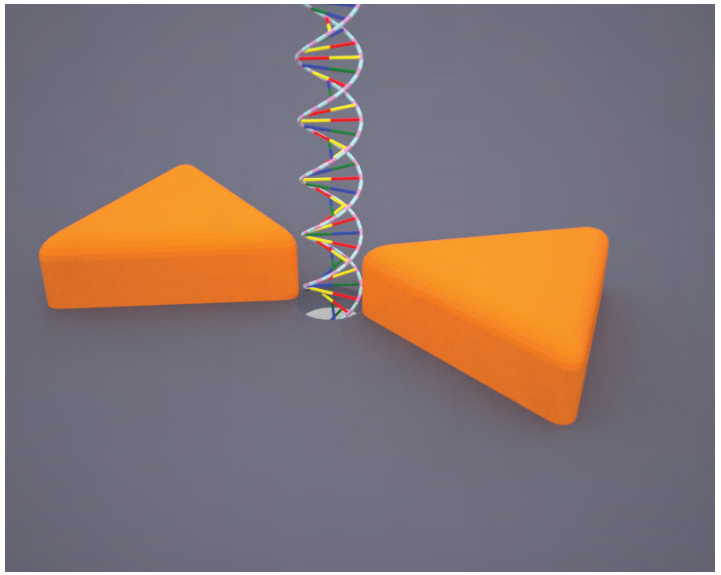
increase DNA mobility 20 fold

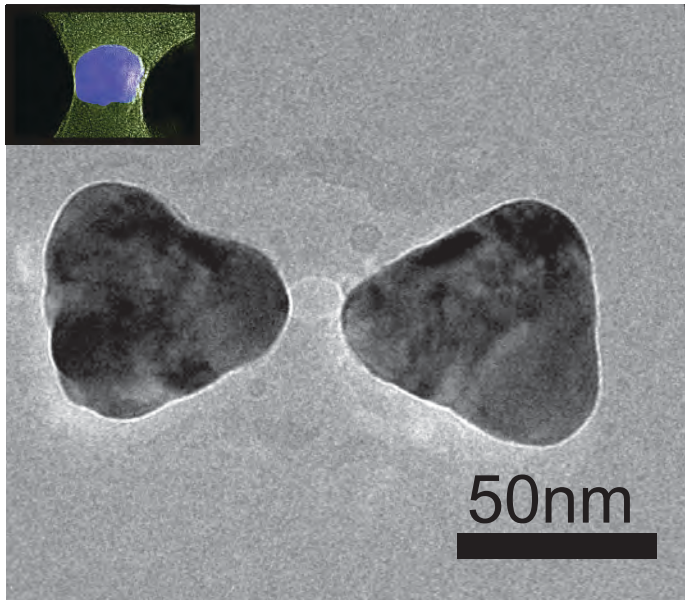
enables controlled displacement at 10mV biases

Plasmonic nanopore tweezers

Cees Dekker and
Magnus Jonsson
TU Delft



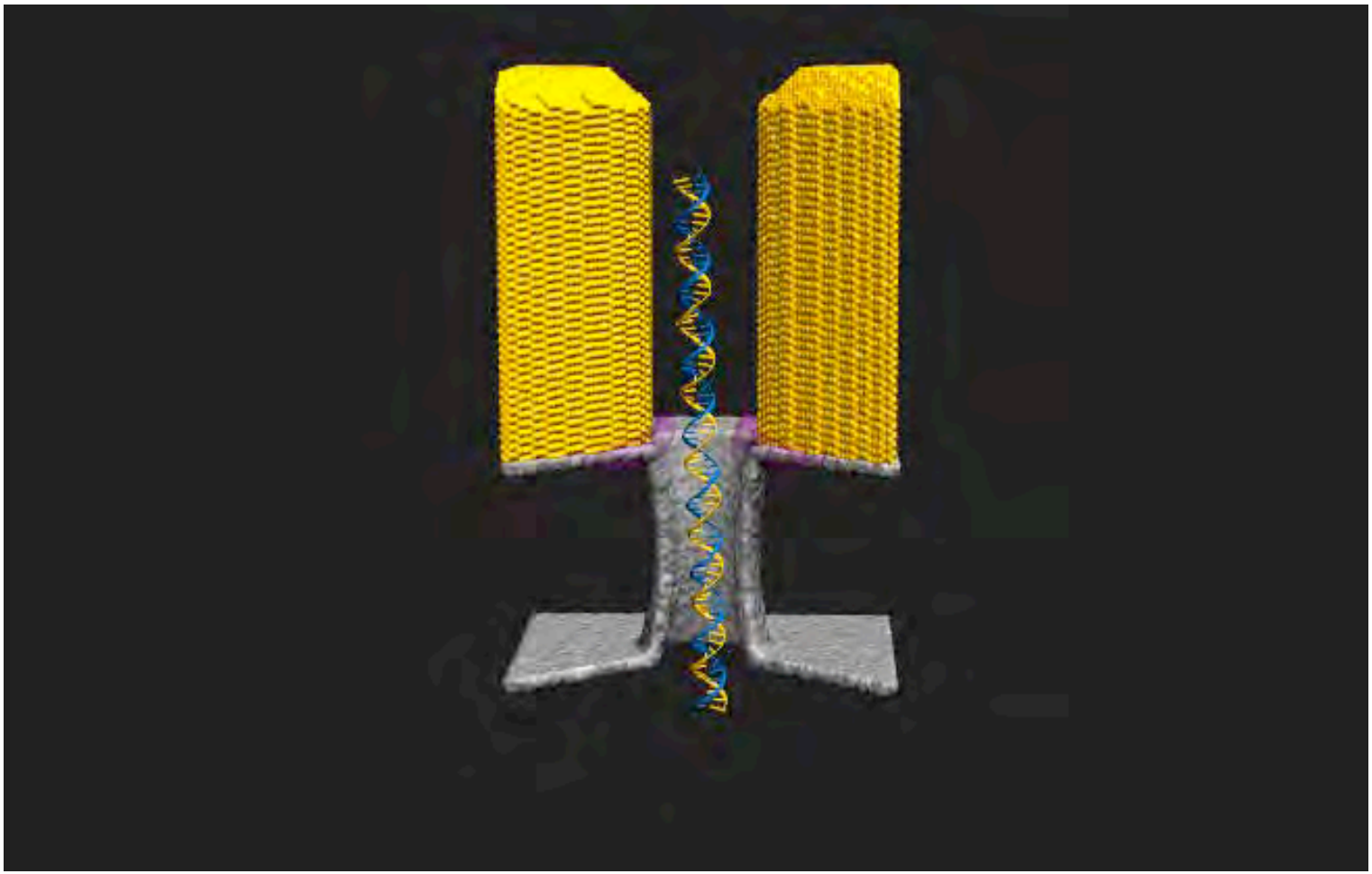




Plasmonic nanopore (TEM)

