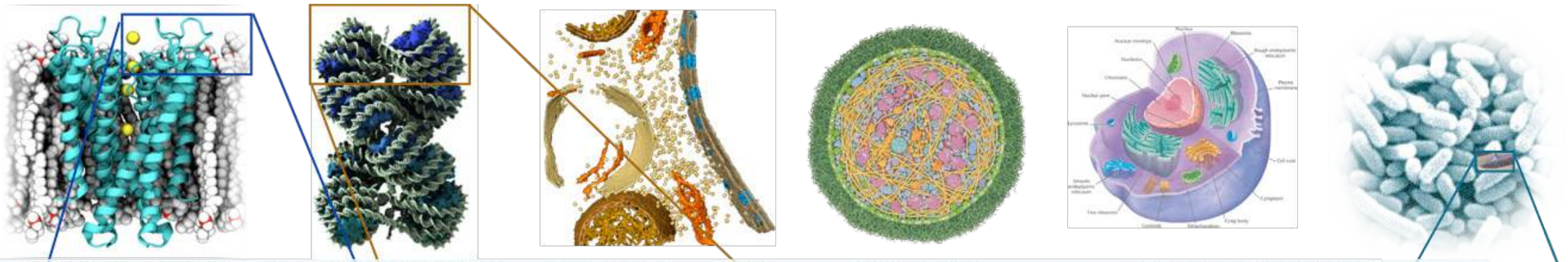
Introduction to MD simulations of DNA systems

Aleksei Aksimentiev

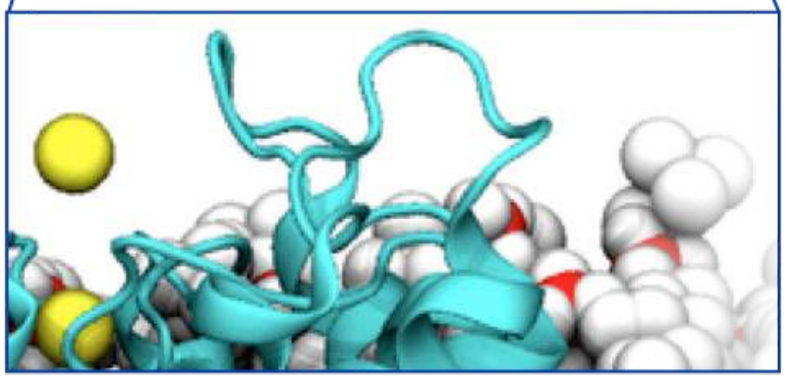
Biological Modeling at Different Scales

spanning orders of magnitude in space and time



all-atom MD (NAMD)

pairwise atomic potentials

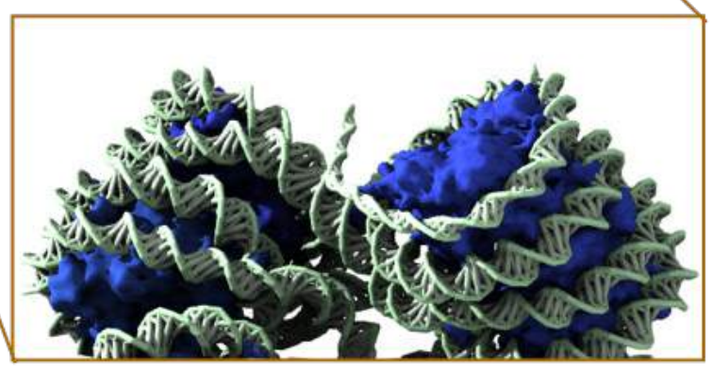


2 fs timestep

up to 10 μs

coarse-grained Brownian Dynamics (ARBD)

pairwise coarse-grained potentials

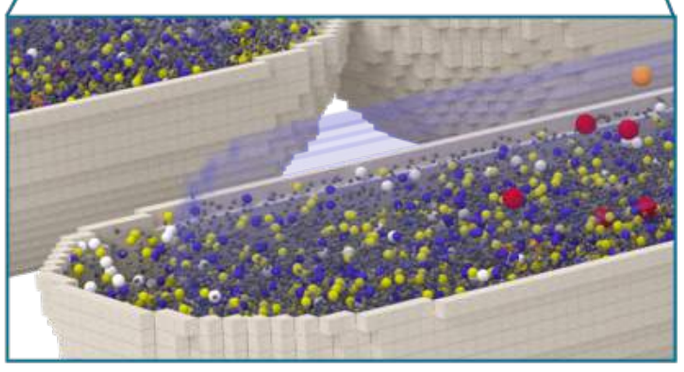


20-500 fs timestep

up to 10 ms

reaction–diffusion (Lattice Microbes)

reaction & diffusion probabilities

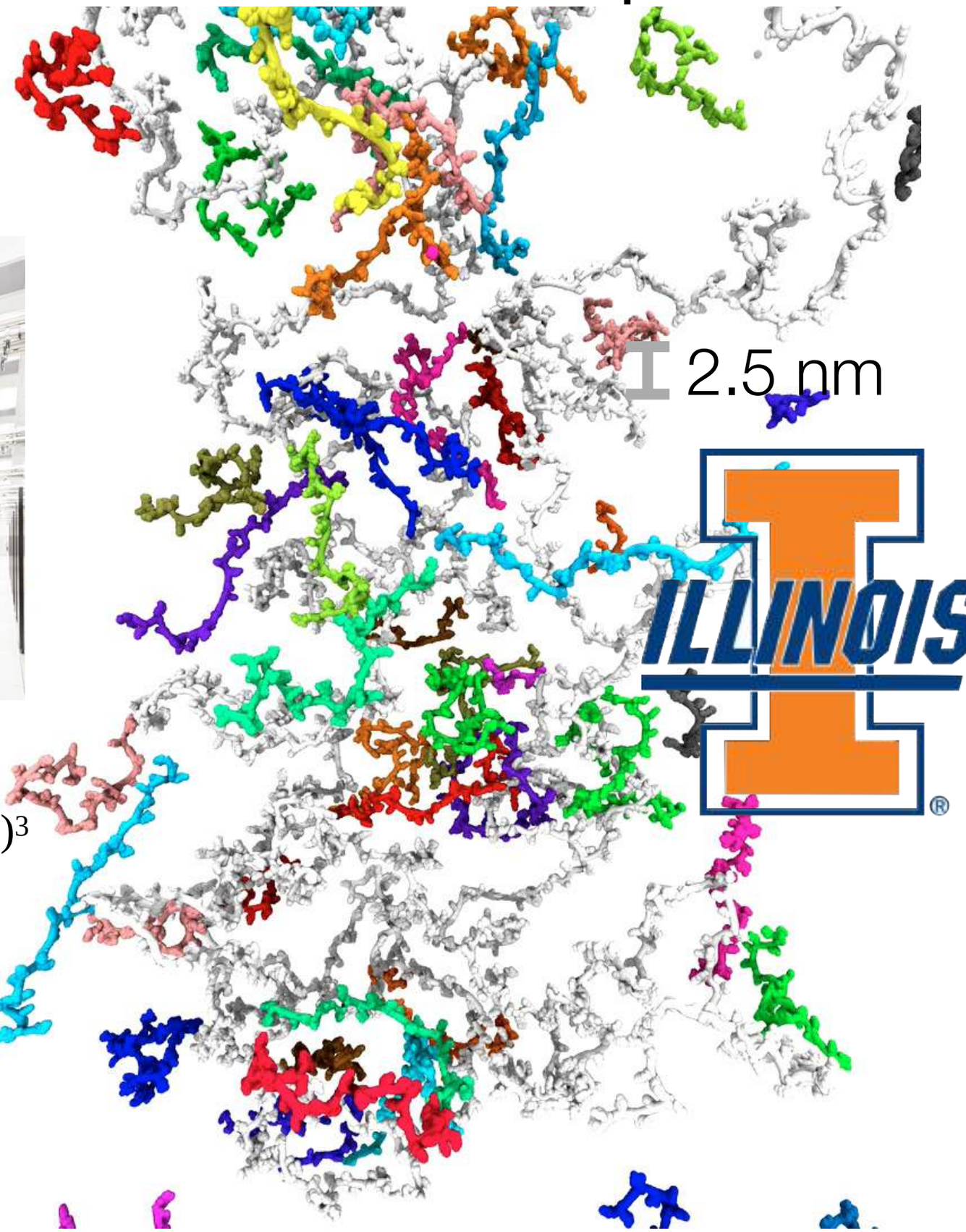


μs timestep

up to days

The computational microscope

Massive parallel computer
Blue Waters (UIUC): ~200,000 CPUs



Time scale: ~ 0.1-100 μs

Length scale: 10K - 1,000M atoms or (< 70 nm)^3

Time resolution: 2 fs

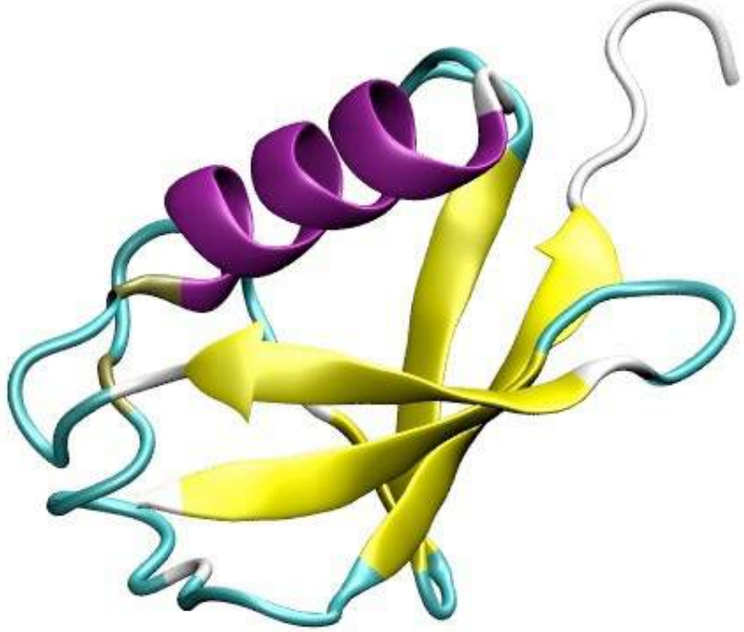
Spacial resolution: 0.1 A

Atoms move according to classical mechanics
(F= ma)

Interactions between atoms are defined by
the molecular force field

What is Molecular Dynamics?

$$m_i \frac{d^2 \vec{r}_i}{dt^2} = \vec{F}_i = -\vec{\nabla} U(\vec{R})$$

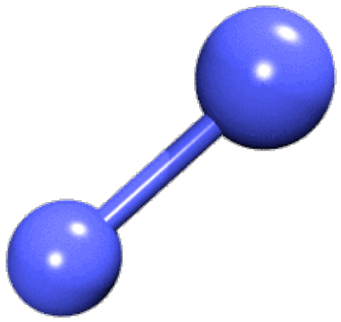


Energy function has two parts:

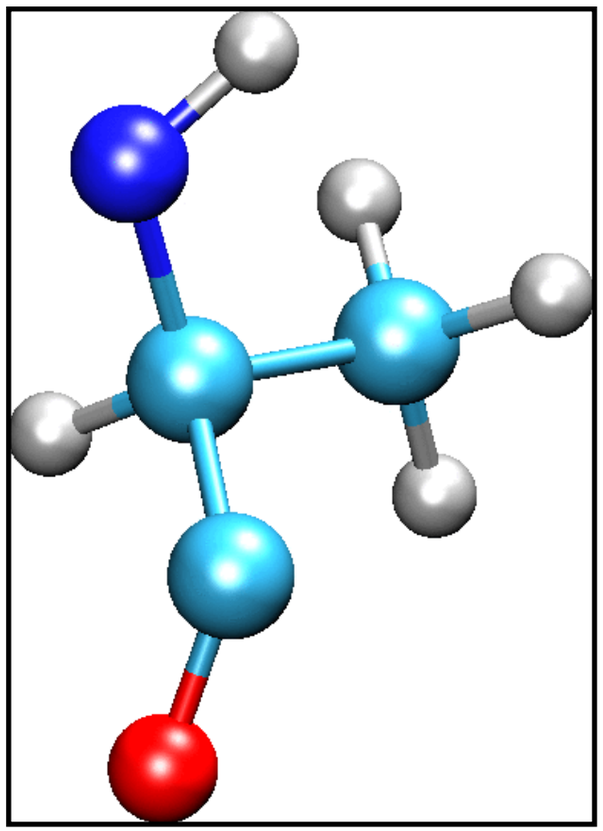
- chemical bond interactions

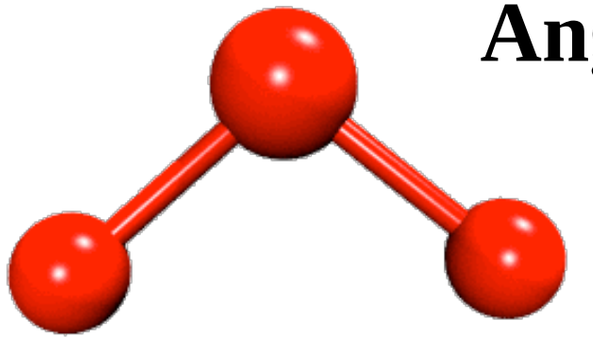
- non-bonded interactions

Chemical Structure



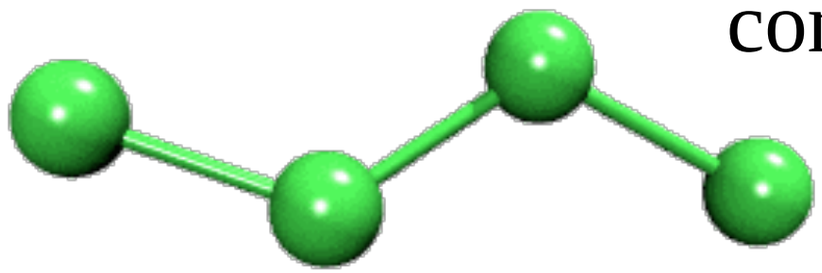
Bonds: Every pair of covalently bonded atoms.

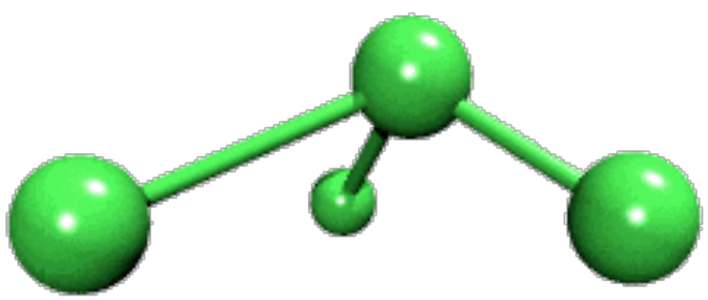




Angles: Two bonds that share a common atom form an angle.

Dihedrals: Two angles that share a common bond form a dihedral.



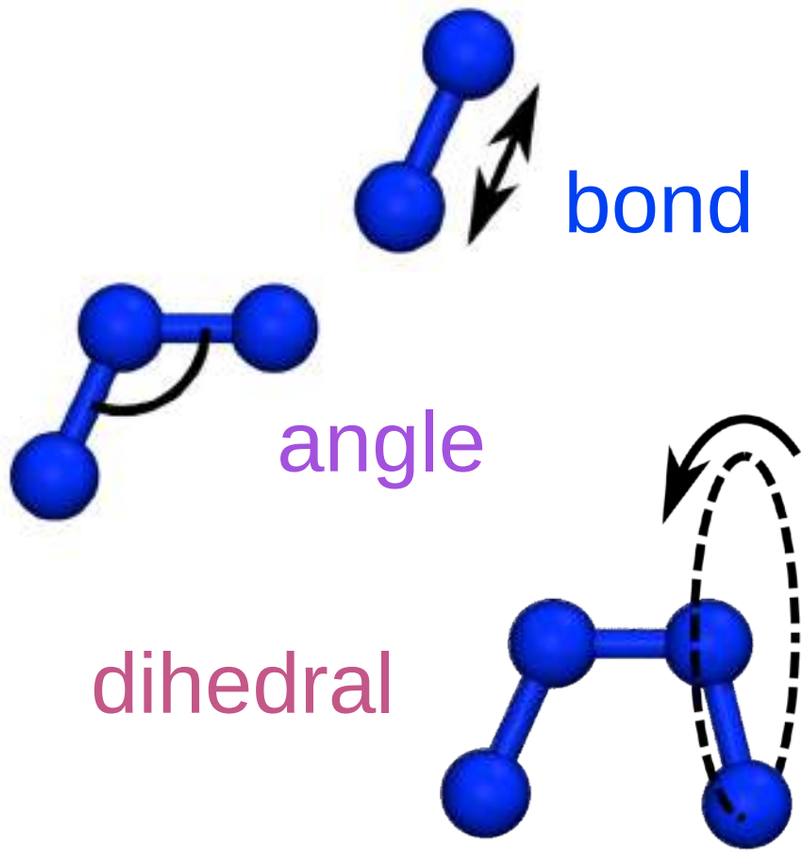


Impropers: Any *planar* group of four atoms forms an improper.

$$m_i \frac{d^2 \vec{r}_i}{dt^2} = \vec{F}_i = -\vec{\nabla} U(\vec{R})$$

The MD method models atoms with point particles interacting through classical potentials

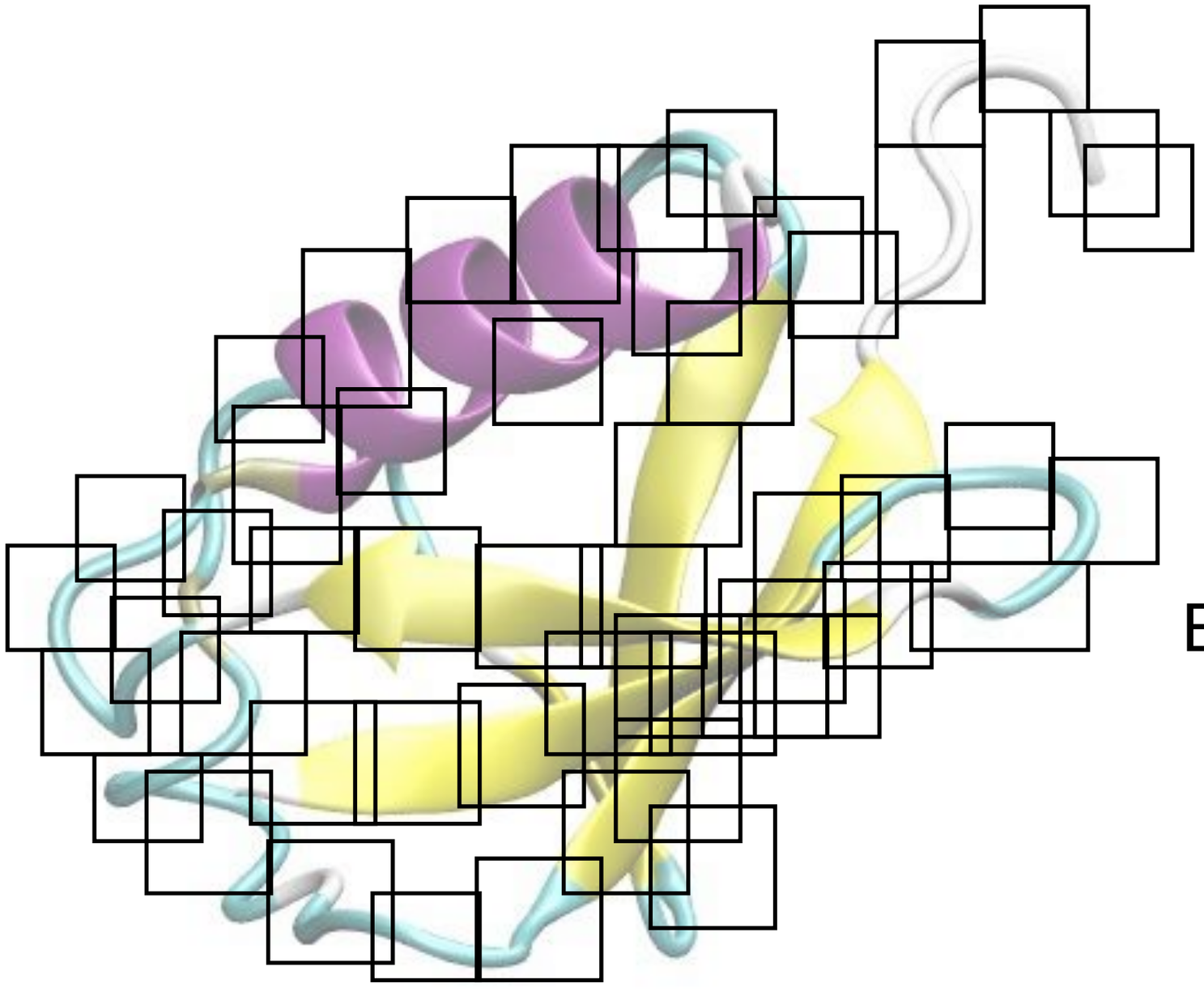
$$U = \sum_{\text{bonded}} \Big\{ k(r_{ij} - r_0)^2 + k_\theta(\theta - \theta_0)^2 + k(1 + \cos(n\psi + \phi)) \Big\} + \sum_{i>j} \Big\{ -U_{\min}\left[\left(\frac{R_{\min}}{r_{ij}}\right)^{12} - 2\left(\frac{R_{\min}}{r_{ij}}\right)^{6}\right] + \frac{C q_i q_j}{\epsilon_0 r_{ij}} \Big\}$$



Lennard-Jones
(van der Waals)

electrostatic

MD force field: a LEGO approach



- Parametrize parts of the structure

- Assemble the parts

Example: a protein is a collection of 20 amino acids

Bonding cannot change(!)

To run MD you'll need…

Computer (multi-core/GPU or cluster)

MD code (NAMD, Gromacs, Charmm, …)

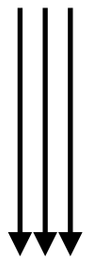
Input coordinates (typically .pdb): specifies initial state of the system

Protein structure file (typically .psf): specifies chemical bond information

Parameter file: provides atom-type specific values to interacting potentials

Configuration file (.namd or similar): run-type parameter, temperature, etc

Constraints or other simulation-specific files (typically .pdb)



Output: MD trajectory (.dcd file): describes how coordinates change in time

Analysis tools (VMD, python, etc.

What is MD good for?

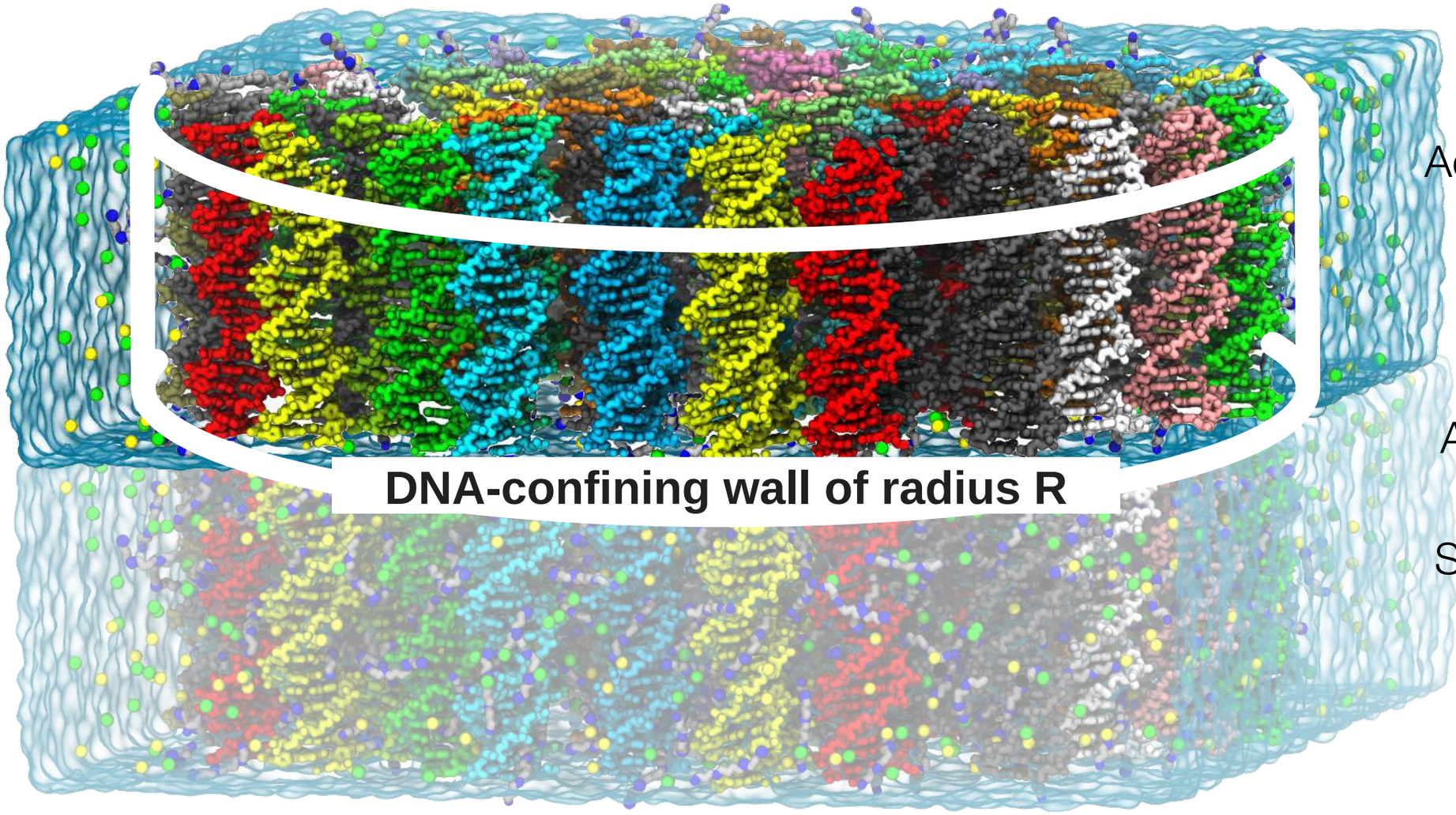
Minimum requirements:

- Well-defined question
- Atomic-detail structure (or disordered state)
- Minimum chemistry
- Volume of 60 x 60 x 60 nm^3 or less
- Processes taking less than 100 microseconds

Typical questions:

- What is the equilibrium structure in physiological environment?
- What is the free-energy cost of going from A to B?
- What is the path from A and B?
- How does the structure respond to external force or field?
- What is going on in my experiment?

All-Atom Molecular Dynamics Simulation of DNA Condensates



Add **64 DNA** helices

Add **polyamine cations (+4)**

Add 150 mM **NaCl**

Add explicit **water**

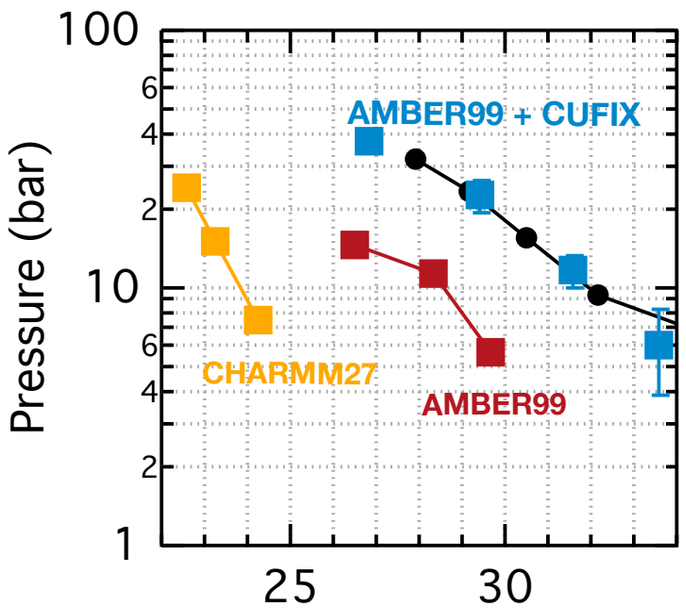
Apply a half-**harmonic wall potential** only to DNA

Solve the equation of motion (F= ma) under **periodic boundary condition** in all directions

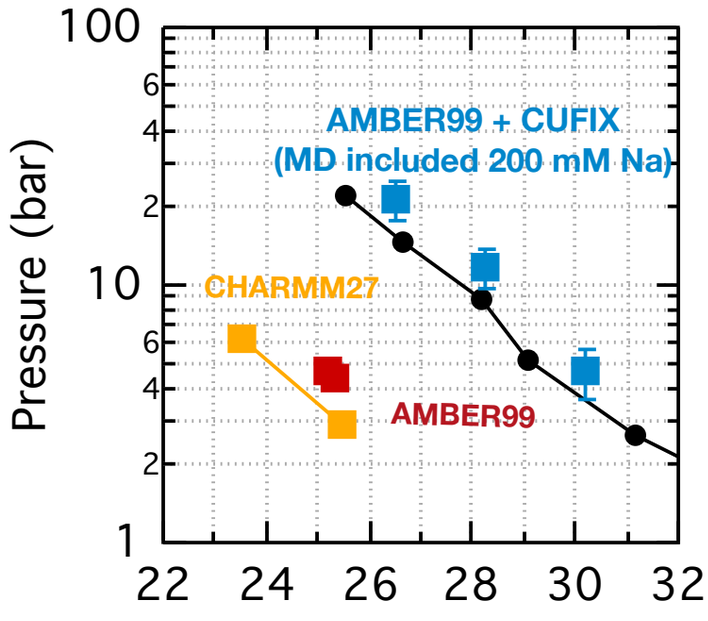
CUFIX Improves Simulations of DNA Condensates

http://bionano.physics.illinois.edu/CUFIX

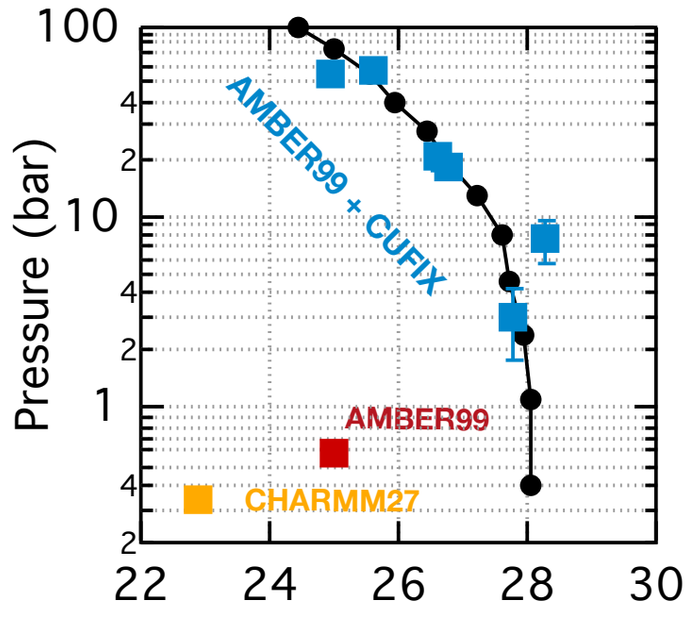
[Na] = 250 mM



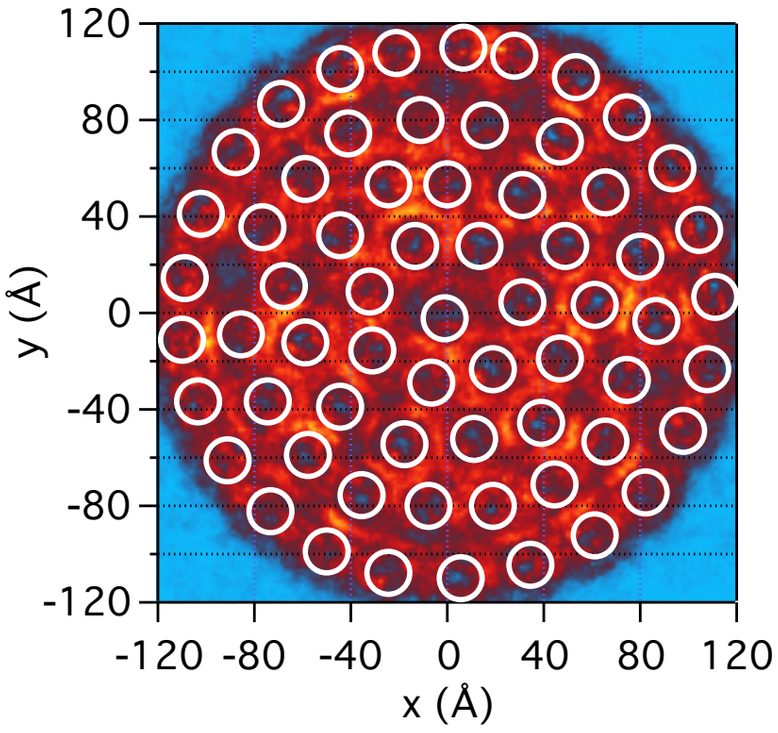
[Mg] = 20 mM



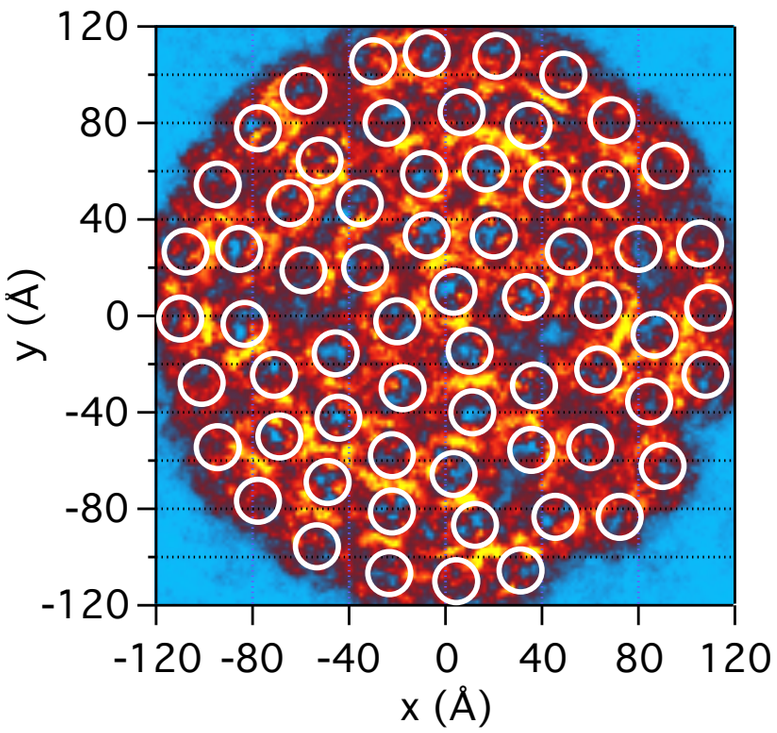
[spermine] = 2 mM



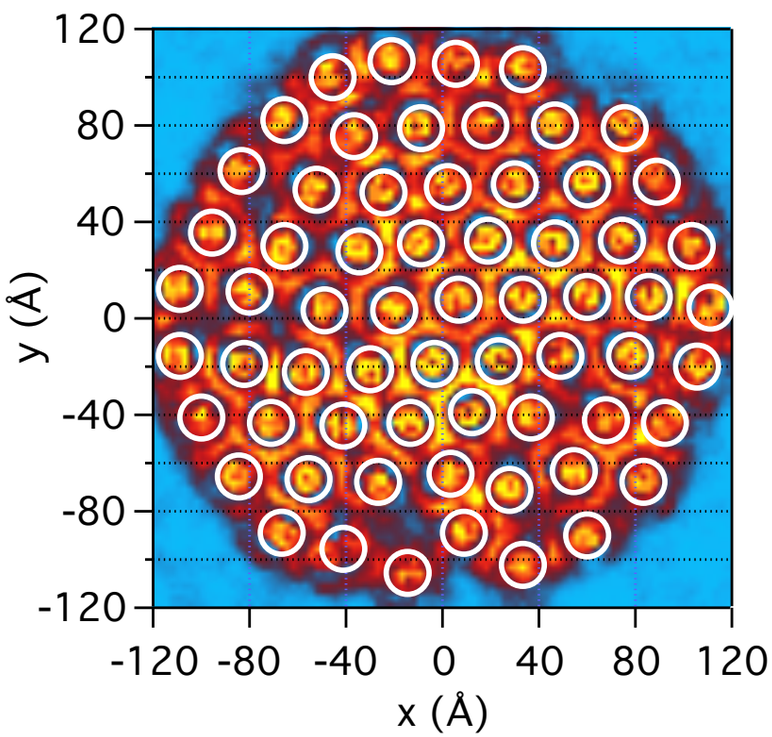
DNA-DNA distance (Å)



DNA-DNA distance (Å)



DNA-DNA distance (Å)