Main idea: use nanometer-focused light
to directly trap biomolecules

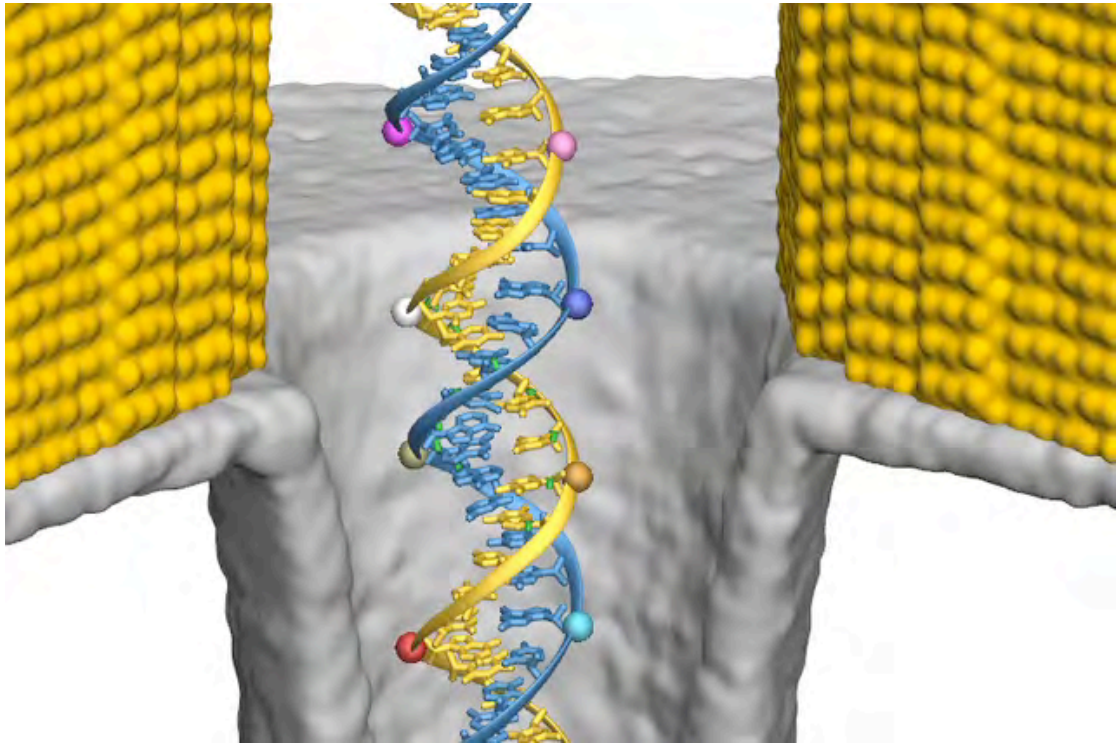
MD simulations plasmonic trapping

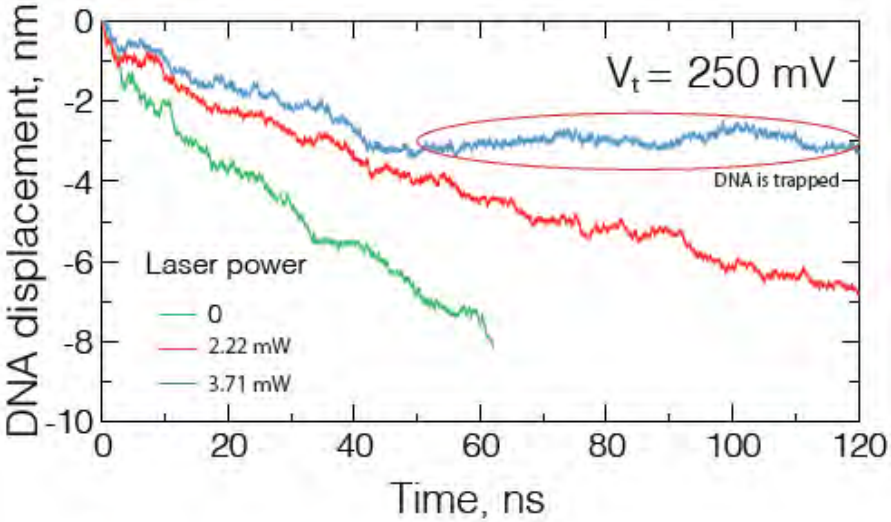


Optical field is found by solving Maxwell's equations (FDTD)

FDTD is couples to MD simulations through grid forces as F~grad(E^2)