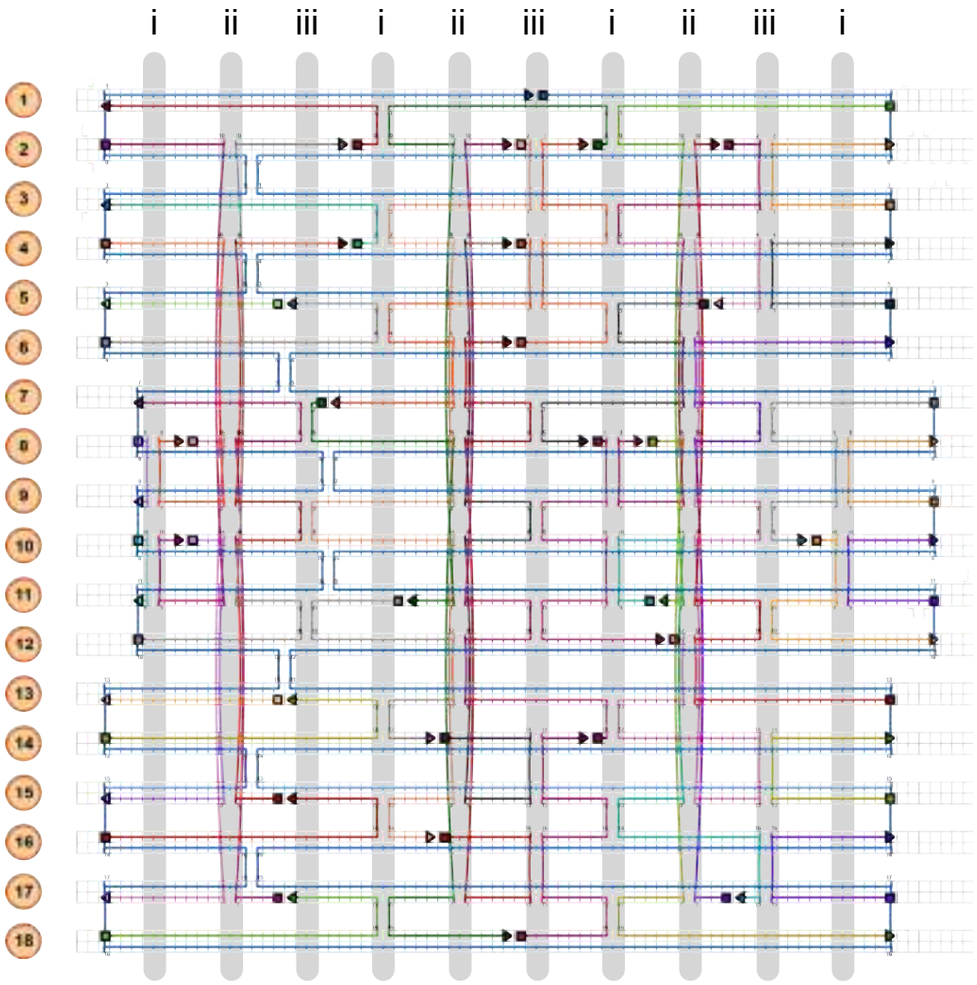


Yoo & Aksimentiev, *NAR* 2016

From caDNAno to all-atom

Jejoong Yoo

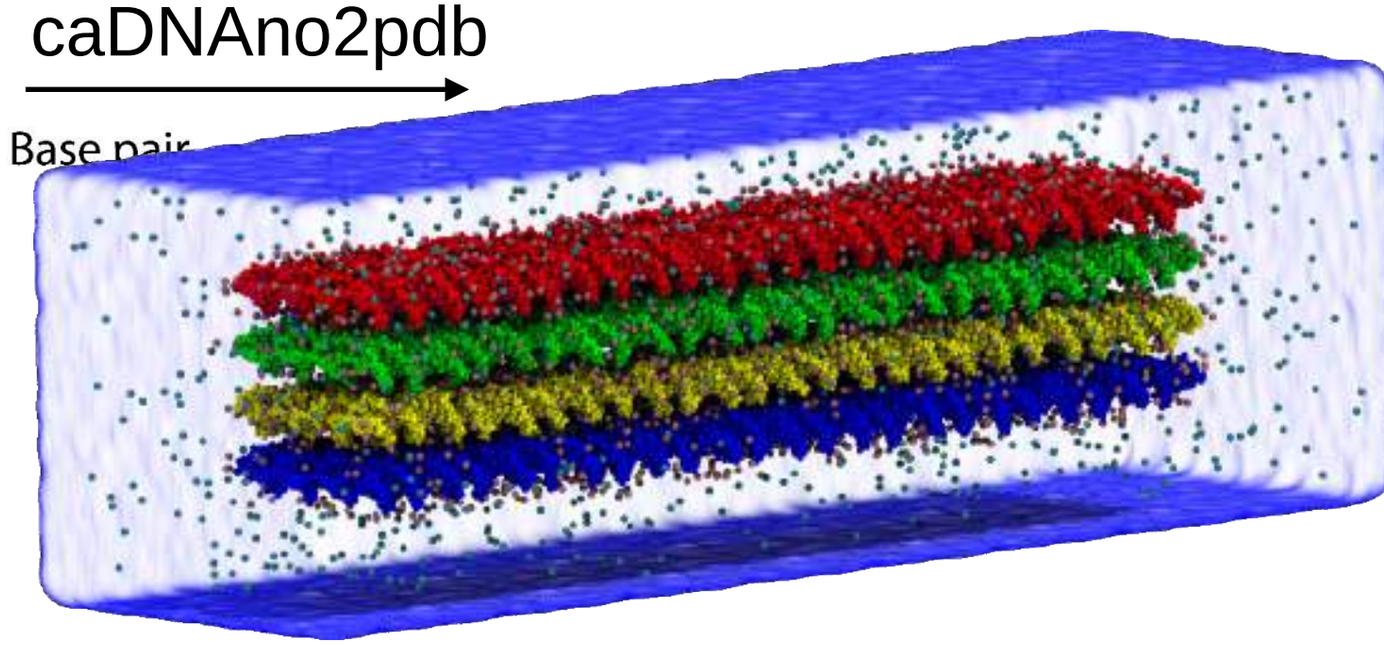
Cadnano design



SM. Douglas,…, WM. Shih,
Nucleic Acids Res., 2009

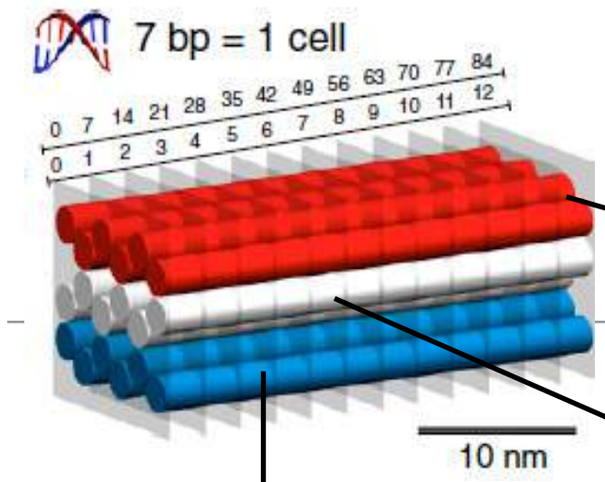
Solvated structure

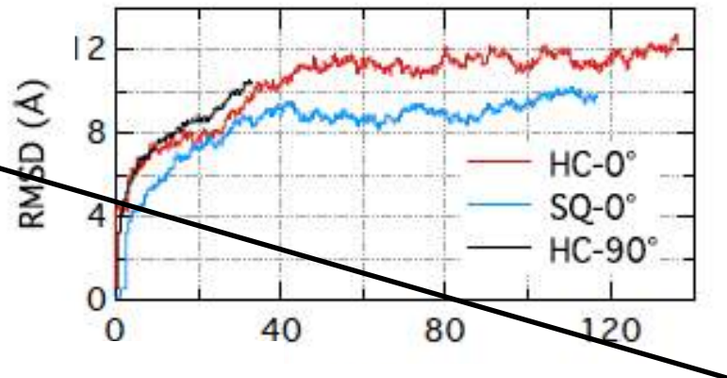
caDNAno2pdb

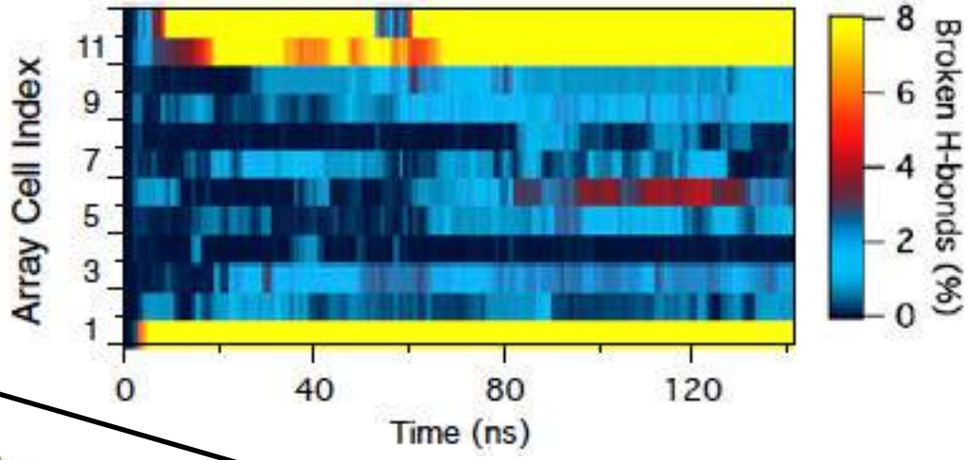


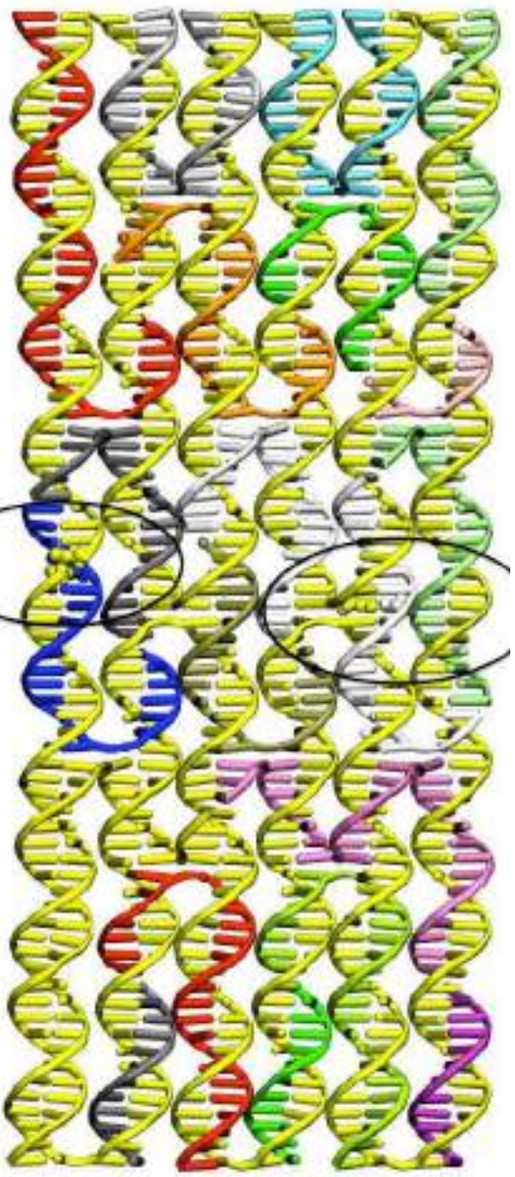
- CHARMM36 force field
- Explicit water
- [$MgCl_2$] ~ 10 mM
- NAMD
- 1 to 3M atoms
- 500 to 1,000 CPUs

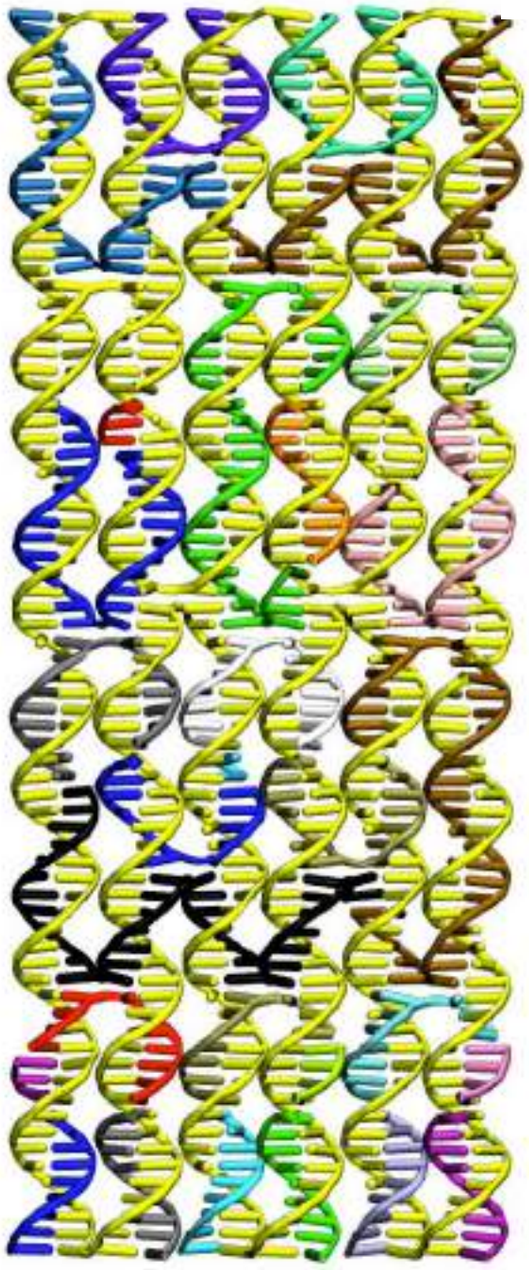
Structural dynamics

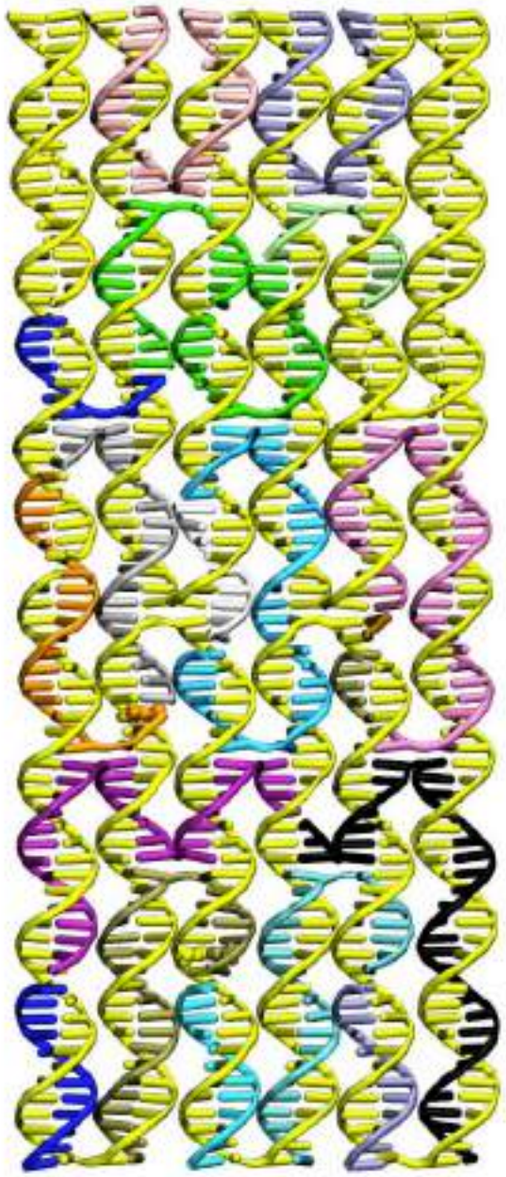






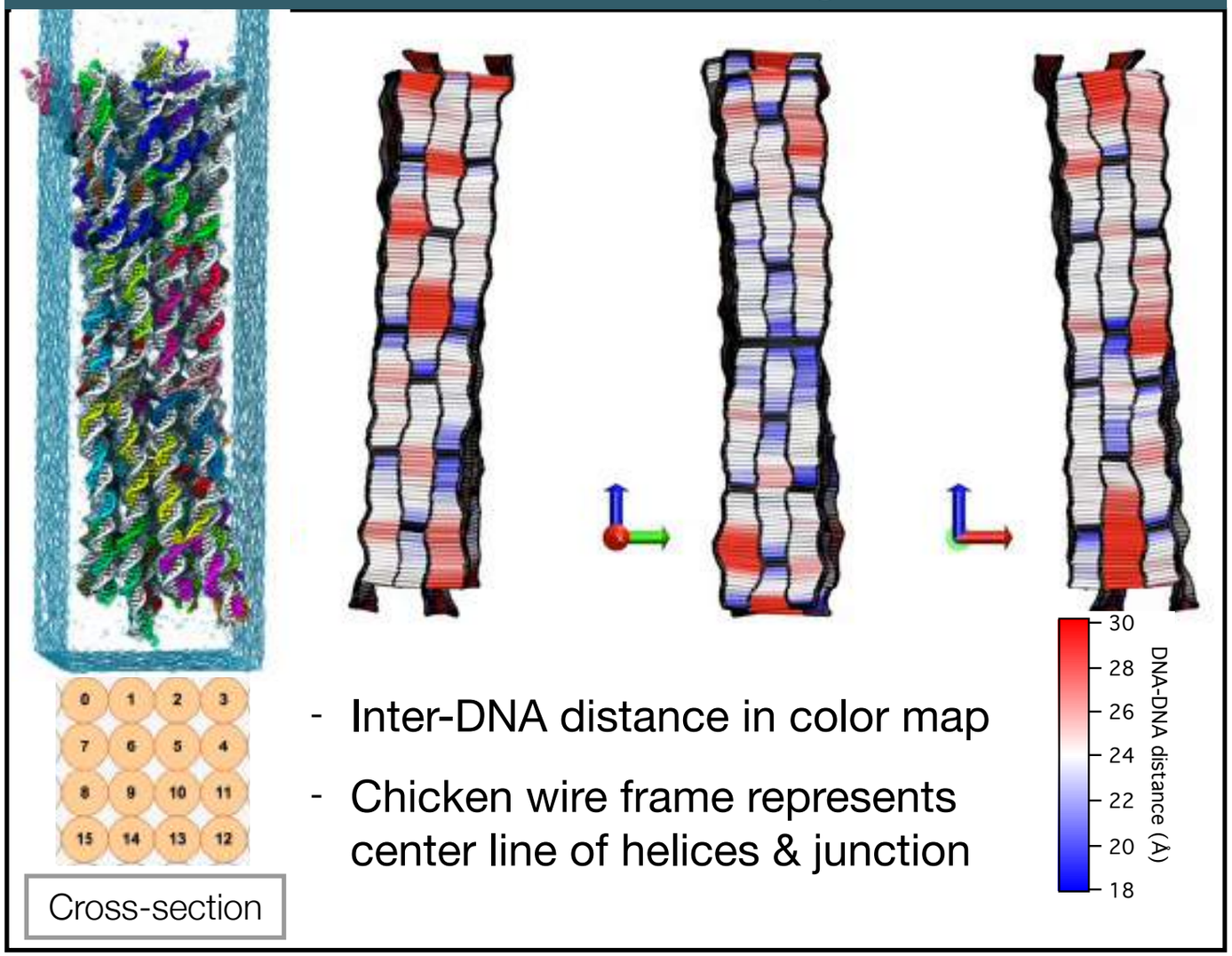






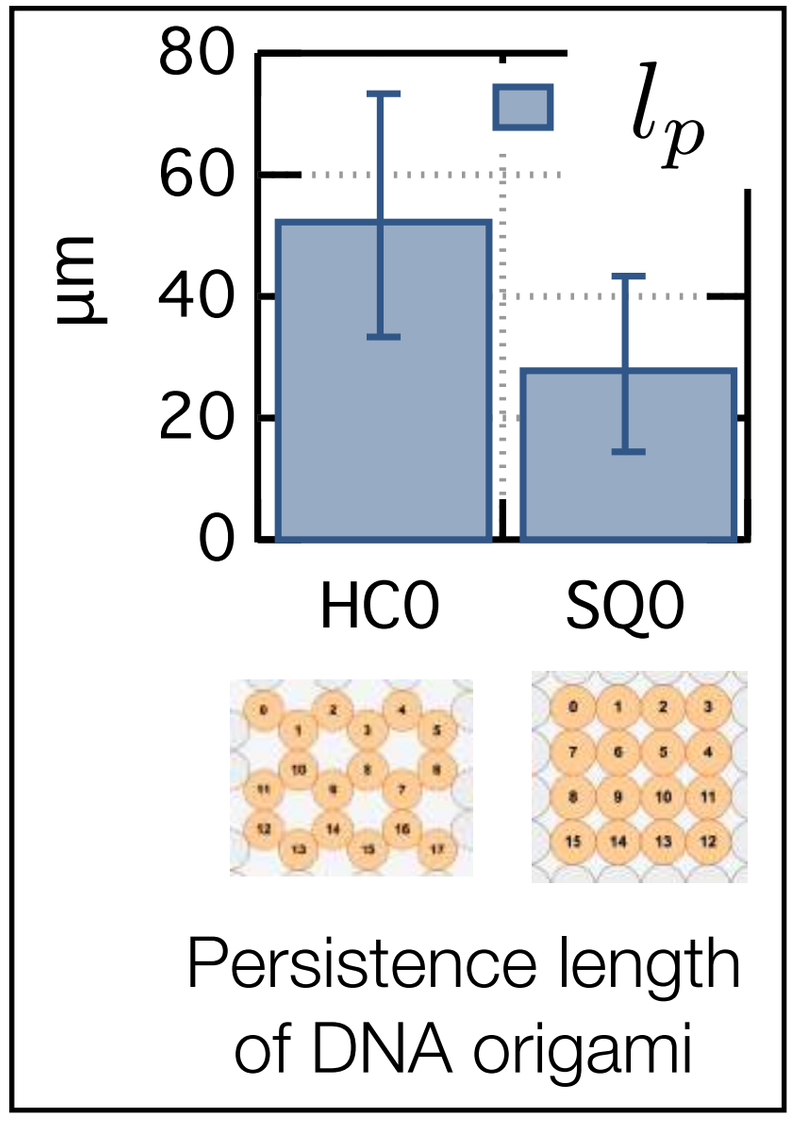
Structural fluctuations reveal local mechanical properties

Structural fluctuation of DNA origami nanorod



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

Yoo and Aksimentiev, PNAS 110:20099 (2013)



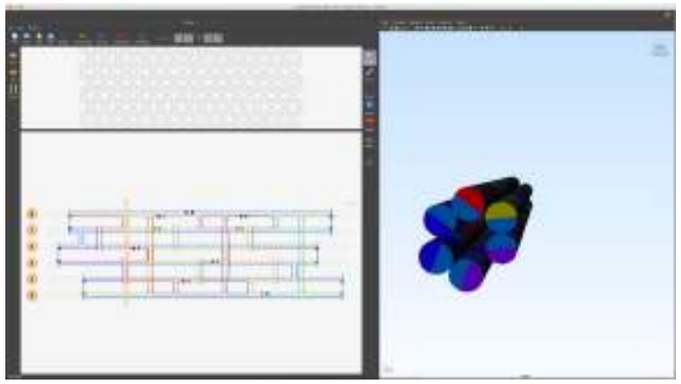
Persistence length of DNA origami

Simulations predict higher rigidity for honeycomb-lattice design

A Practical Guide to DNA Origami Simulations Using NAMD

— Walk through the protocol for all-atom simulations of DNA origami using the NAMD package

Cadnano design

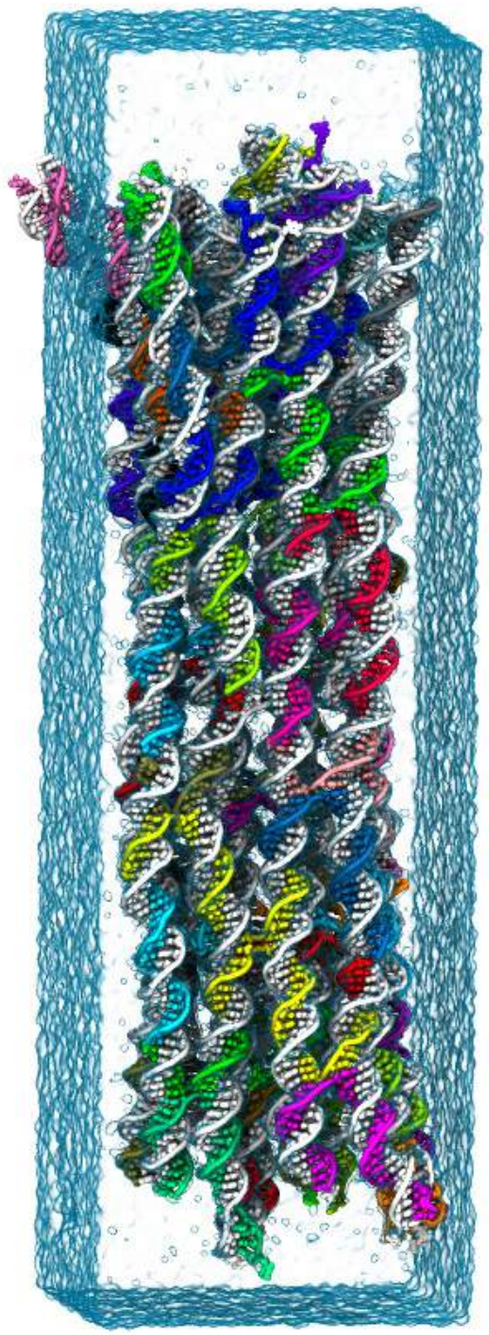


cadnano2pdb web server

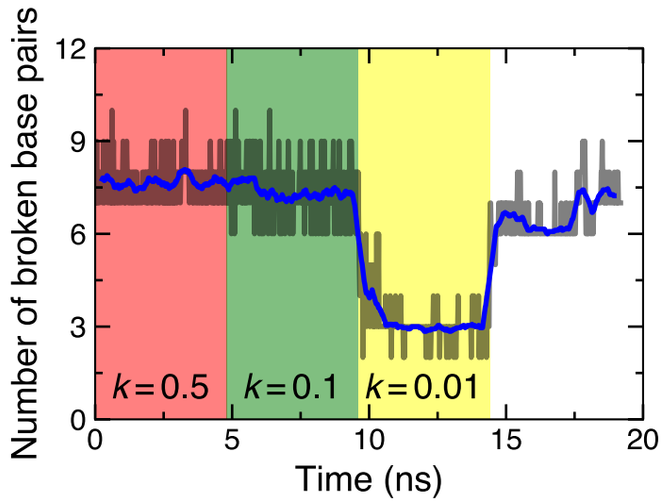
All-atom model

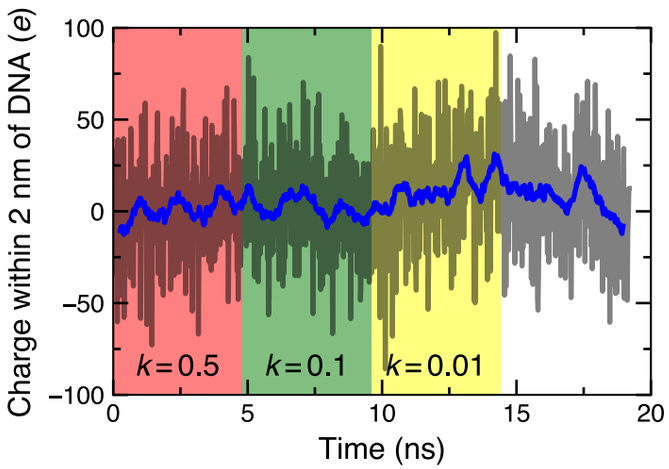
After optimization

All-atom structure in a $MgCl_2$ solution



Perform MD simulation and analysis

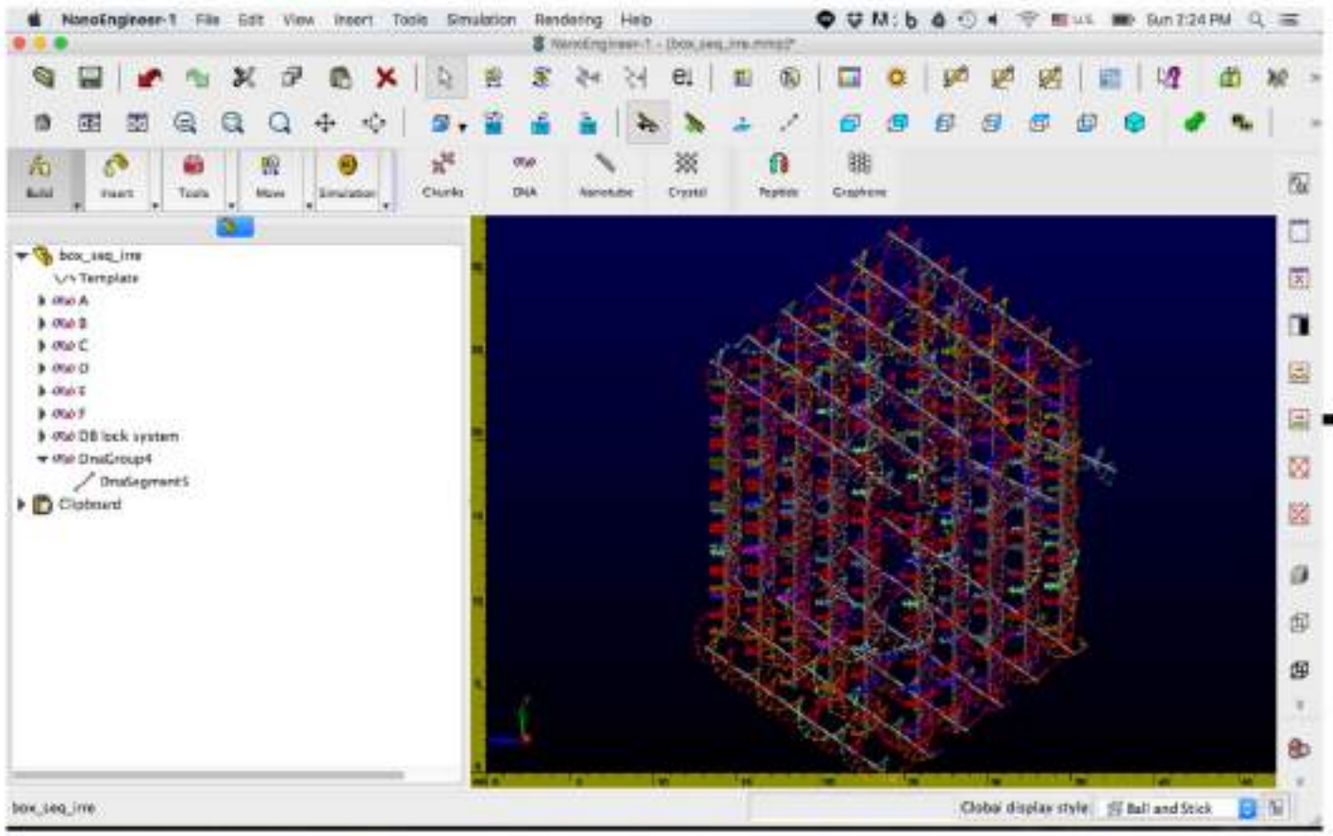


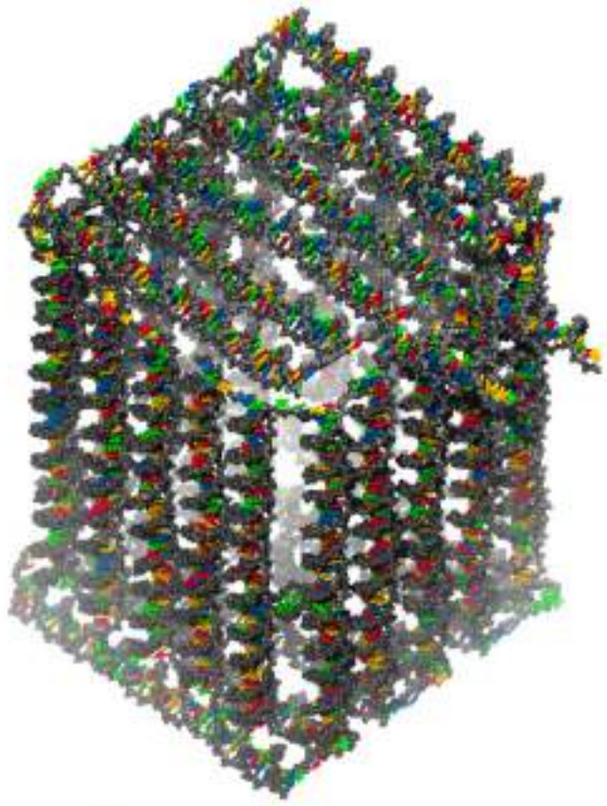


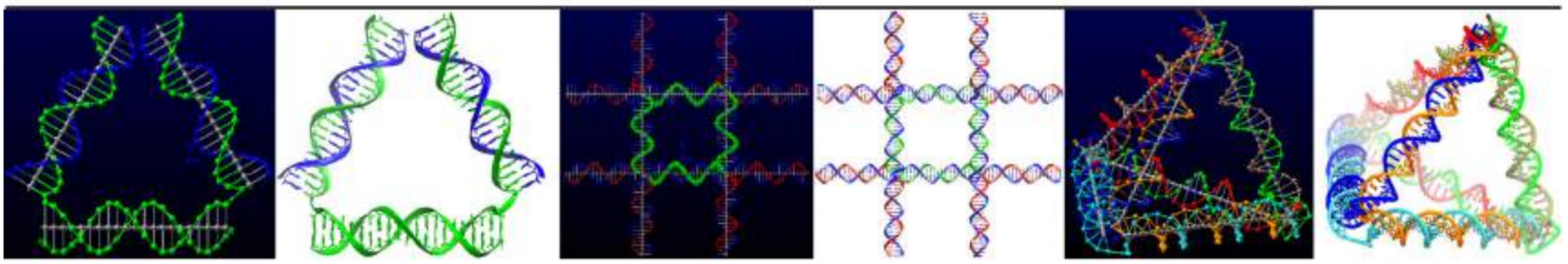
NanoEngineer-1

All-atom PDB

Chen-Yu Li

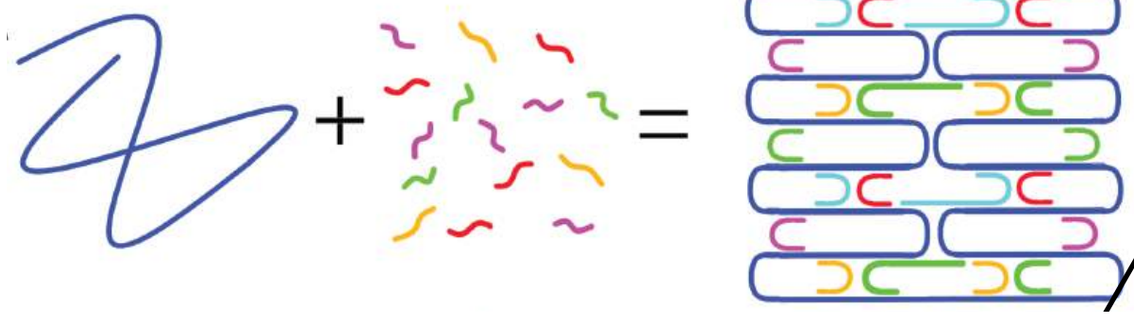


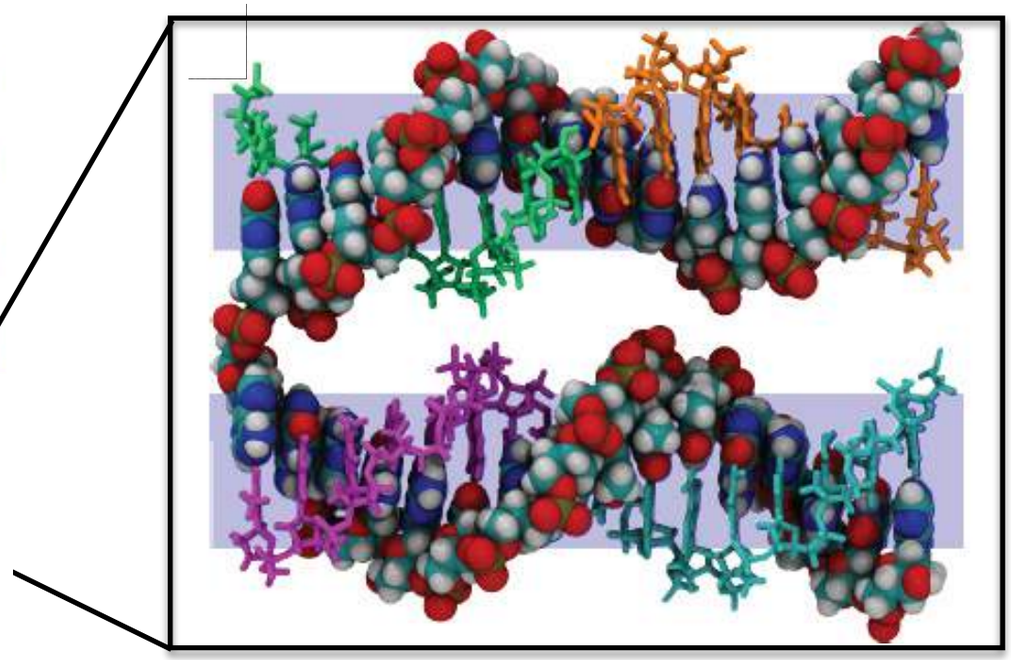




Tiled DNA nanostructures

DNA Origami

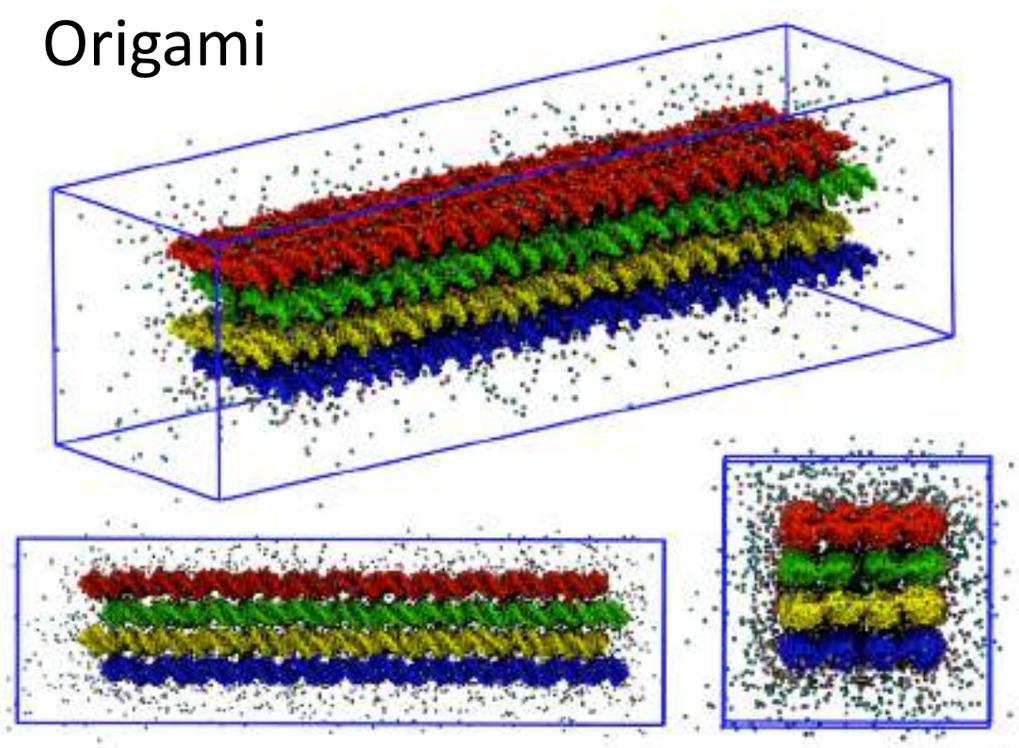




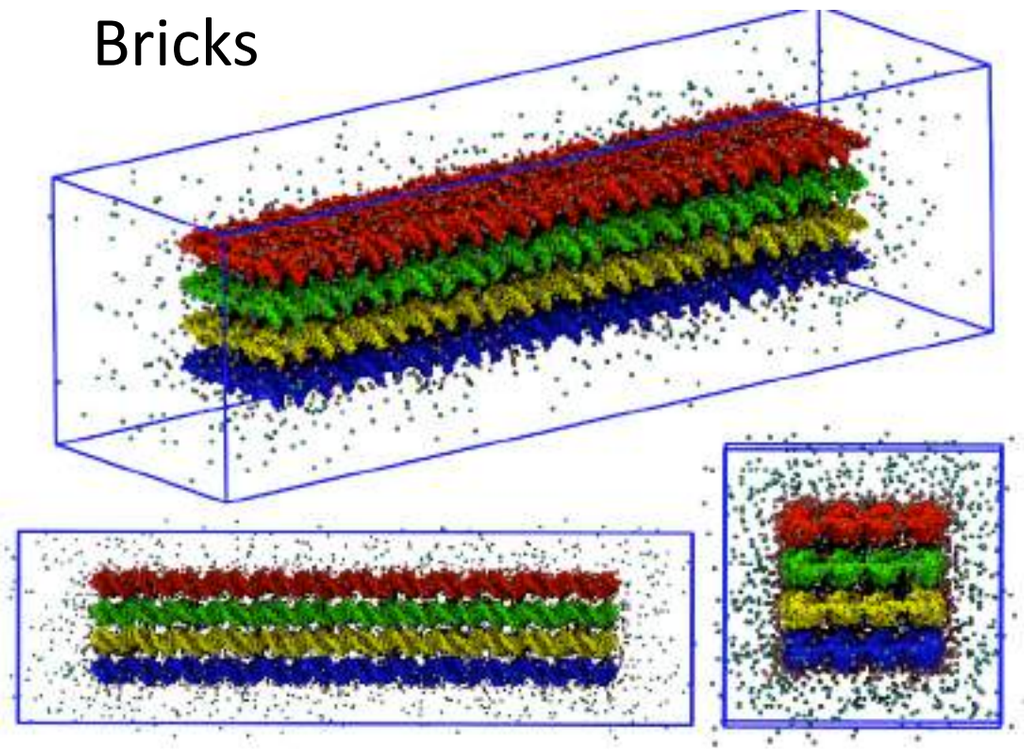
Identical nucleotide sequence in both structures

All-atom MD 165 ns each

Origami



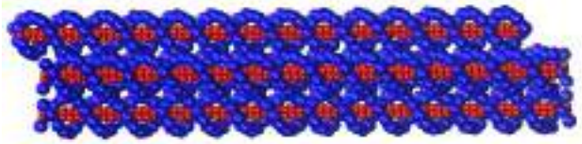
Bricks

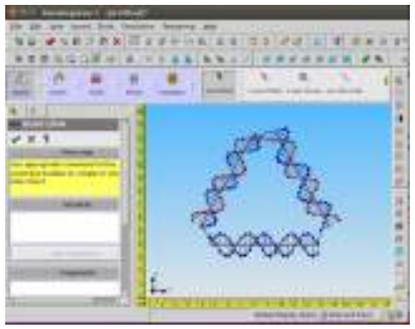


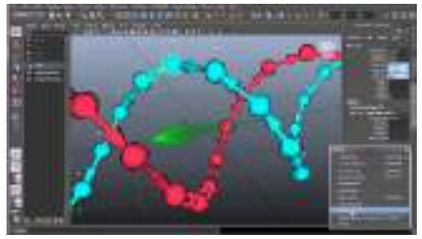
Slone et al., New J. Phys. 18:055012 (2016)

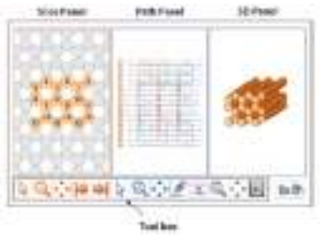
nanohub.org/resources/legogen

ENRG MD tool kit : a universal all-atom structure converter









oxDNA

Nanoengineer

vHelix

CaDNAnano

DAEDALUS: DNA Origami Sequence Design Algorithm for User-defined Structures

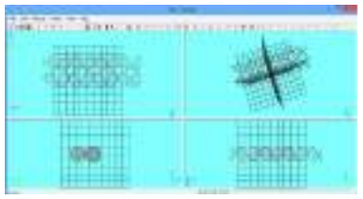
Submission Page

DAEDALUS

CanDo

NAB

Tiamat



```
transformmol(mat_drz,m,NULL);
mergestr(m1,"A","last",m,"sense","first");
freemolecule (m);
n=NULL;
s="a";
                    }
m_temp=copymolecule (m1);
mat_x  = newtransform (17.32,10.,0.,0.,0.,0.);
transformmol(mat_x,m_temp,NULL);
putpdb ("dna2.pdb",m_temp);
mergestr(m_final,"D","last",m_temp,"A","first");
```

enrgmd tool-kit

#enrgmd hextube.json

Toolkit

NAMD all-atom MD Simulation Files

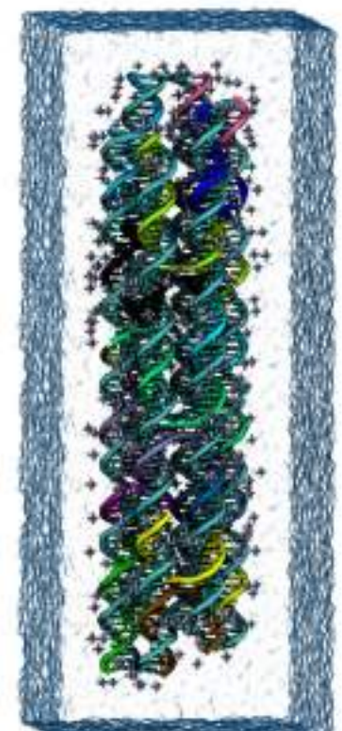
hextube.psf

hextube.pdb

hextube.namd

hexube.exb

CHARMM parameters

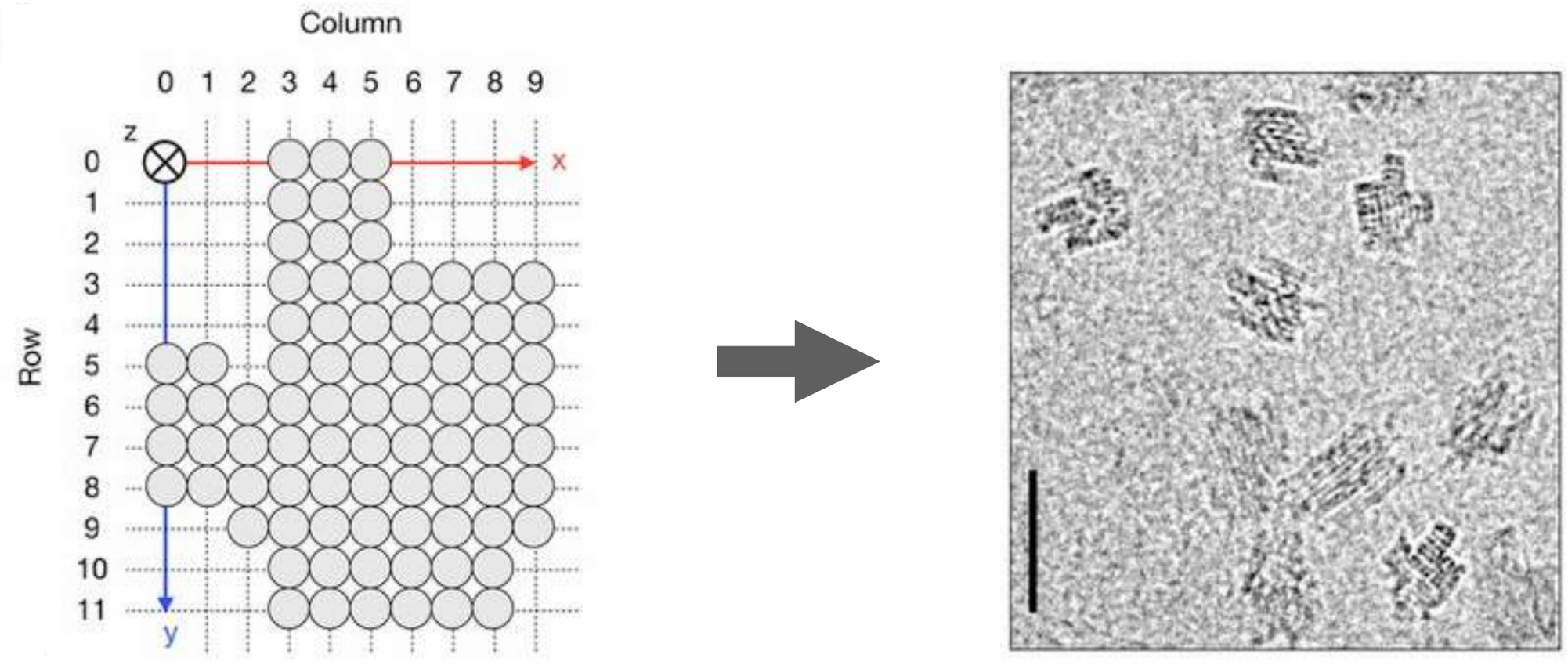


Cryo-EM reconstruction versus all-atom simulation

High-resolution cryo-electron microscop

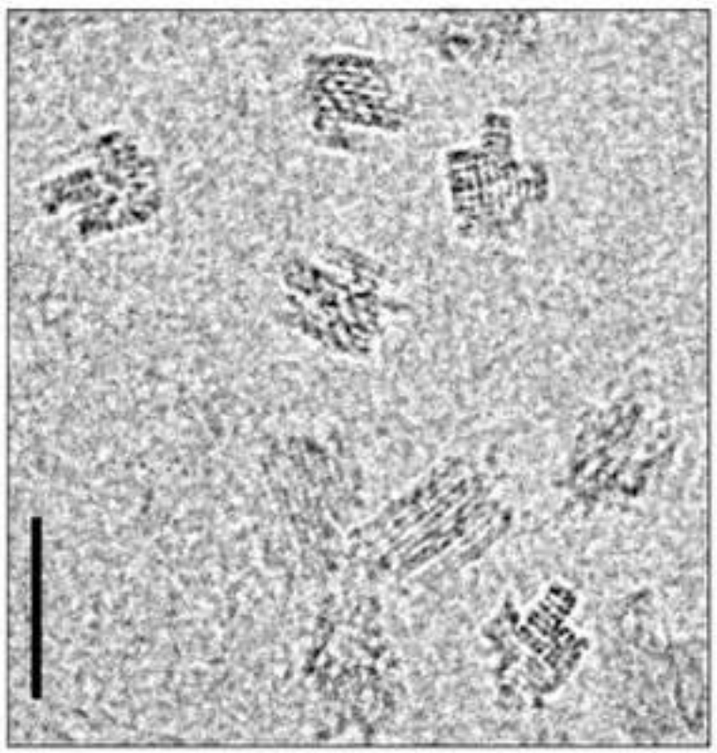
Petascale computer system

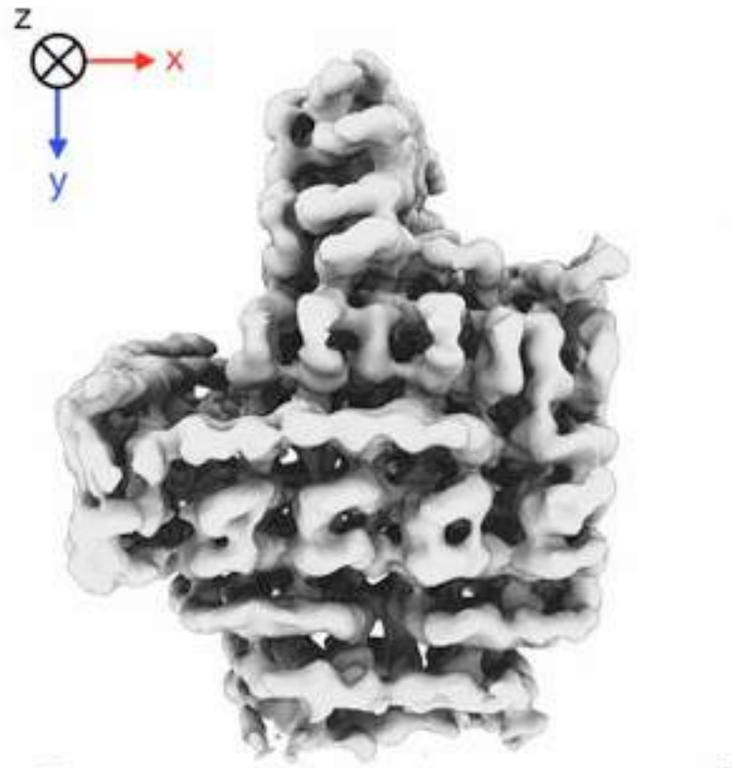
Cryo-EM reconstruction versus all-atom simulation