Proof of principle simulations: trapping





Focused optical field arrests DNA motion

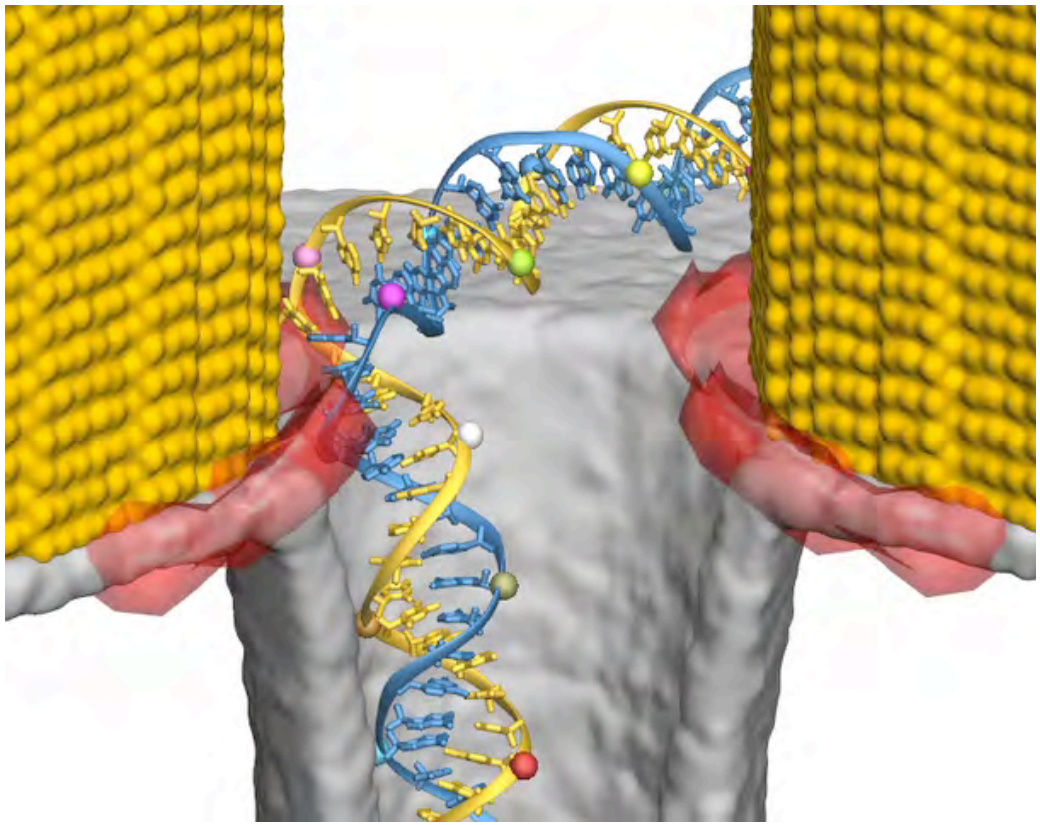
Red arrows represent plasmonic forces on individual nucleotides

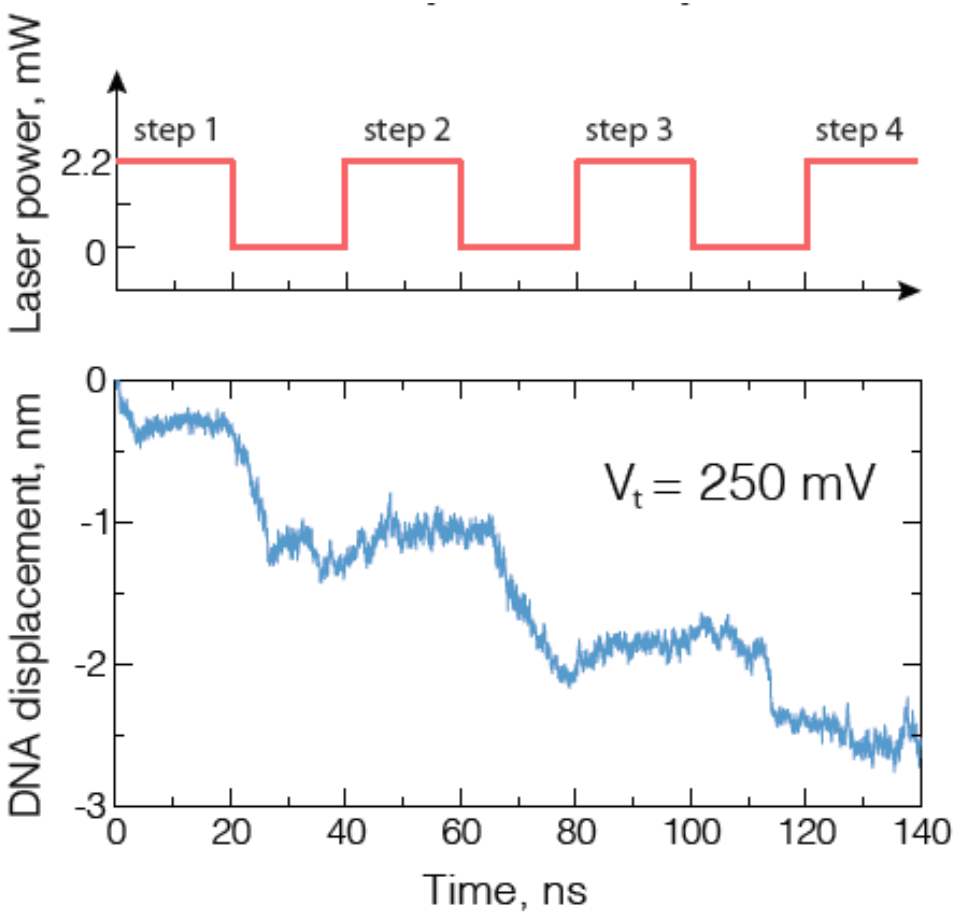
Optical field is found by solving Maxwell's equations (FDTD, Lumerical)

FDTD is couples to MD simulations through grid forces as F~grad(E^2)

Maxim Belkin

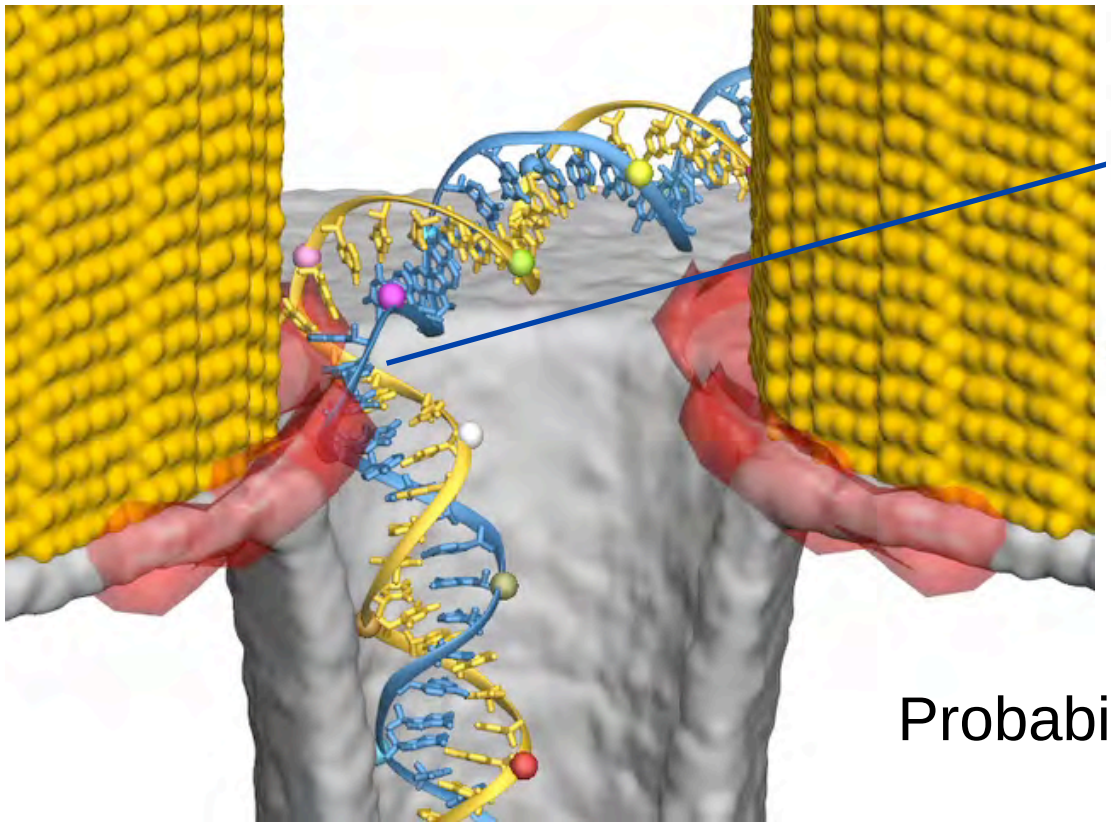
Stepping dsDNA by modulation of optical field