Bai *et al*, PNAS 109:20012 (2012)

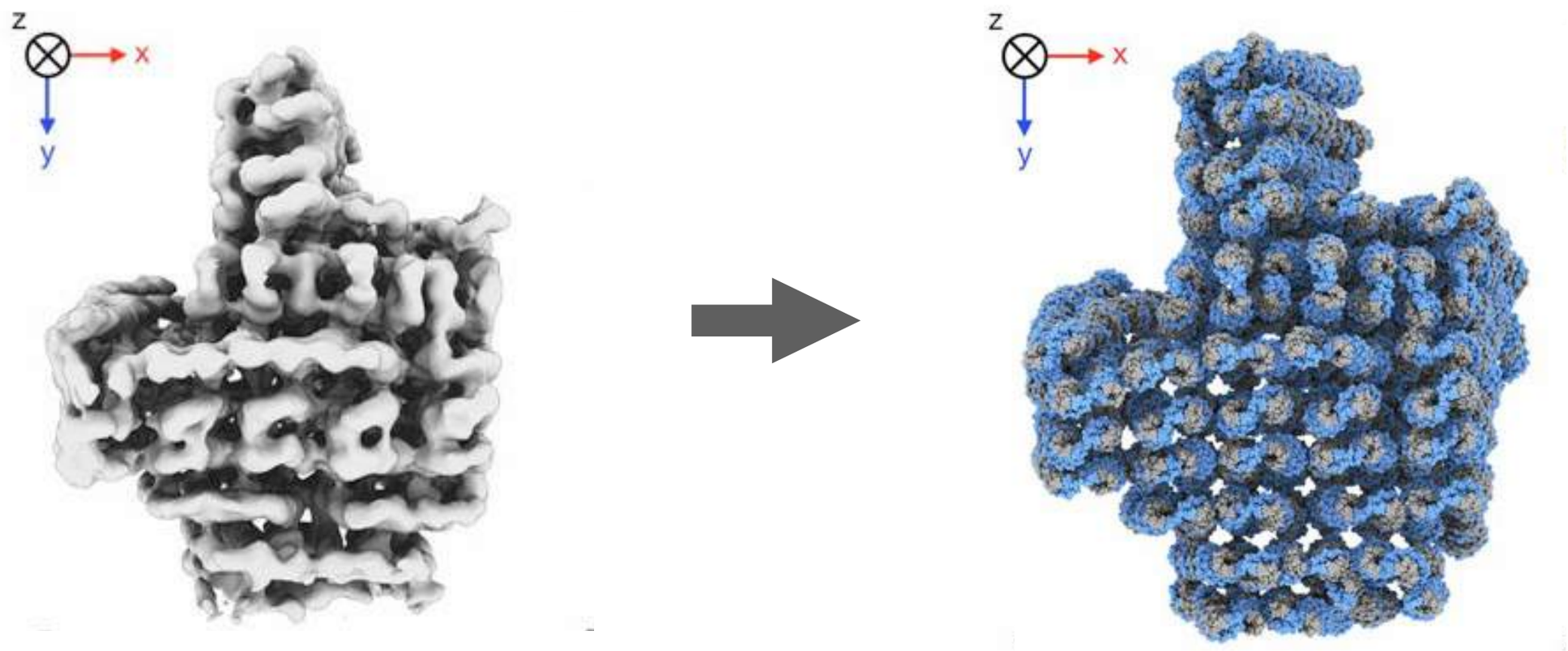
Cryo-EM reconstruction versus all-atom simulation





Bai *et al*, PNAS 109:20012 (2012)

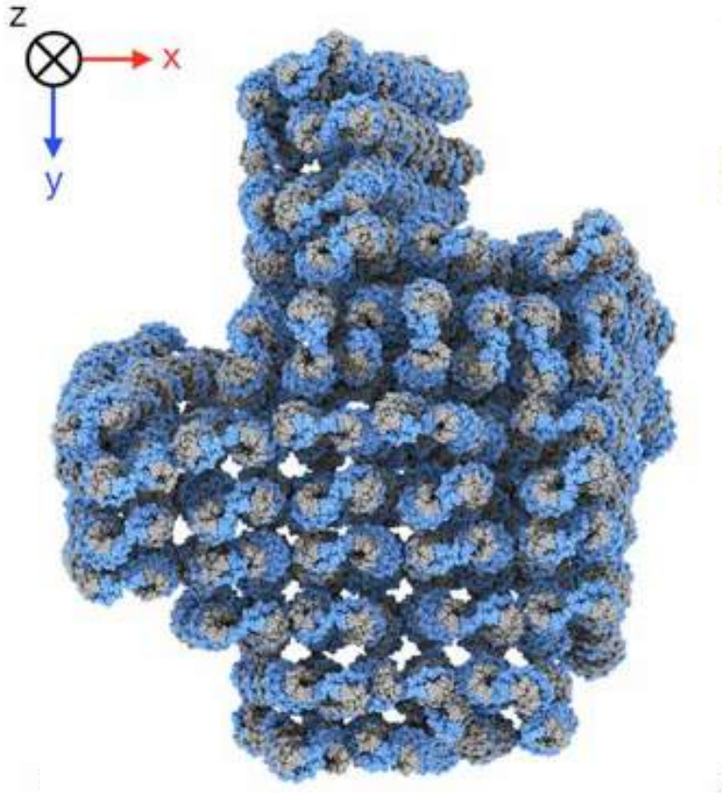
Cryo-EM reconstruction versus all-atom simulation



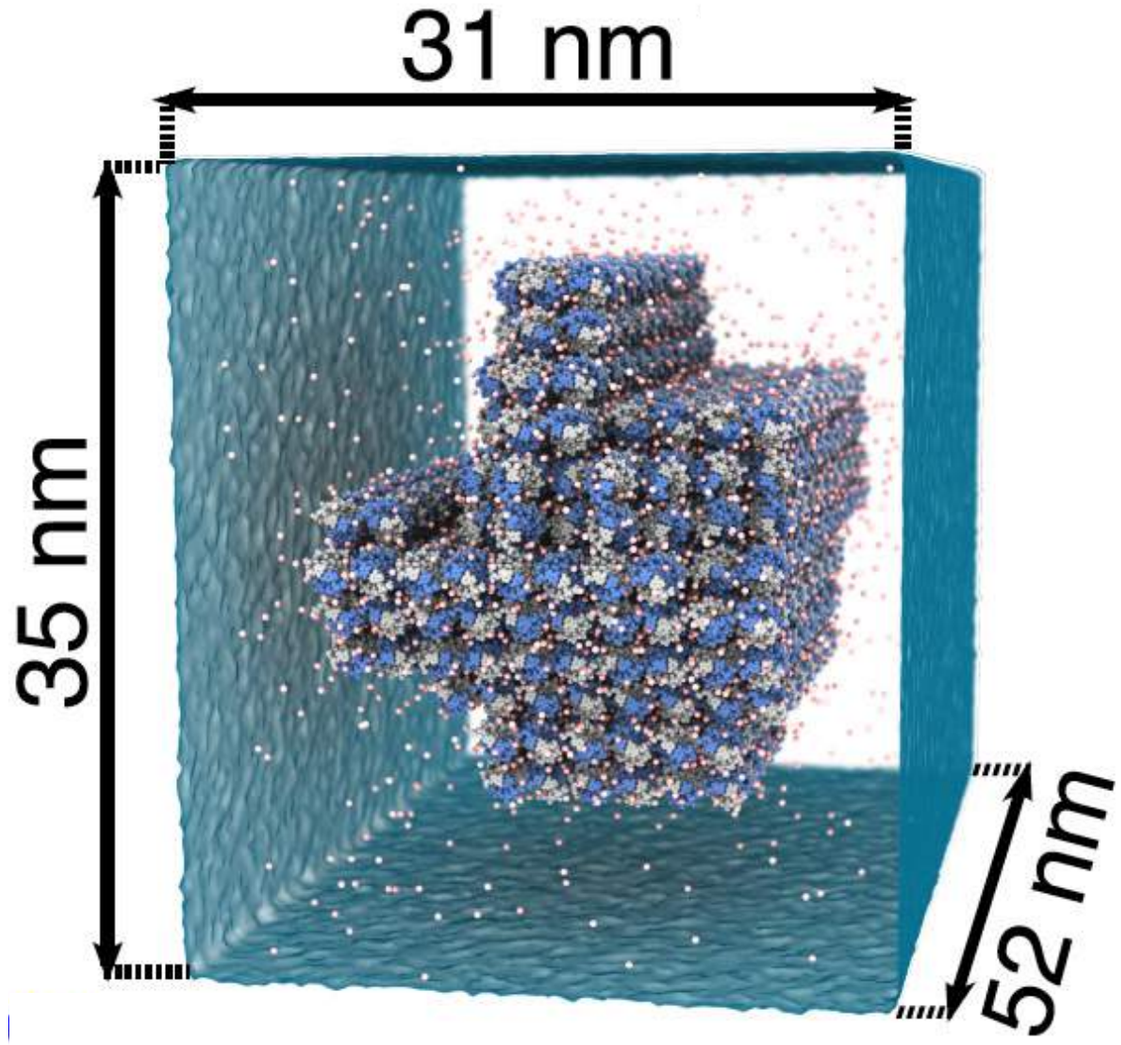
Pseudo-atomic model

Bai *et al*, PNAS 109:20012 (2012)

MD simulation of the cryo-EM object starting from a caDNAno design

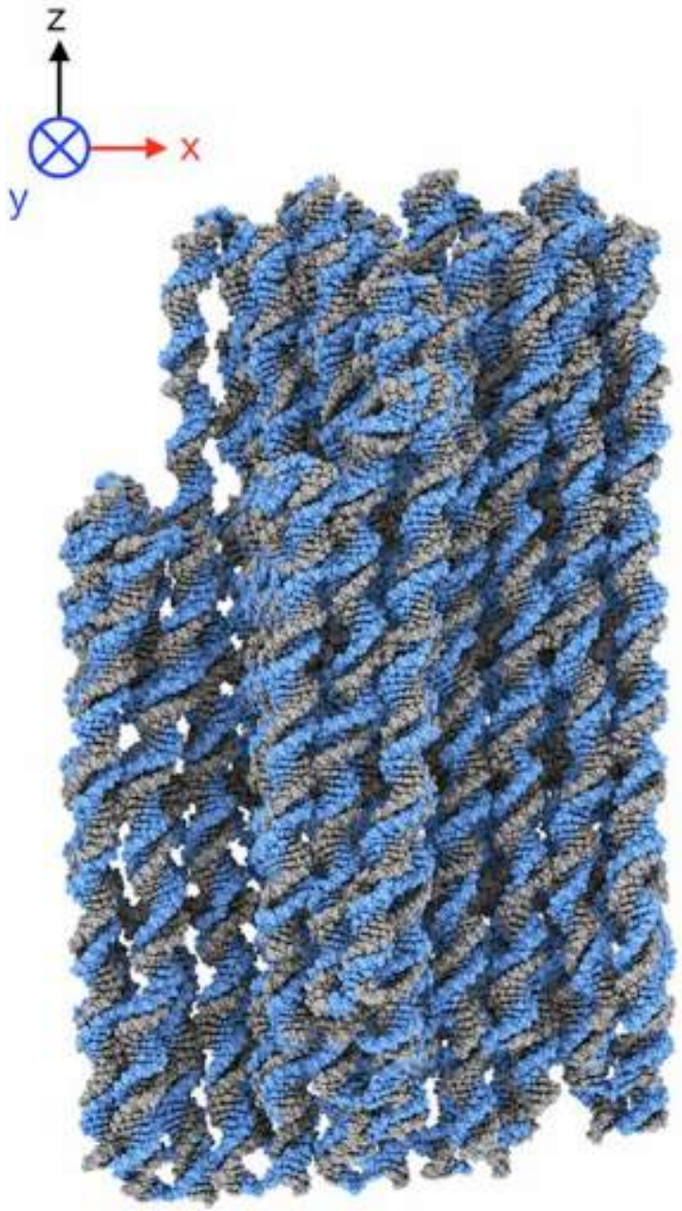


Bai *et al*, PNAS 109:20012 (2012)

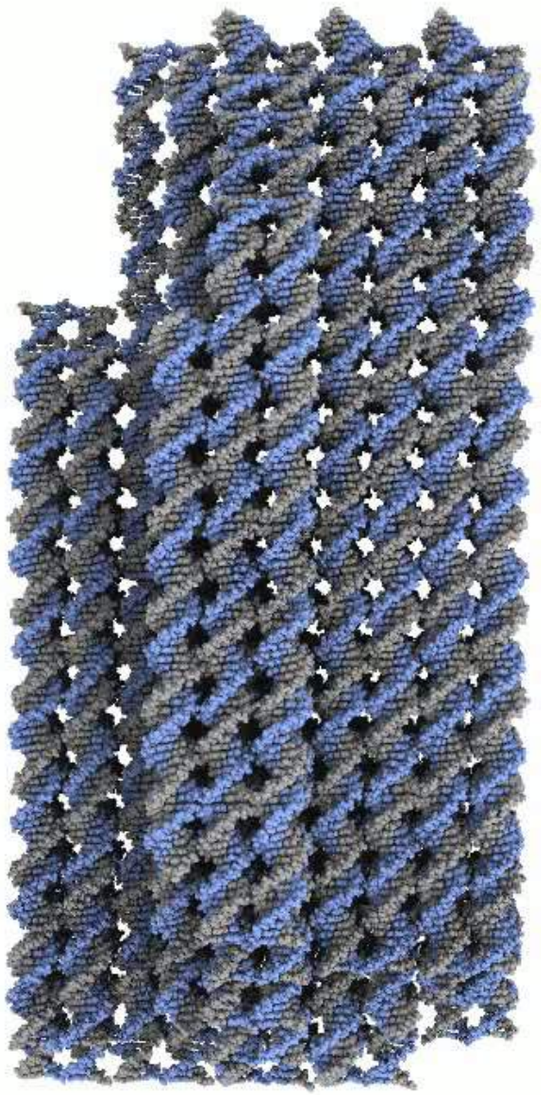


7M atom solvated model
~200 ns MD trajectory

MD simulation of the cryo-EM object starting from a caDNAno design



Bai *et al*, PNAS 109:20012 (2012)



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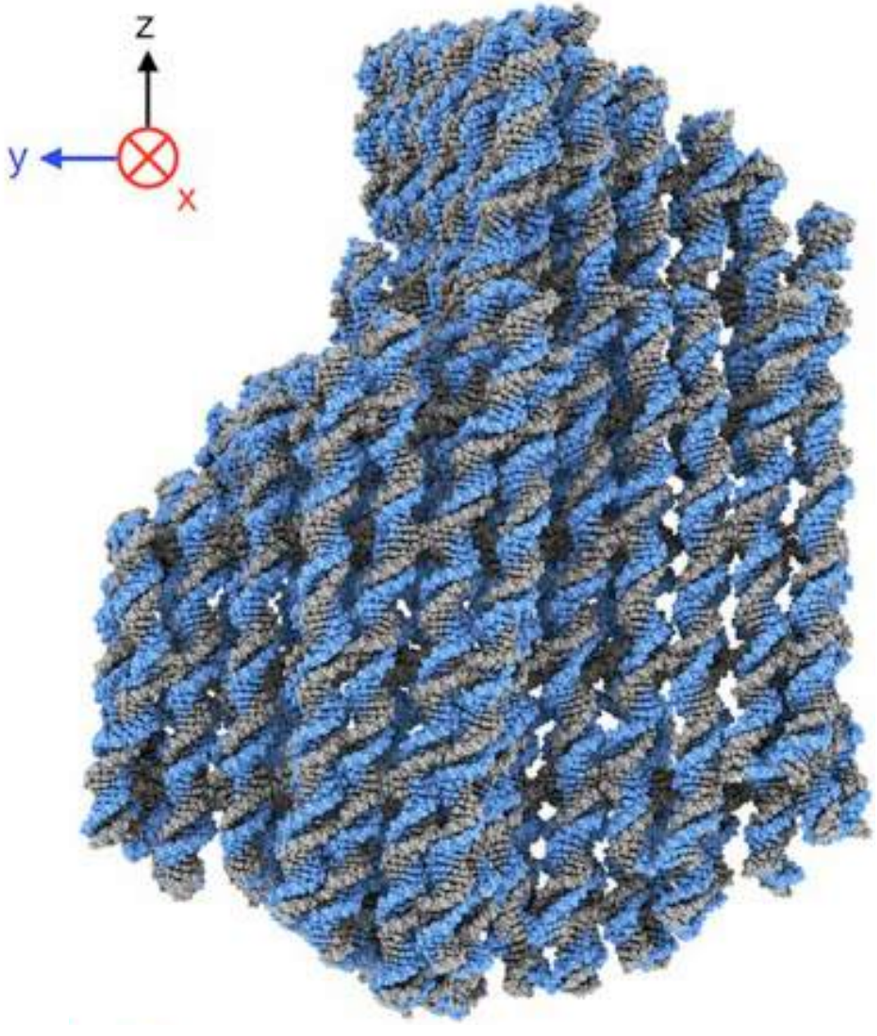
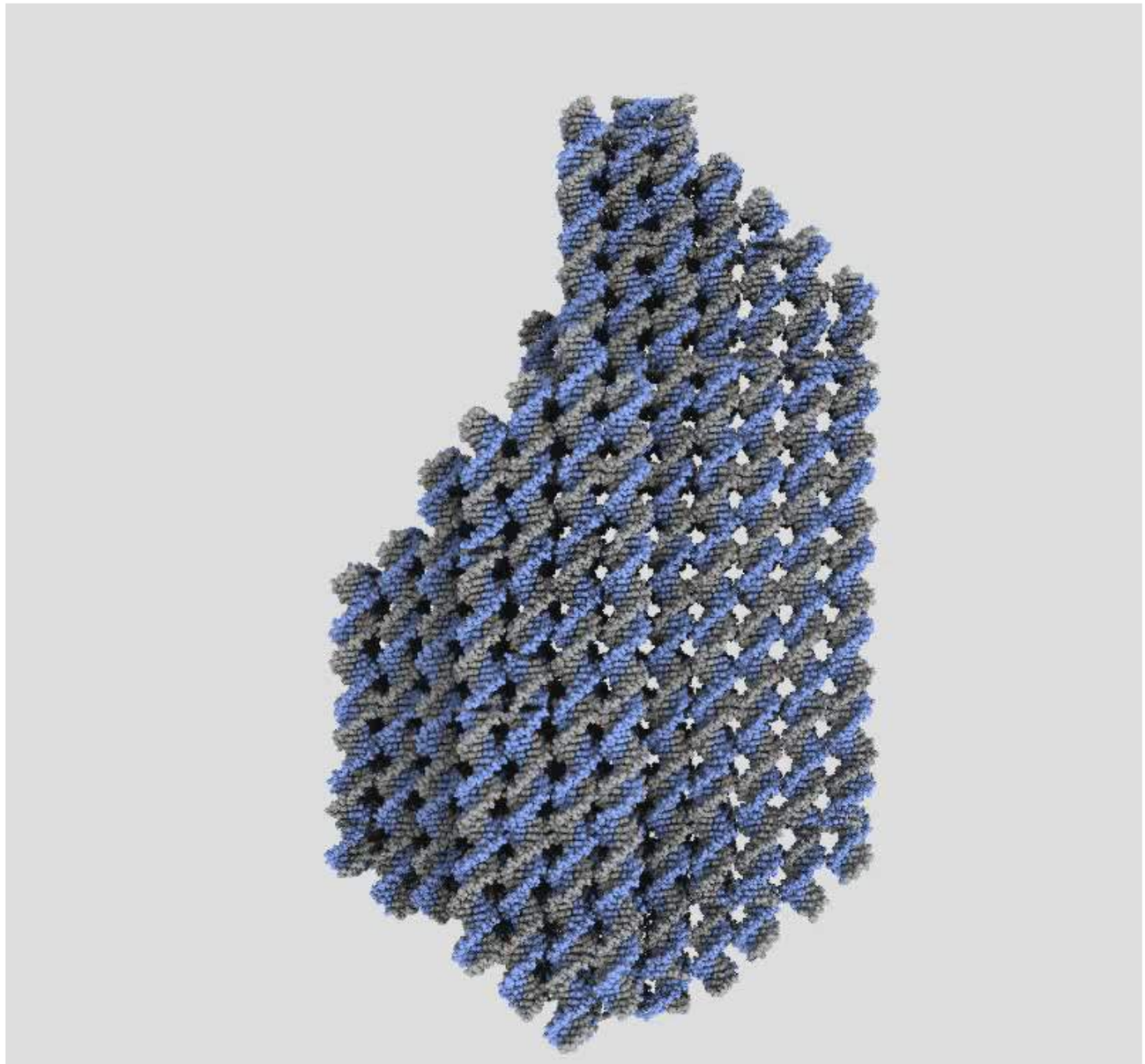
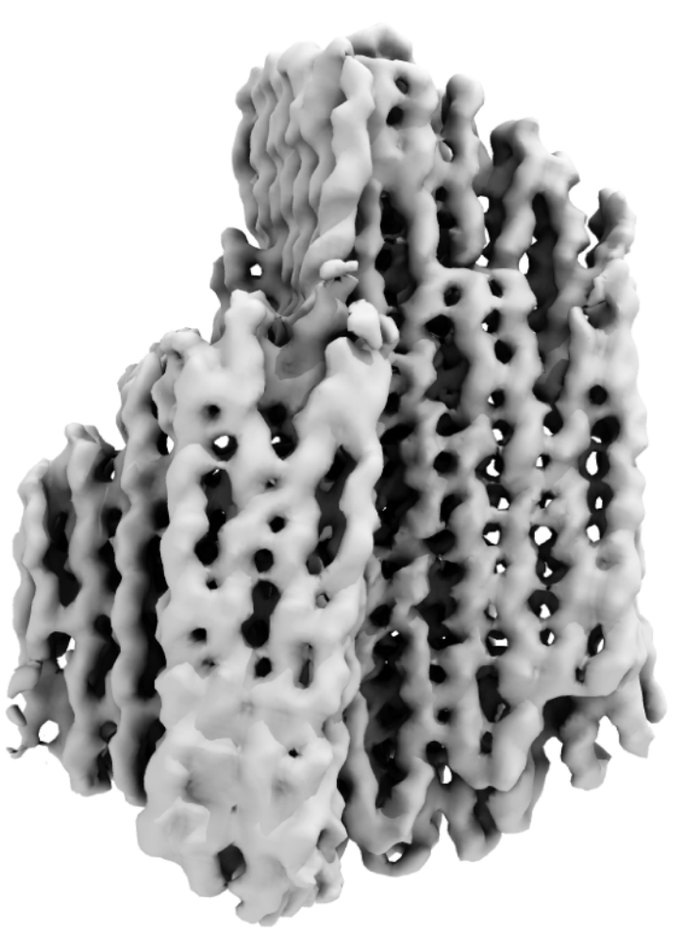


Bai *et al*, PNAS 109:20012 (2012)

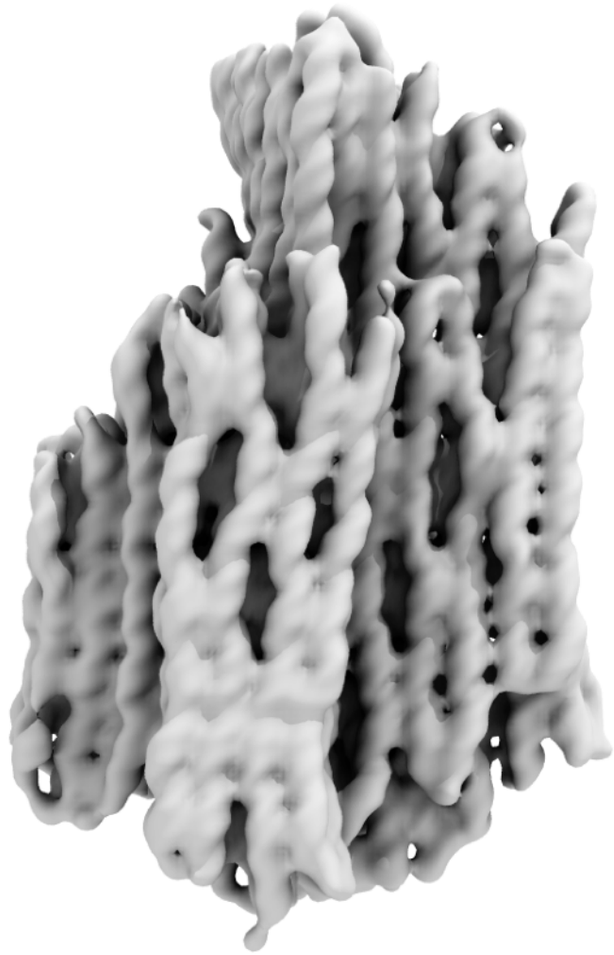


7M atom solvated model
~200 ns MD trajectory

Electron density maps



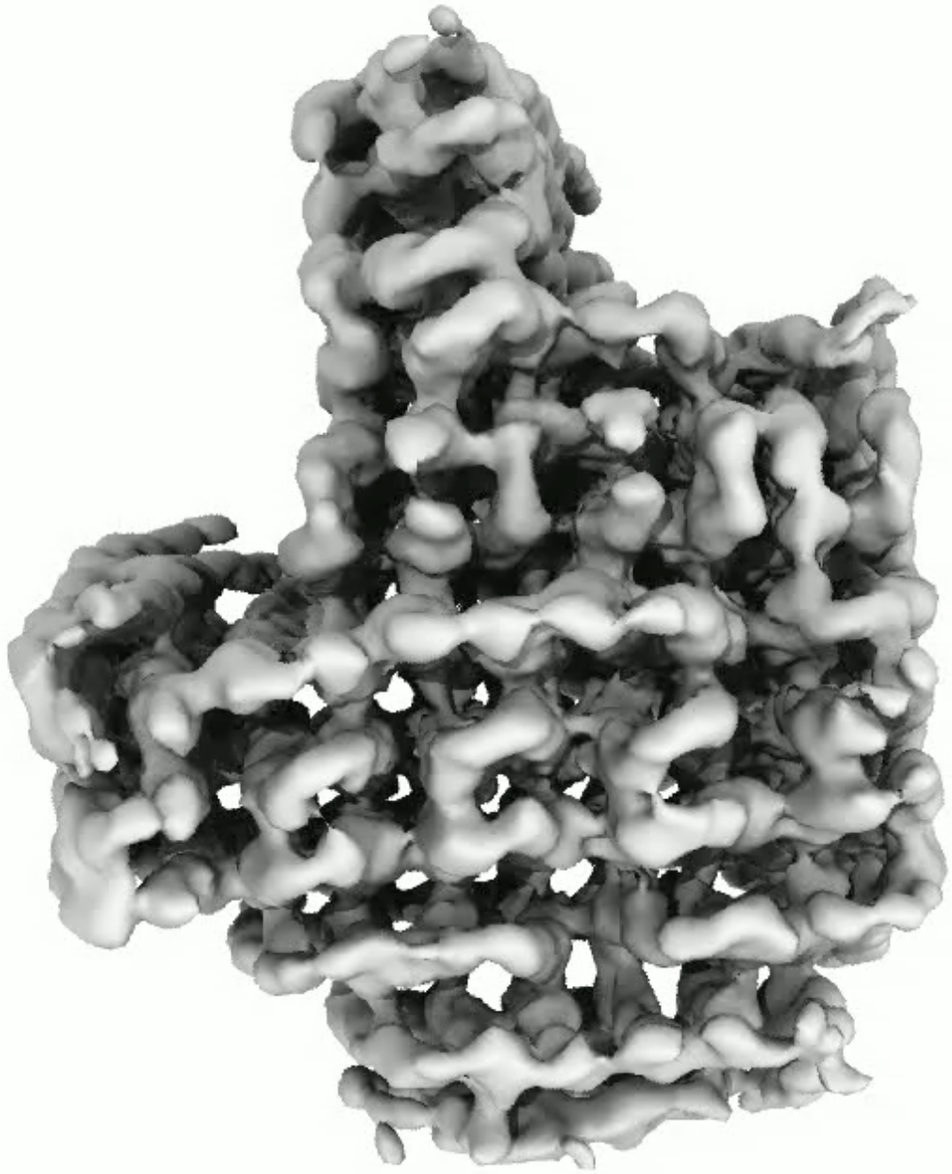
Cryo-EM reconstruction



All-atom MD simulation

Comparison with experiment

Maffeo, Yoo & Aksimentiev, *NAR 44: 3013 (2016)*

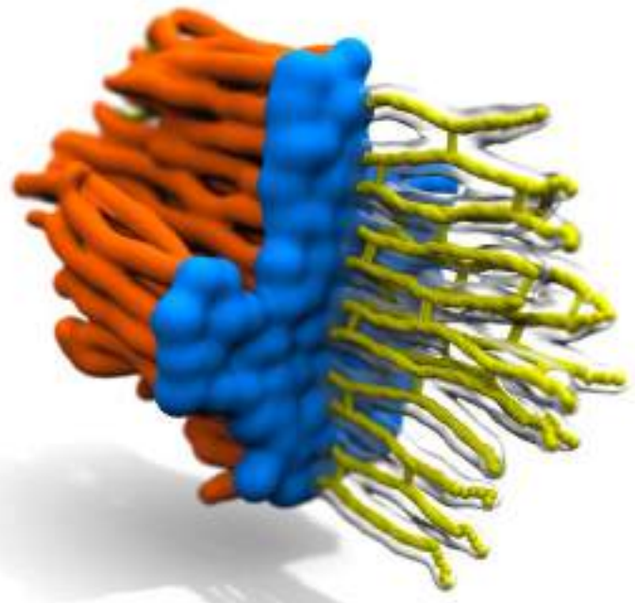


EM density psuedo-atomic model simulation

Making images and animations of DNA nanostructures with VMD

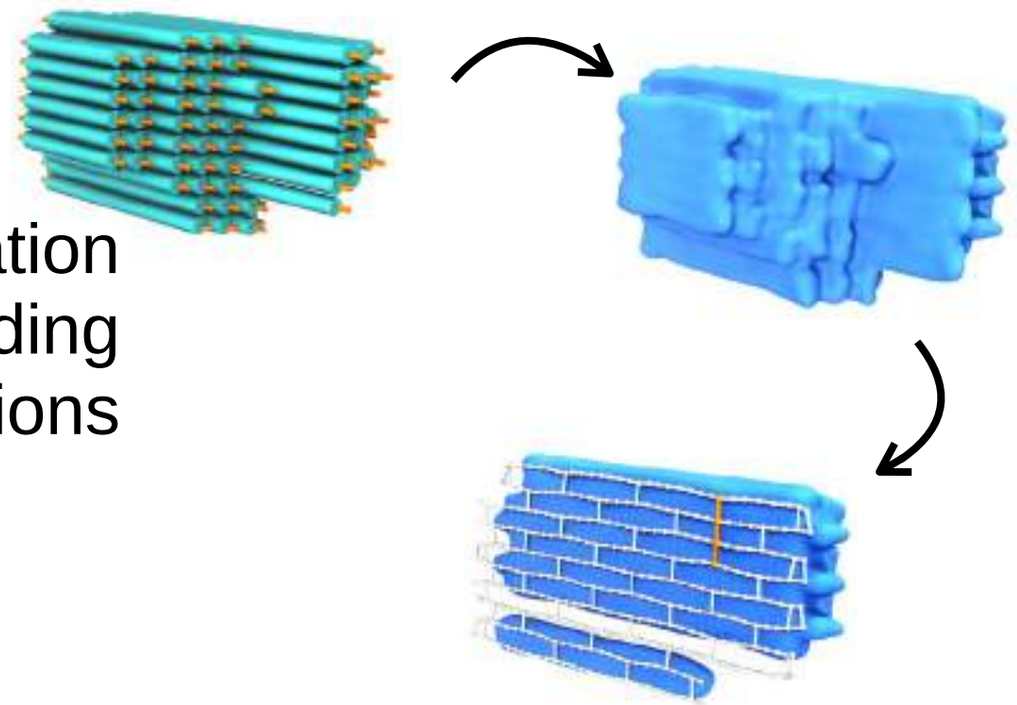
Images from a single structure

Image with multiple representations



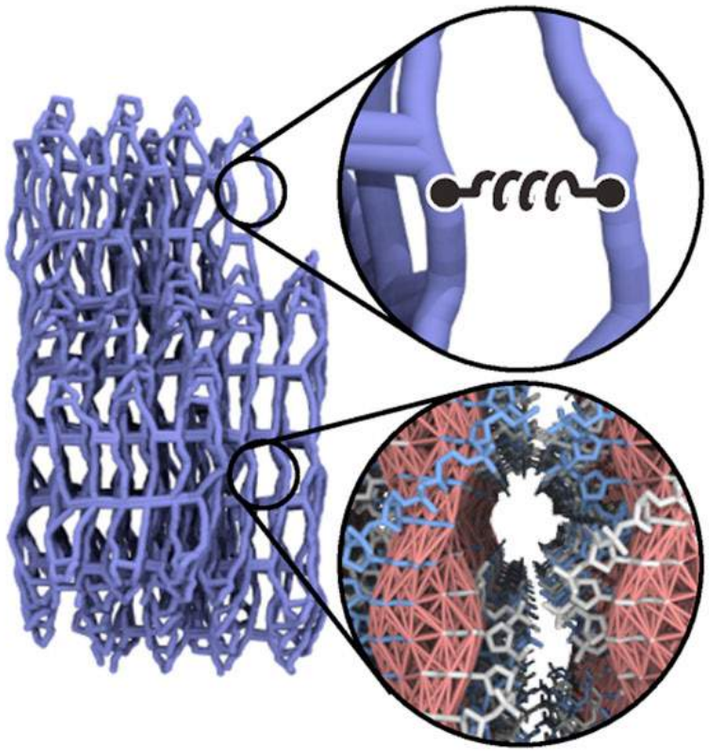
Animation based on a trajectory

Animation including transitions

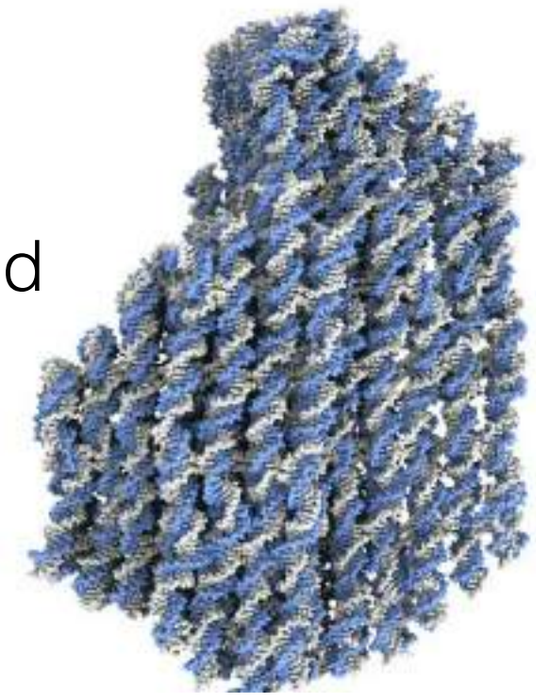


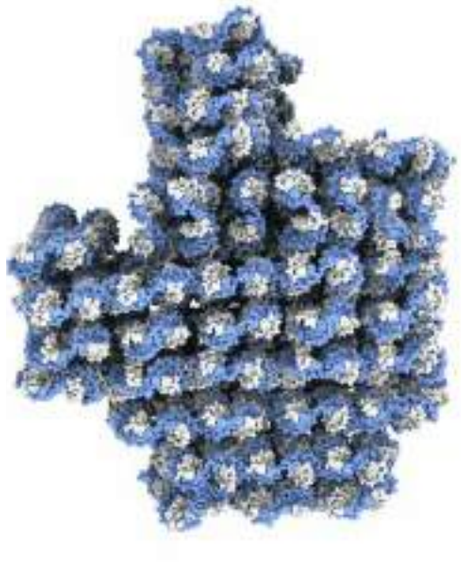
Elastic network of restraints guided MD (ENRG MD)

~10,000 times more efficient

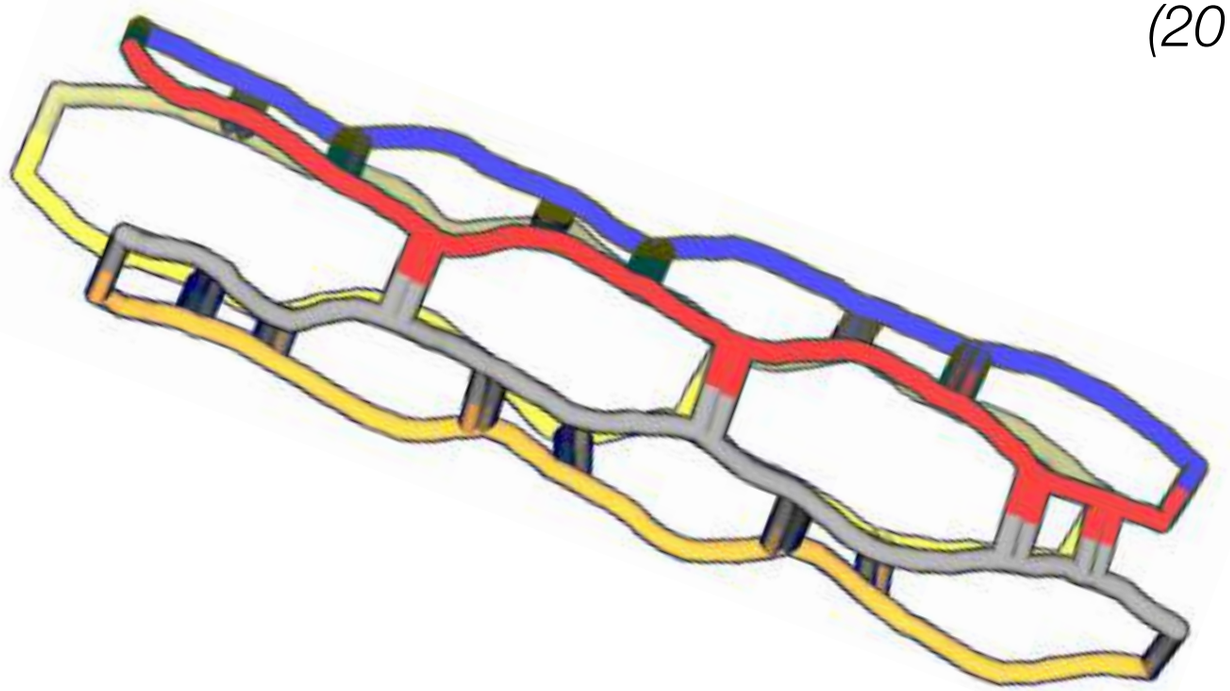


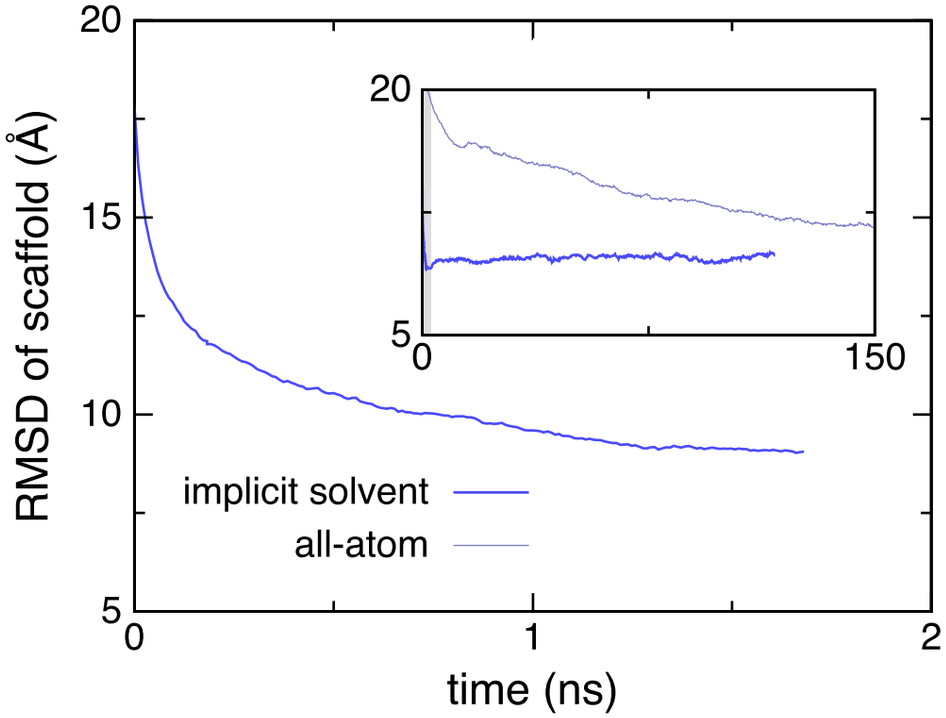
Solvent replaced with elastic network





Maffeo, Yoo & Aksimentiev, *NAR 44: 3013 (2016)*





ENRG MD For Origami Structure Prediction

Upload a DNA origami design .json file

Choose File No file chosen

Select the origami lattice. *

- (•) Square
- ( ) Honeycomb

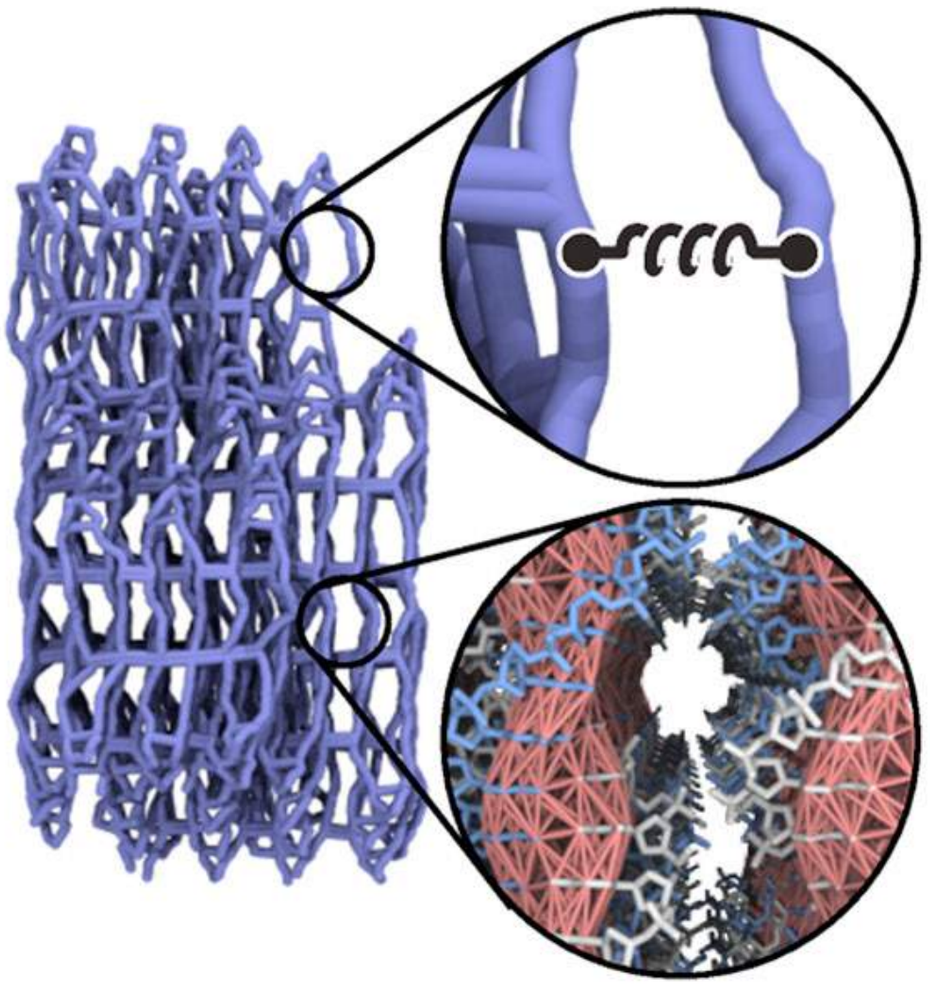
Select the scaffold sequence. *

- (•) m13mp18 (up to 7,249 bases)
- ( ) Custom

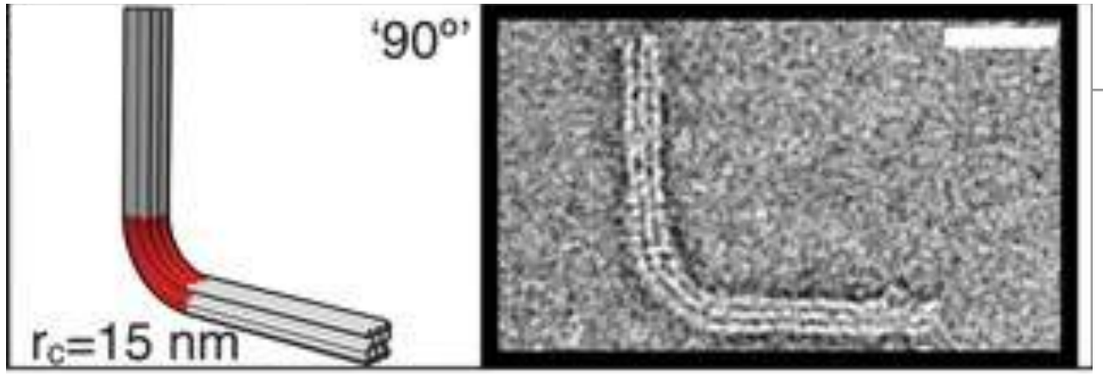
Simulation package *

- (•) NAMD (CHARMM FF)
- ( ) Gromacs (AMBER FF; beta coming soon)