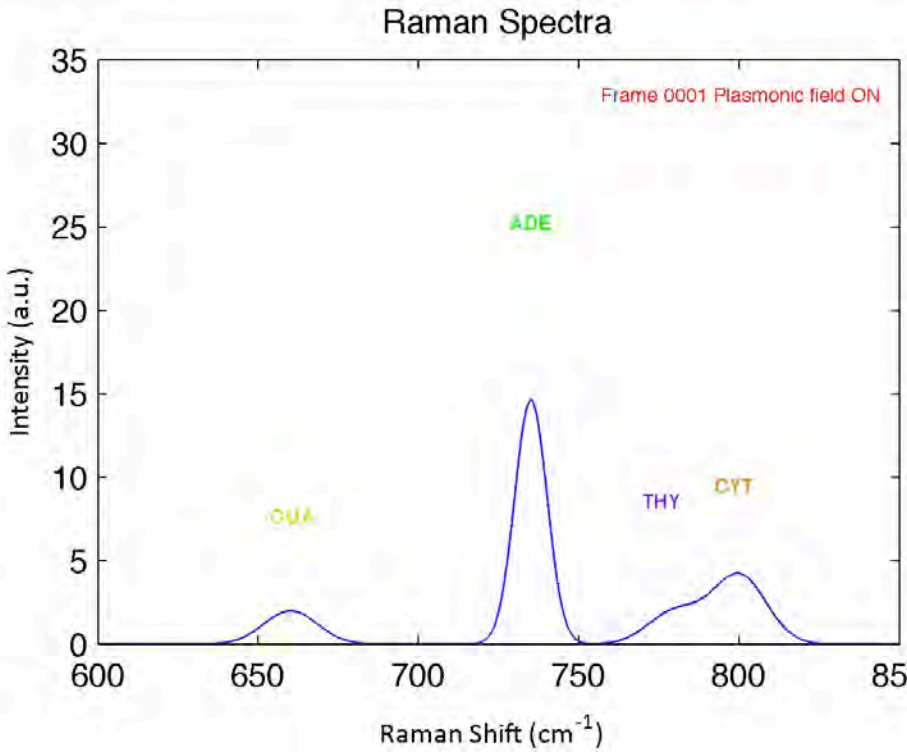




Stepwise motion is achieved by switching on and off the laser beam

Surface-Enhanced Raman Scattering



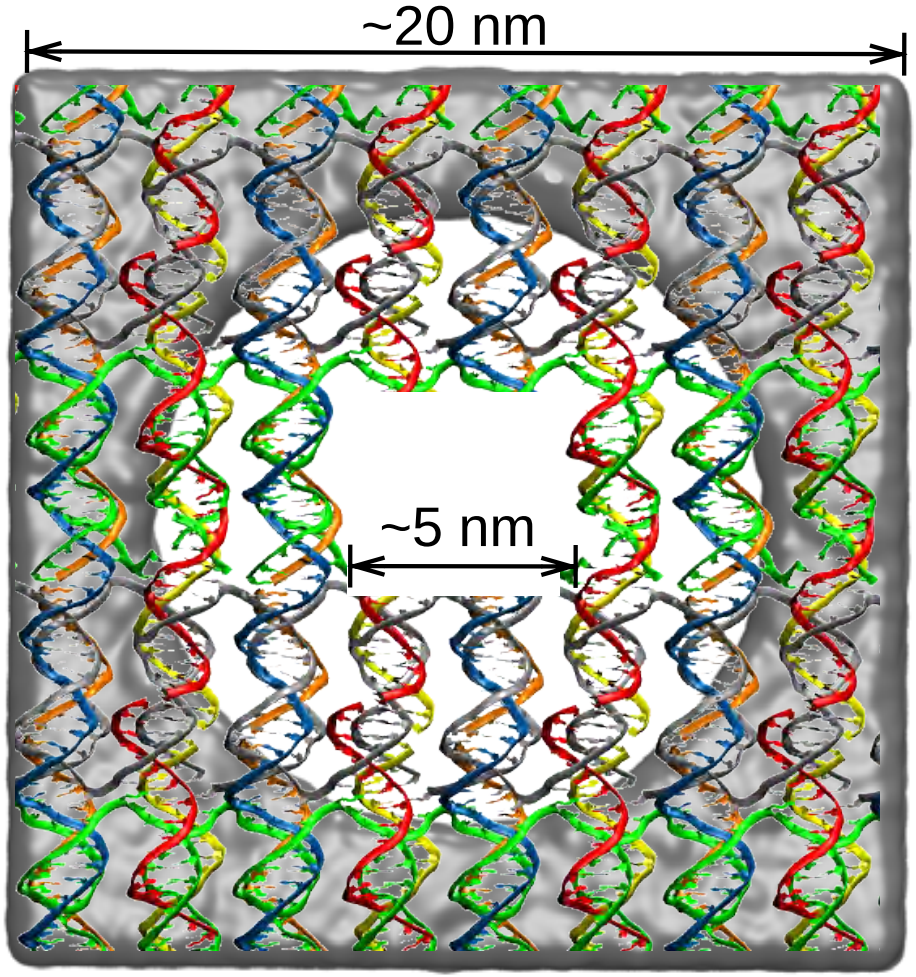


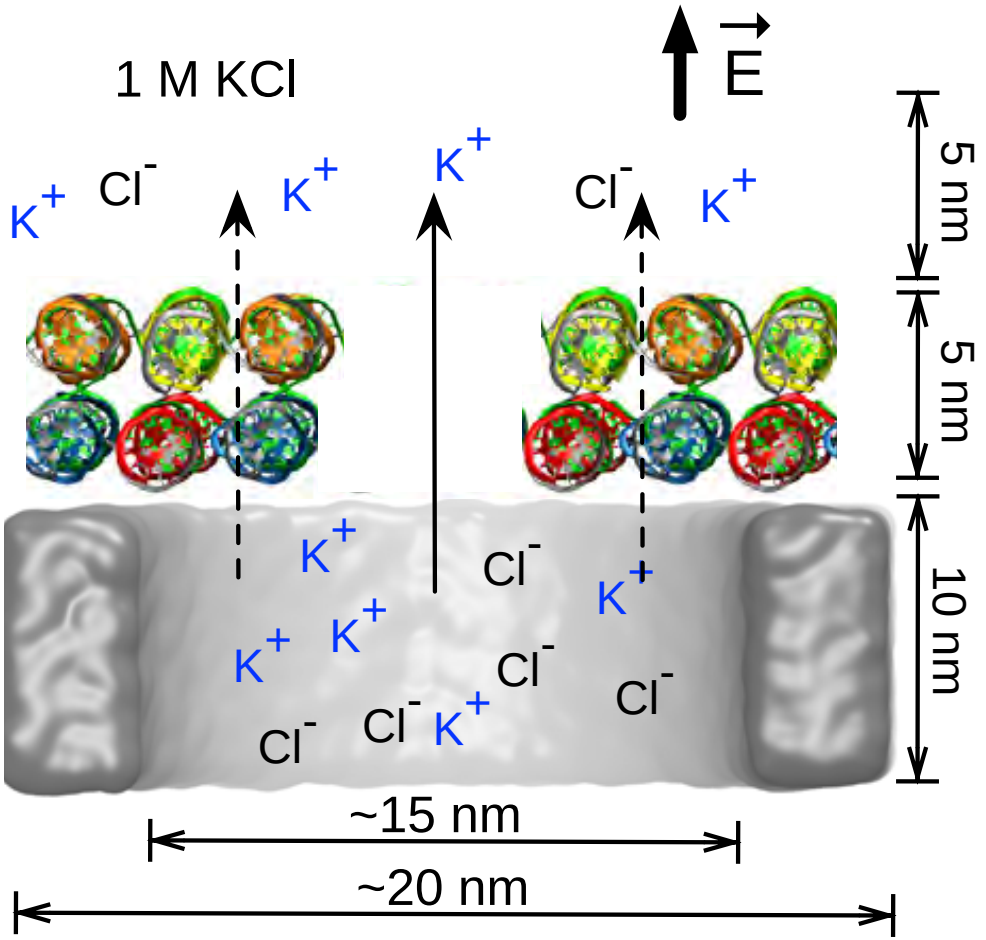
Kneipp K & Kneipp H, Applied Spectroscopy 60:322A

Probability ~ (Field intensity)^4

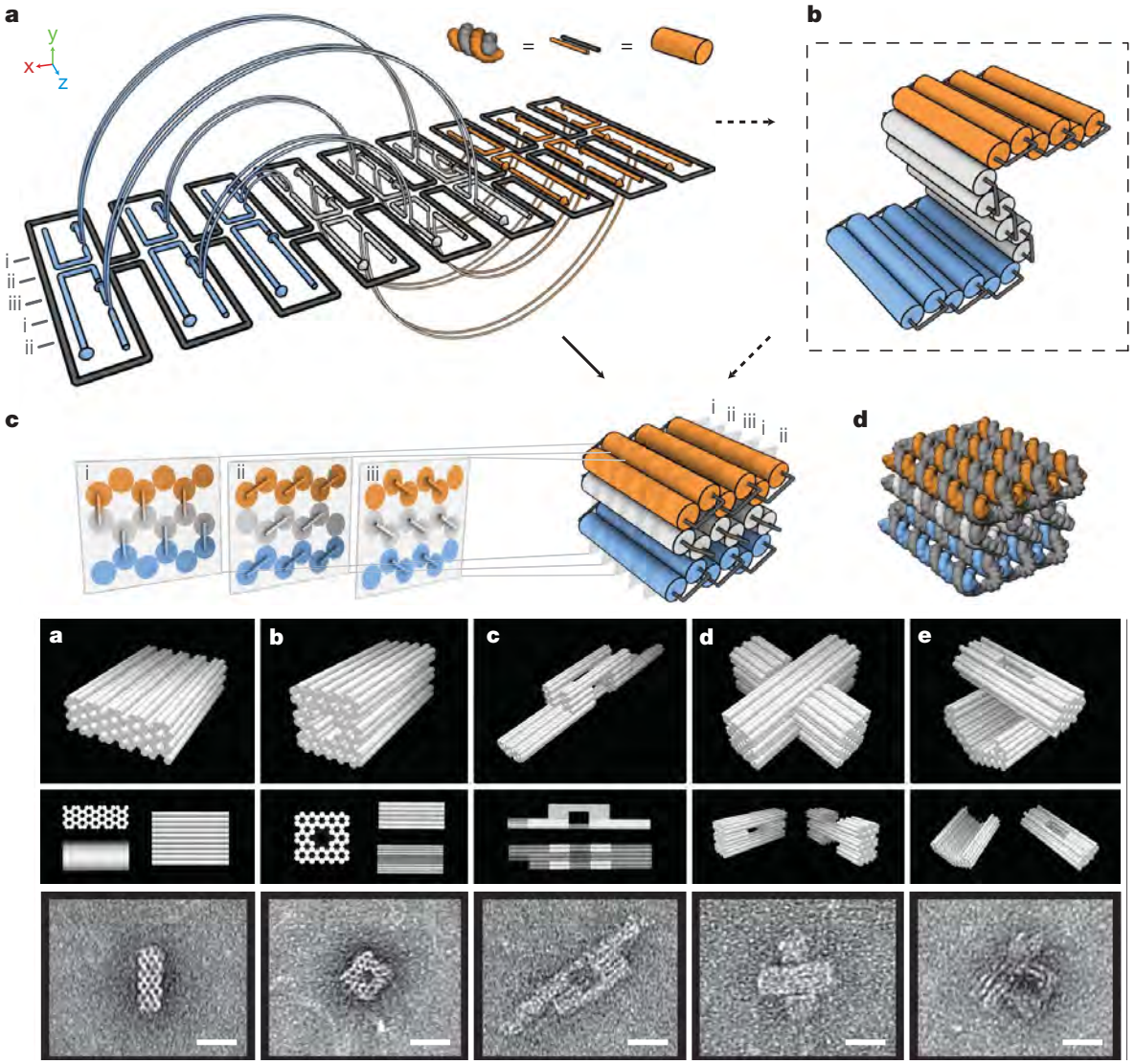
DNA sequence is read by measuring Raman spectra from nucleotides passing through the plasmonic hotspot