Create simulation files

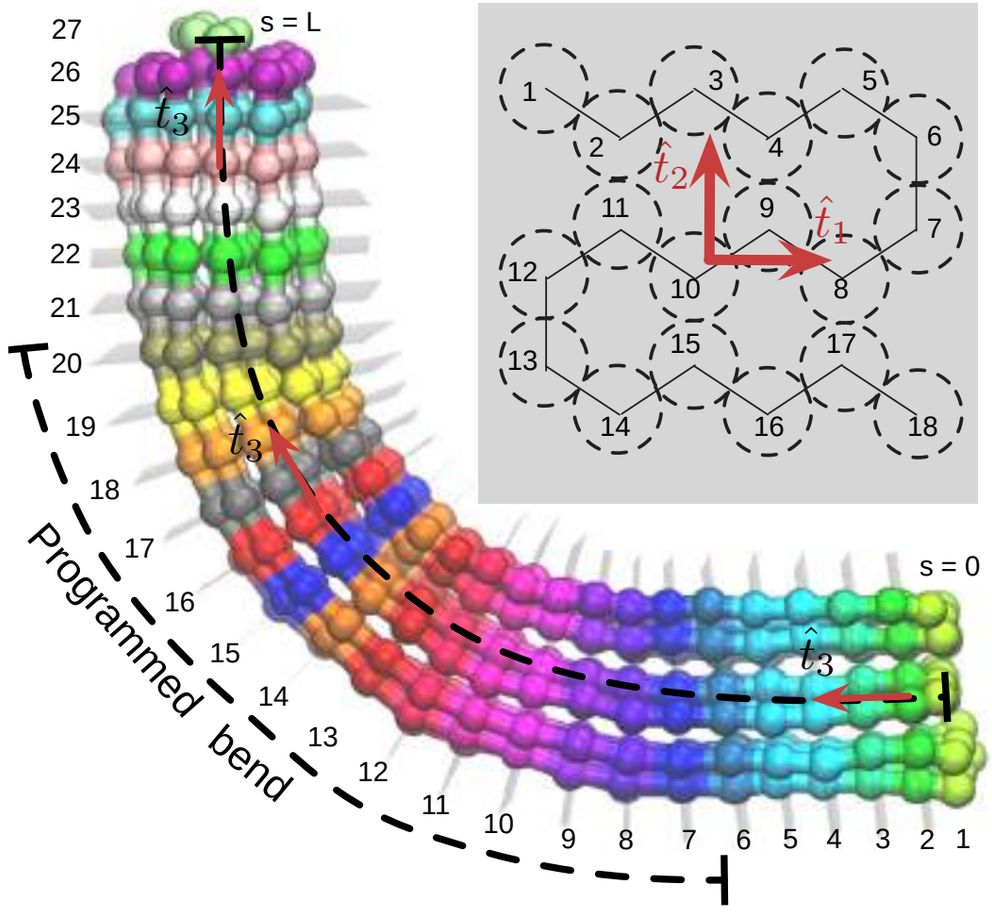


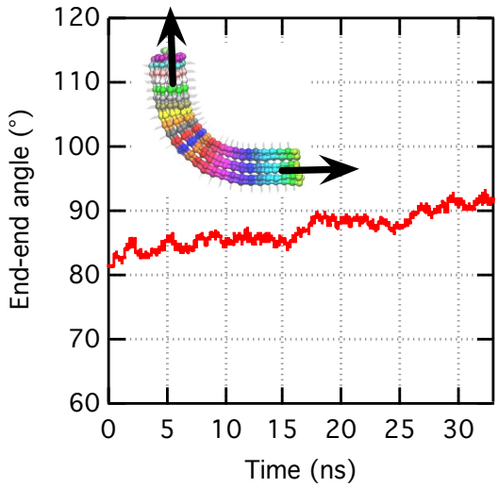
Curved DNA origami systems

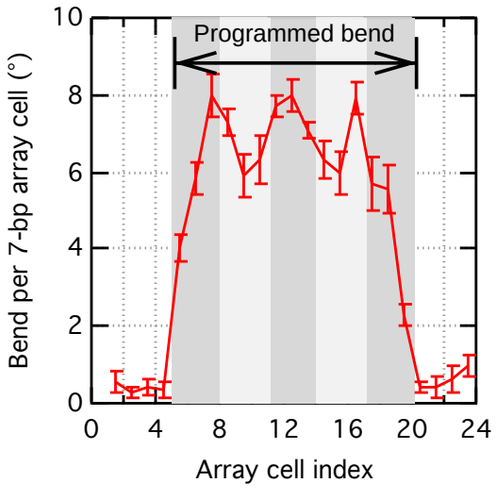


Experiment

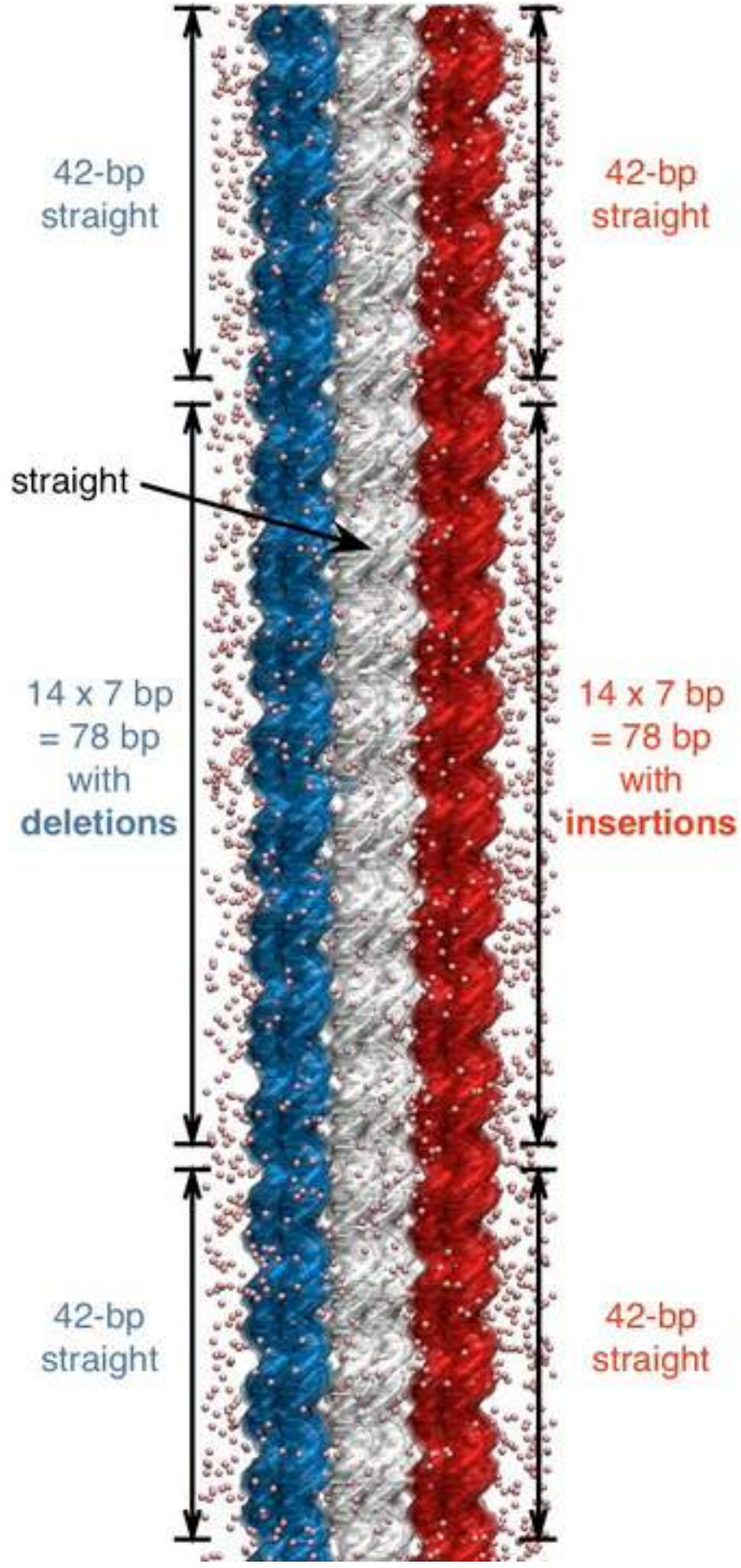
Dietz, H. et al, *Science*, 325



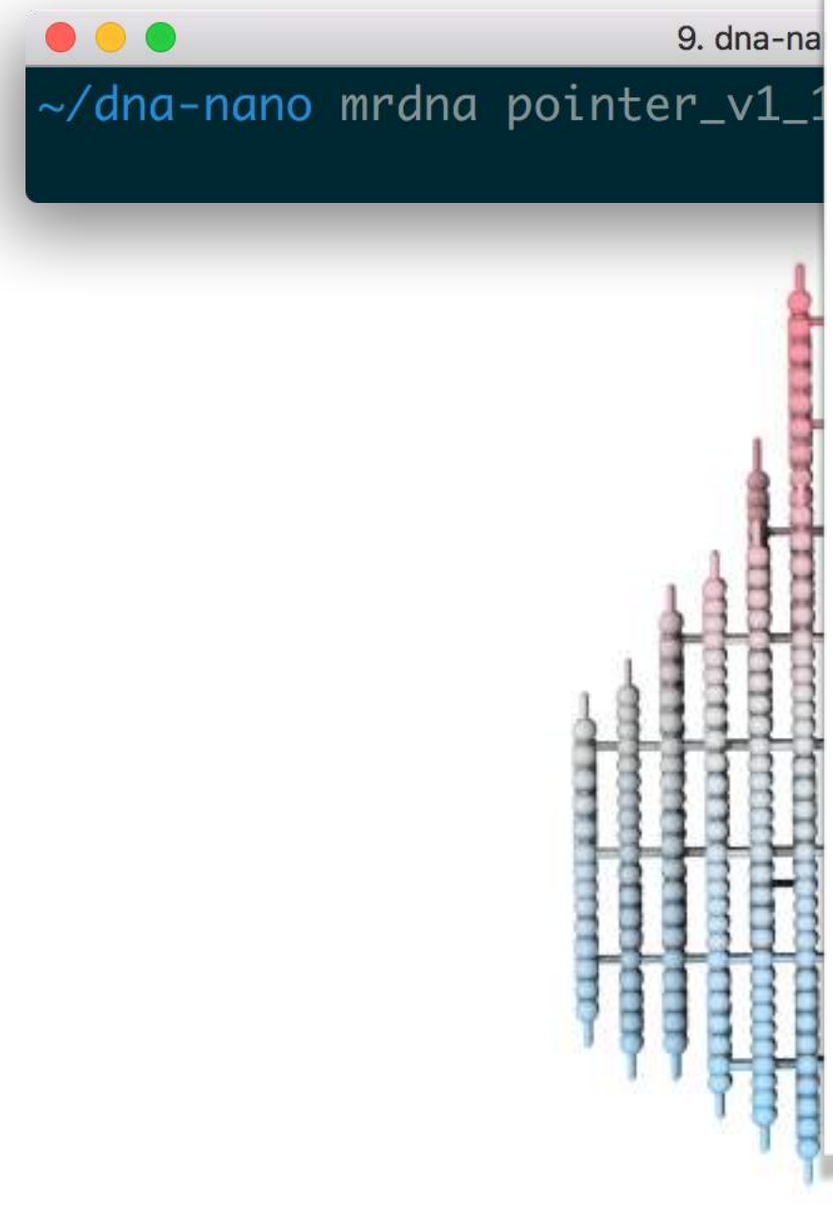


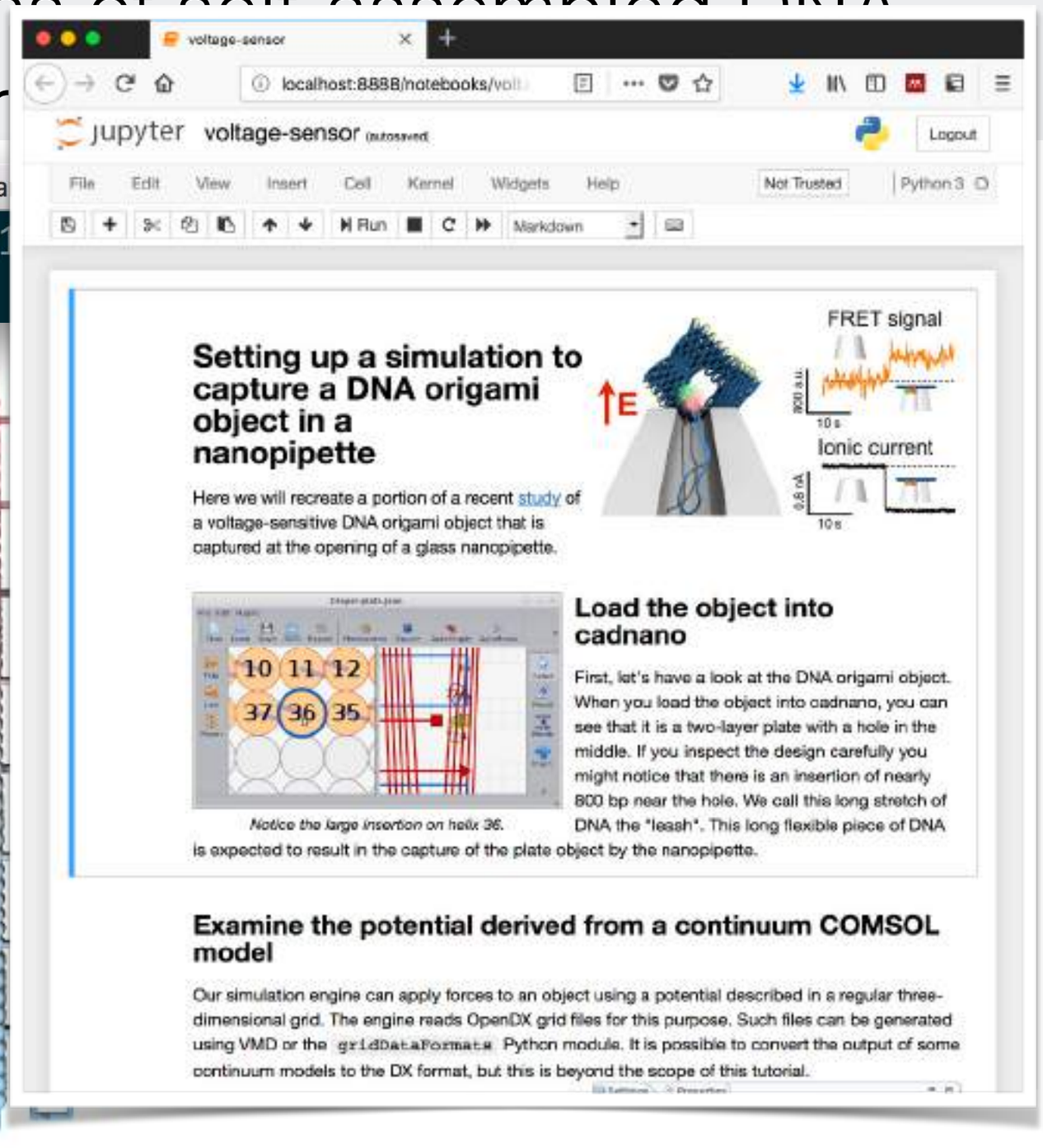


Yoo and Aksimentiev, PNAS 110:20099 (2013)



Multi-resolution simulations of self-assembled DNA nanostr

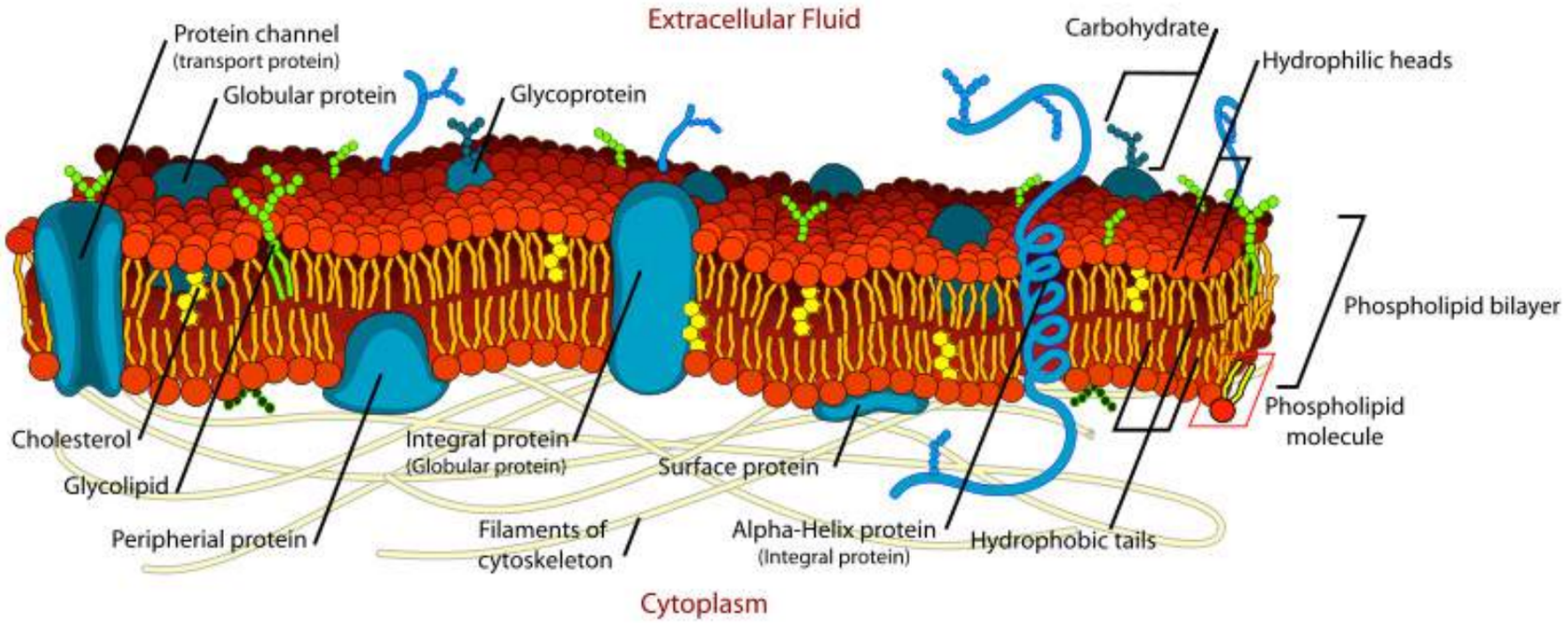




DNA membrane channels

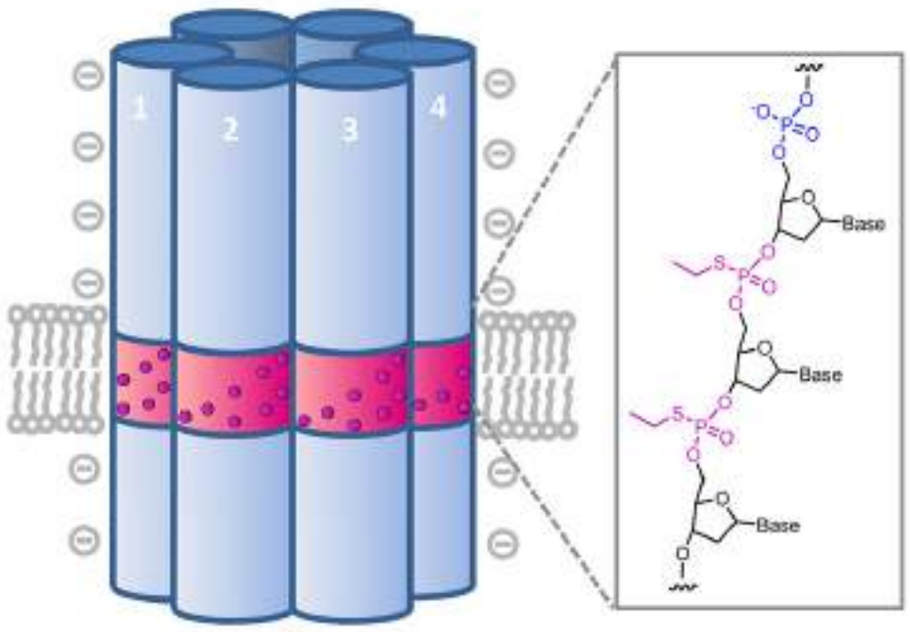
Dr. Ulrich F. Keyser
Cambridge, UK

DNA Ion Channels

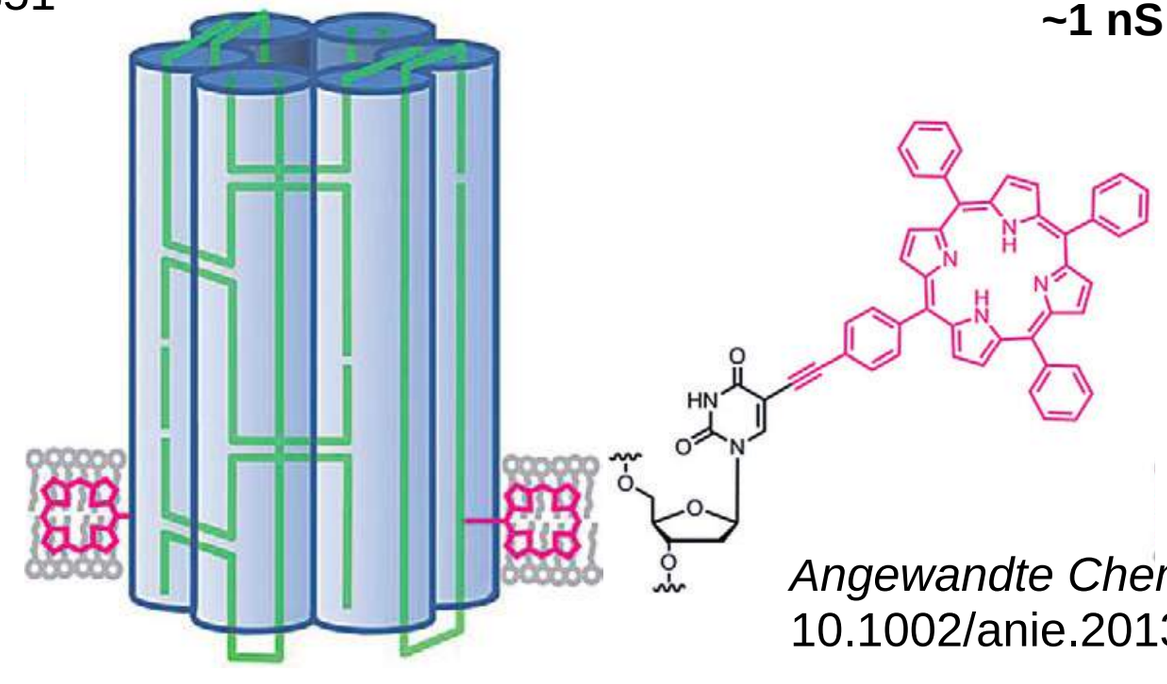


Langecker, M. *et al*., *Science*: 338, 932-936.