Molecular sensing with origami nanopores





Folding of viral genome into 3D objects



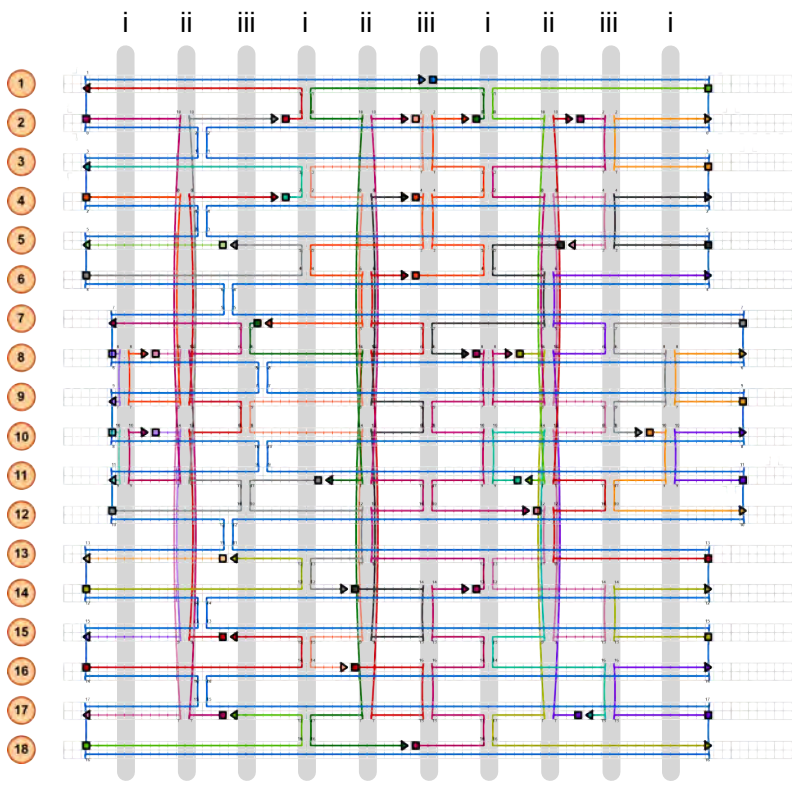
- Short synthetic oligonucleotides (staples) apply spatial constraints to a long viral genome.
- Based on the design of staples, same viral genome can be folded to numerous different shapes.

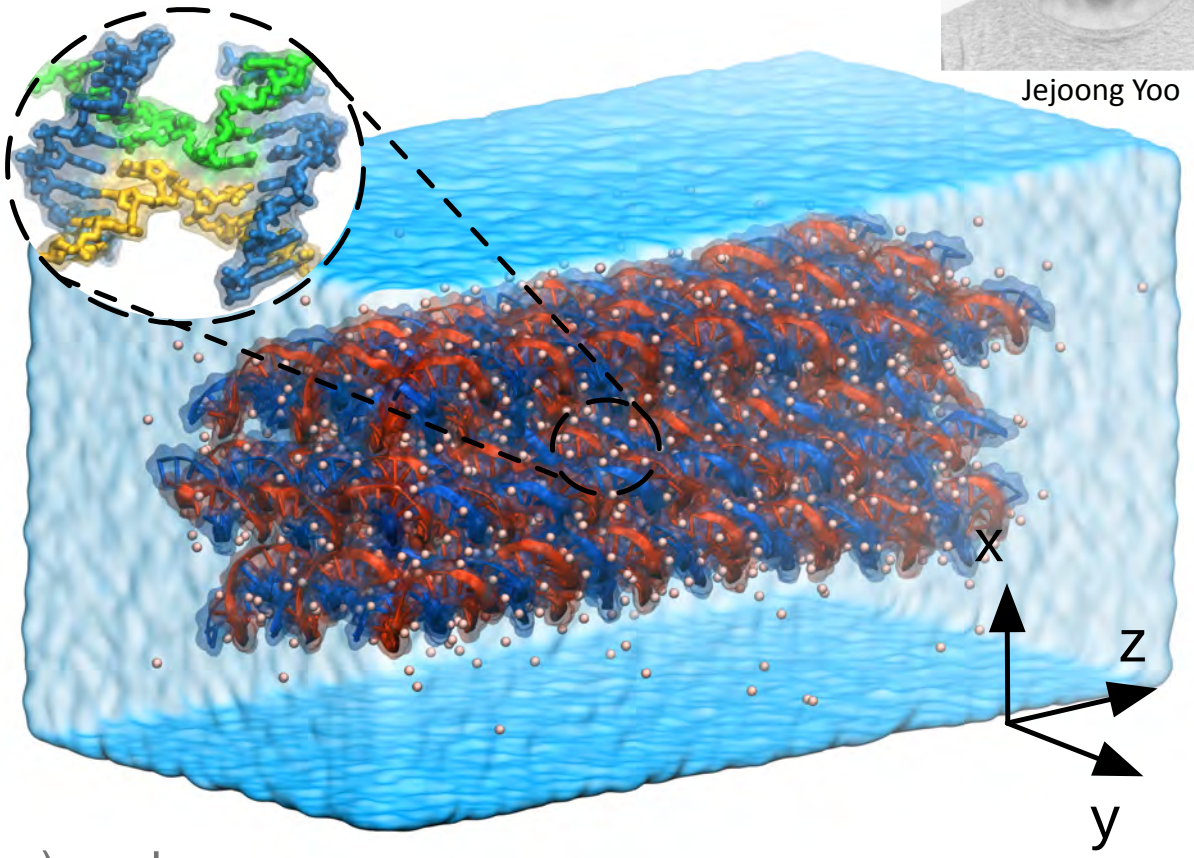
Douglas, S.M., Dietz, H., Liedl, T., Högberg, B., Graf, F. & Shih, W.M., 2009, Self-assembly of DNA into nanoscale three-dimensional shapes, *Nature*, 459(7245), pp. 414-8.

All-atom simulations of DNA origami

Yoo and AA, *PNAS* 110:20099 (2013)

Jejoong Yoo





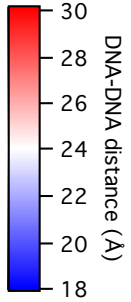
- caDNAno returns topology (json) and sequence (csv) information.

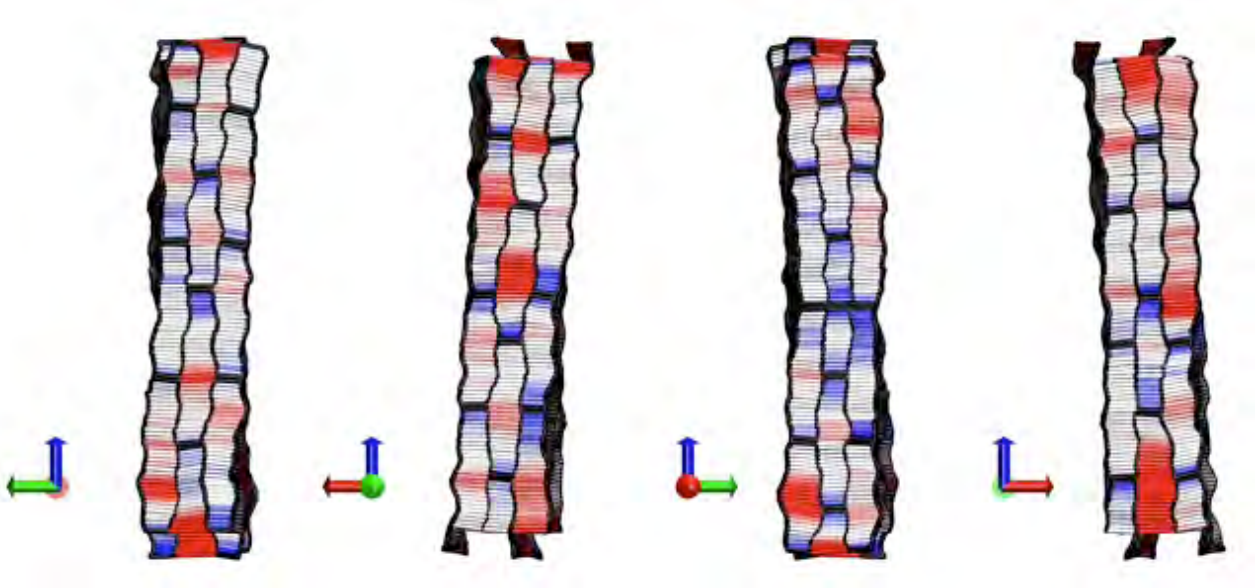
- **cadnano2pdb.pl** combines json and csv files into a PDB file.

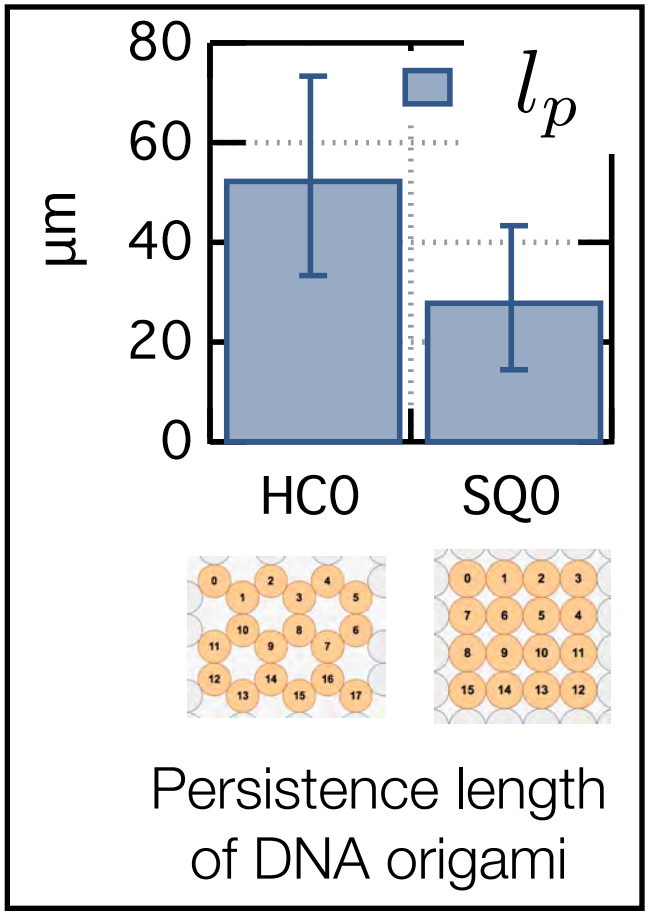
- ✳ CHARMM36 force field
- ✳ Explicit water
- ✳ [$MgCl_2$] ~ 10 mM
- ✳ NAMD
- ✳ 1 to 3M atoms
- ✳ 500 to 1,000 CPUs

Structural fluctuations reveal local mechanical properties

- Chicken wire frame represents center line of helices & junction.
- Inter-DNA distance in color map

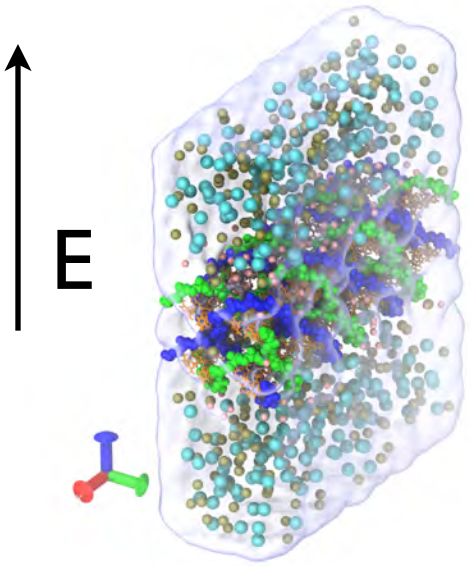


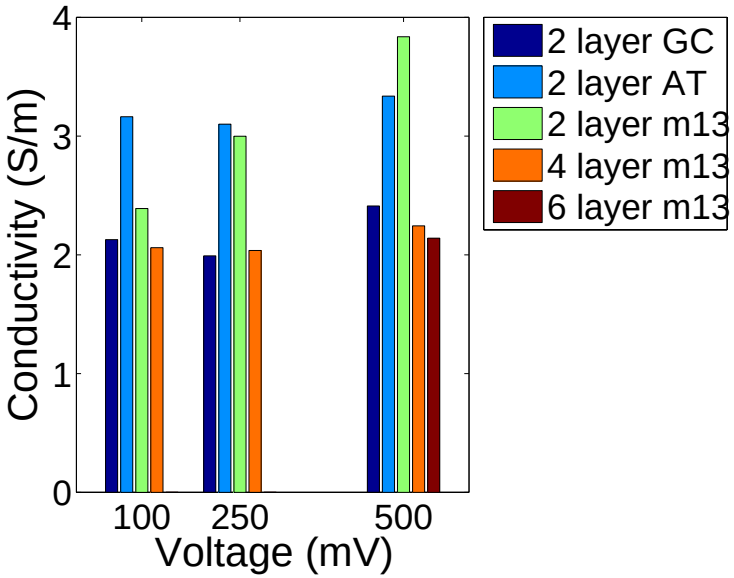


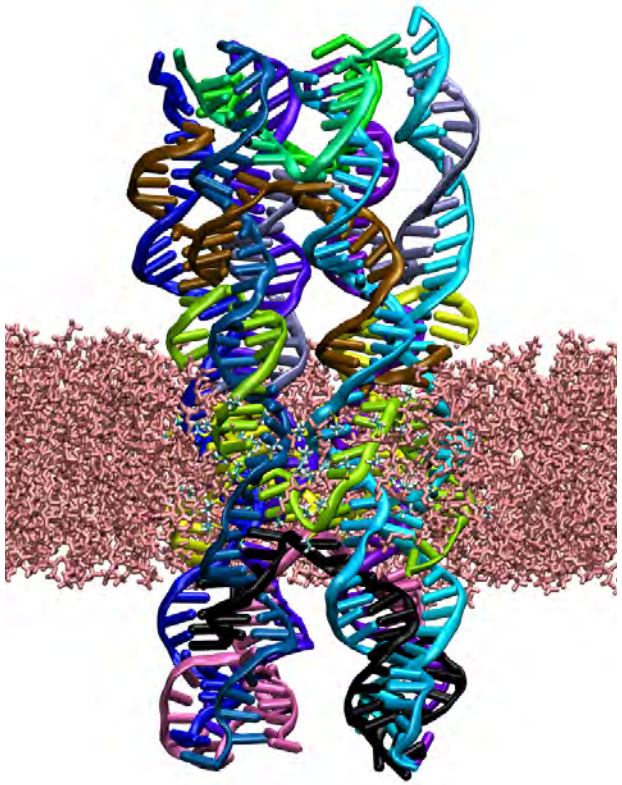


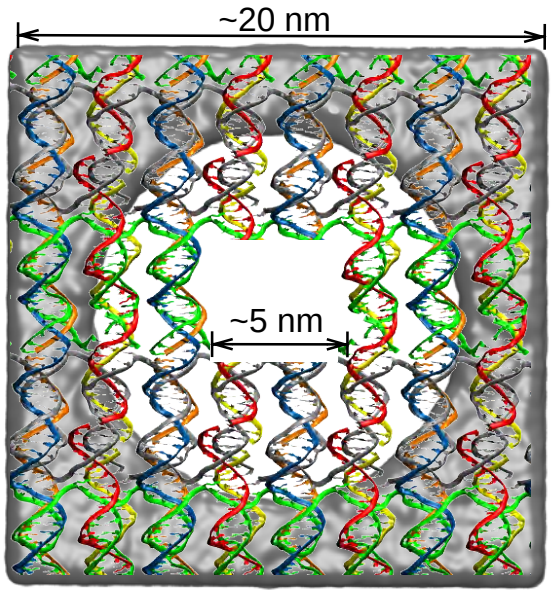
Yoo and AA, *PNAS* 110:20099 (2013)

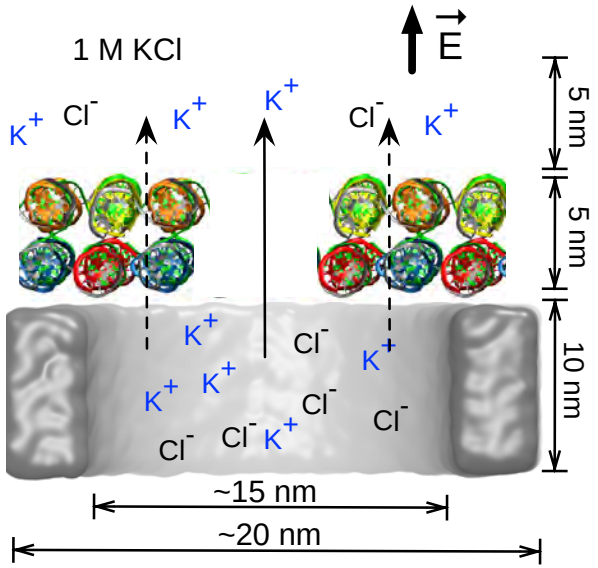
DNA origami nanopore/nanochannel systems

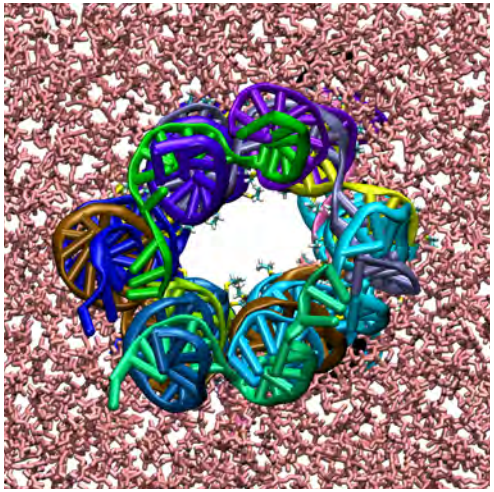












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Jejoong Yoo

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VMD and NAMD