Nano Letters, *13:* 2351

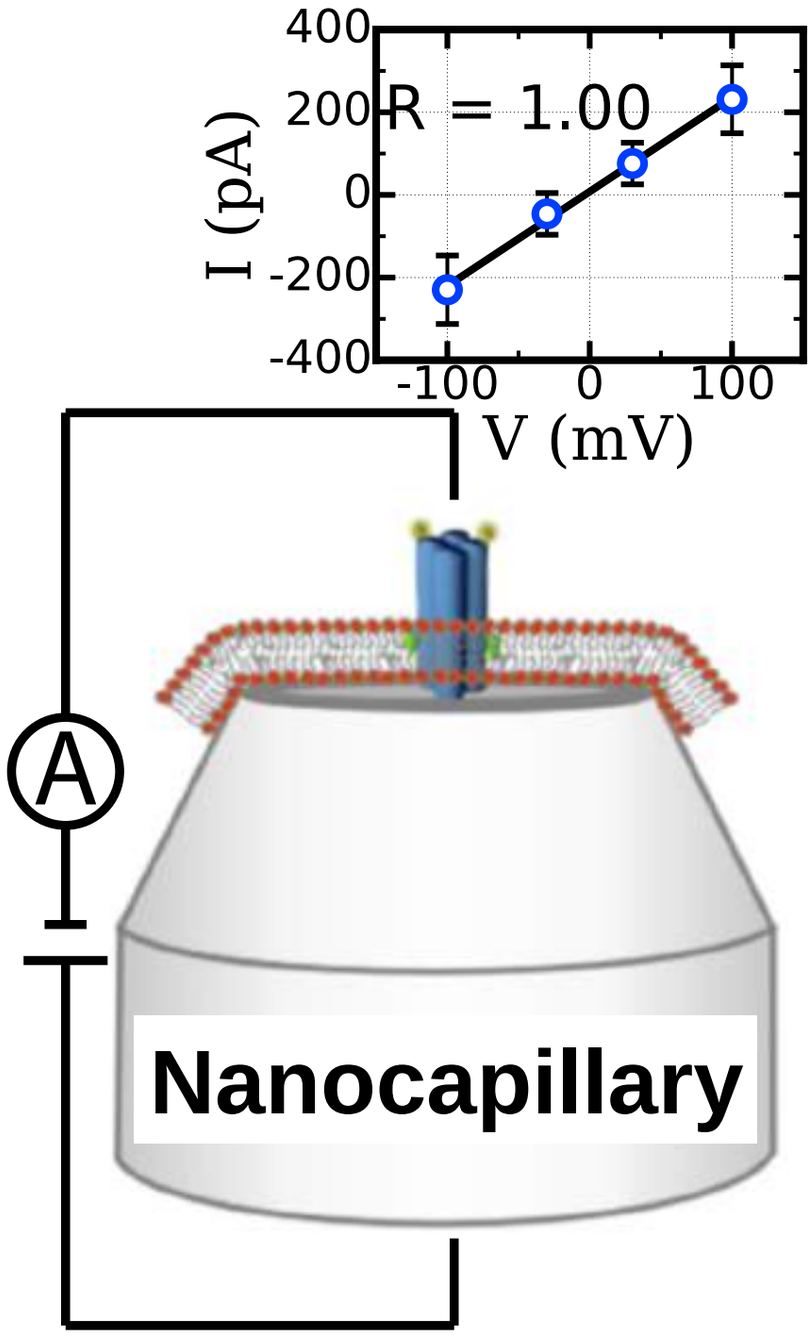


~1 nS conductance

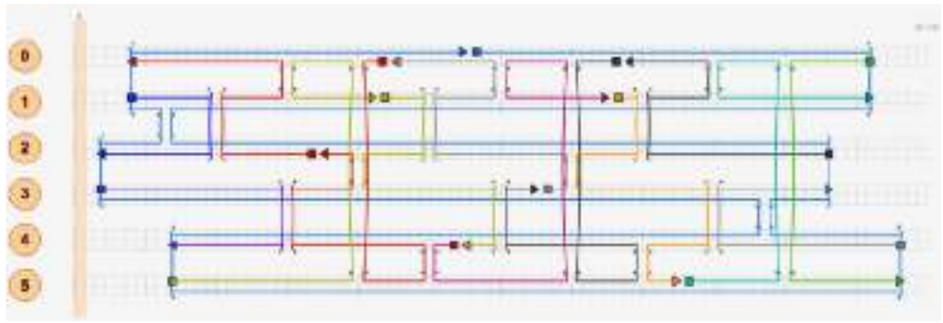


Angewandte Chemie
10.1002/anie.201305765

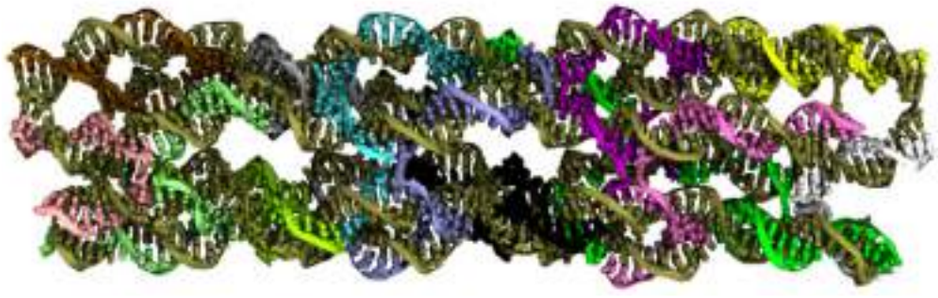
MD simulation of DNA channel conductivity

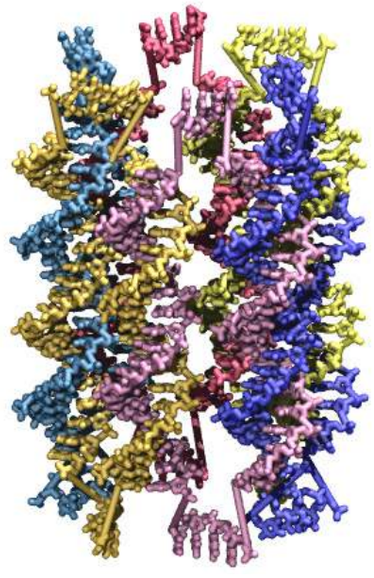


caDNAno *or* NanoEngineer-1



all-atom coordinates

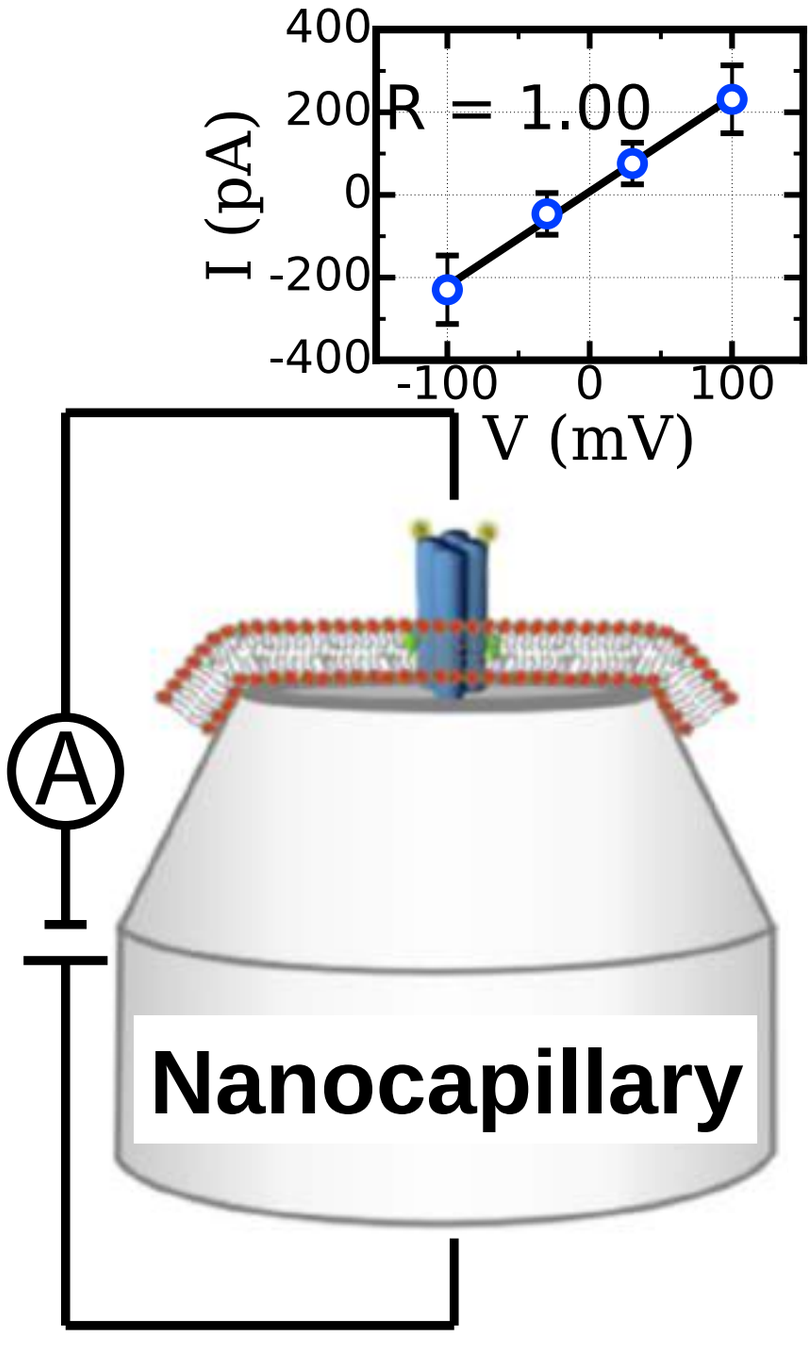


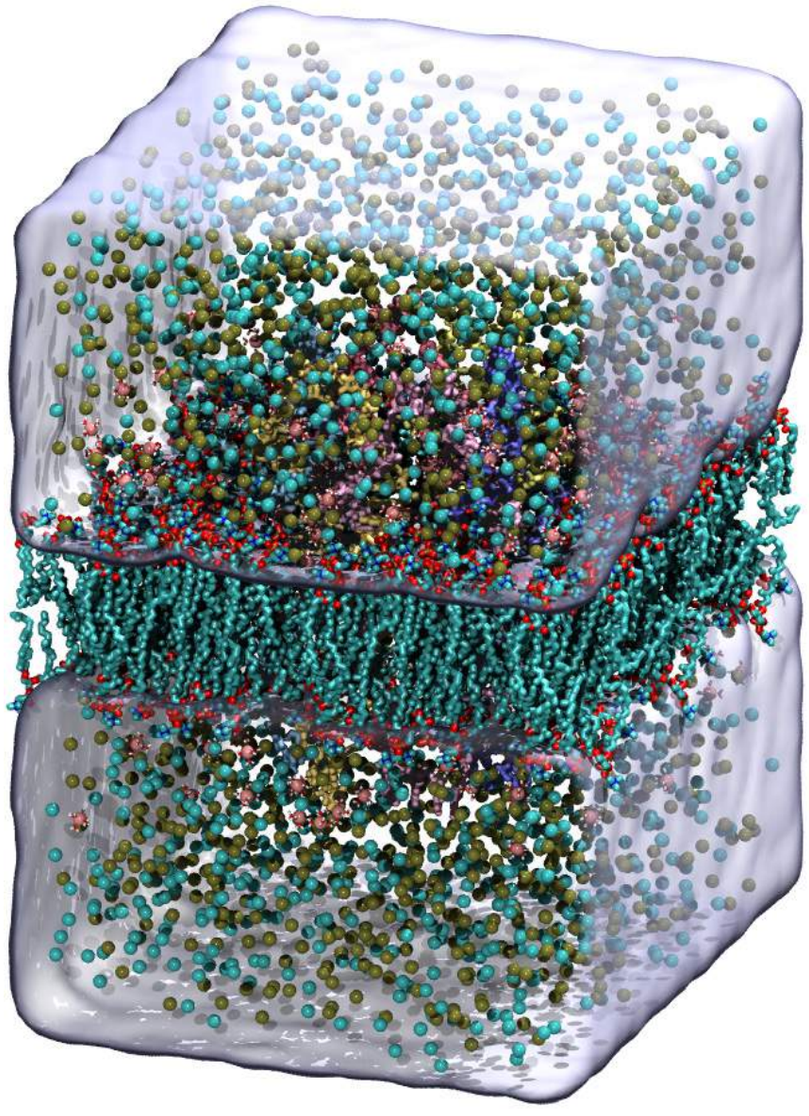


Göpfrich, Kerstin *et al*.,
Nano Lett., 2015, 15(5), 3134−3138.

(Right) design from Burns, Jonathan R. *et al*.,
Nat. Nanotechnol., 2016, 11, 152−156.

MD simulation of DNA channel conductivity





DNA

Optimize

Cholesterol

Lipid

$Mg(H_2O)_6^{2+}$

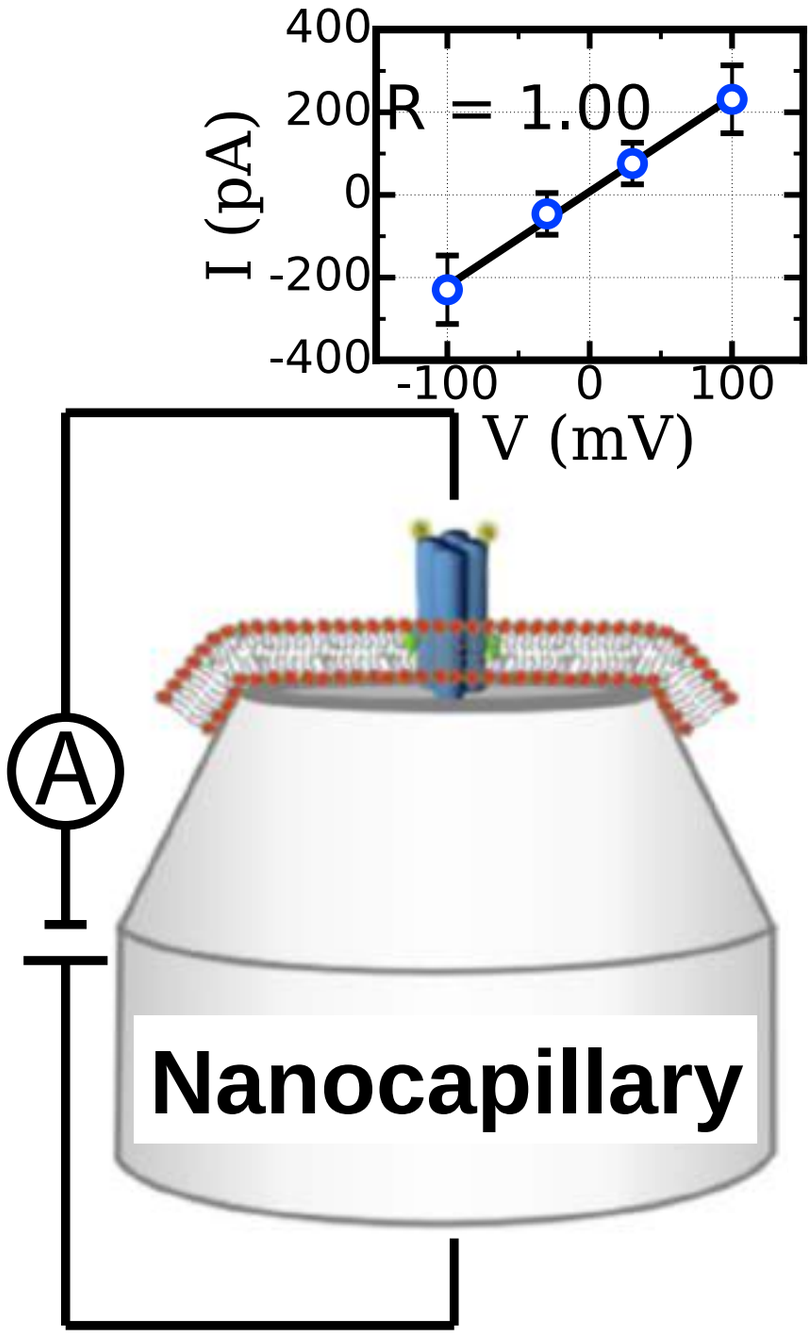
H_2O

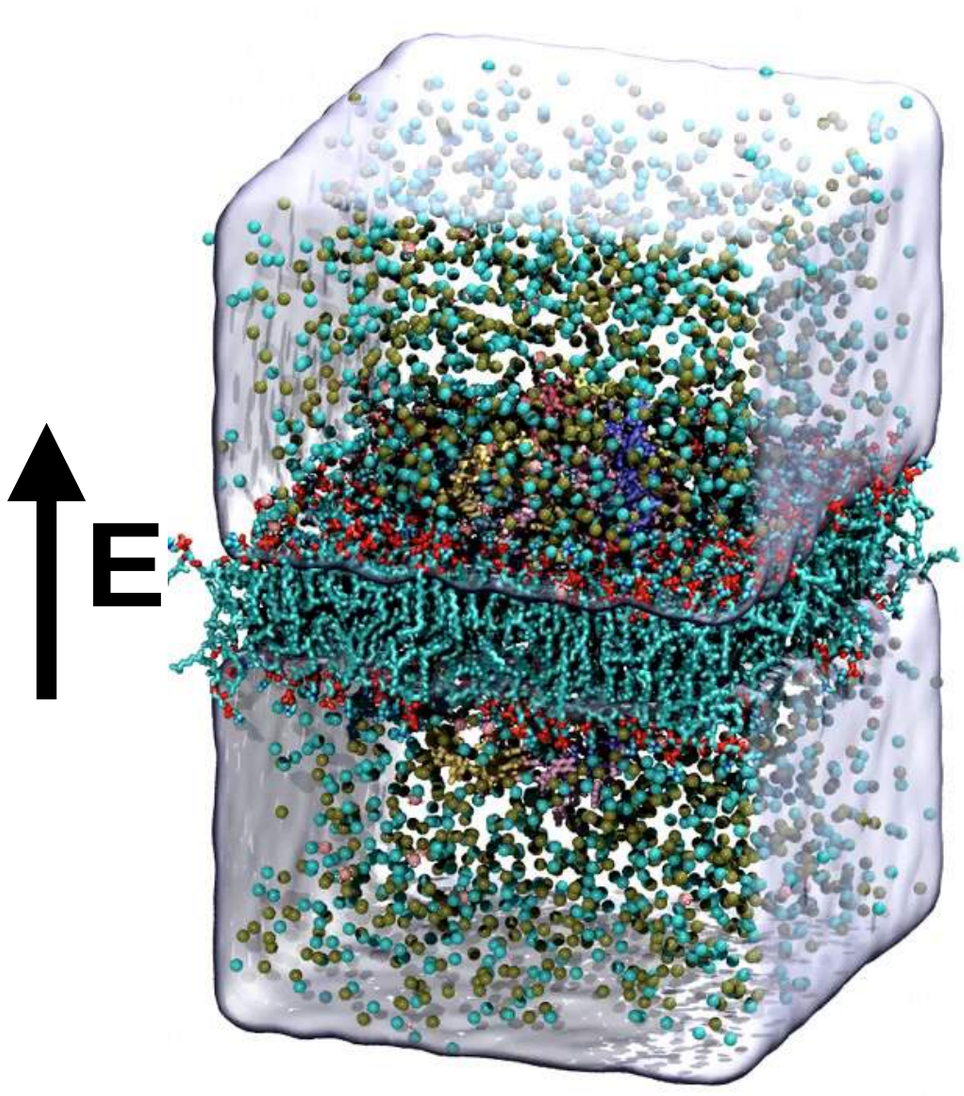
K^+

Cl^-

Göpfrich, Kerstin *et al*.,
Nano Lett., 2015, 15(5), 3134−3138.

MD simulation of DNA channel conductivity





DNA

Optimize

Cholesterol

Lipid

$Mg(H_2O)_6^{2+}$

H_2O

K^+

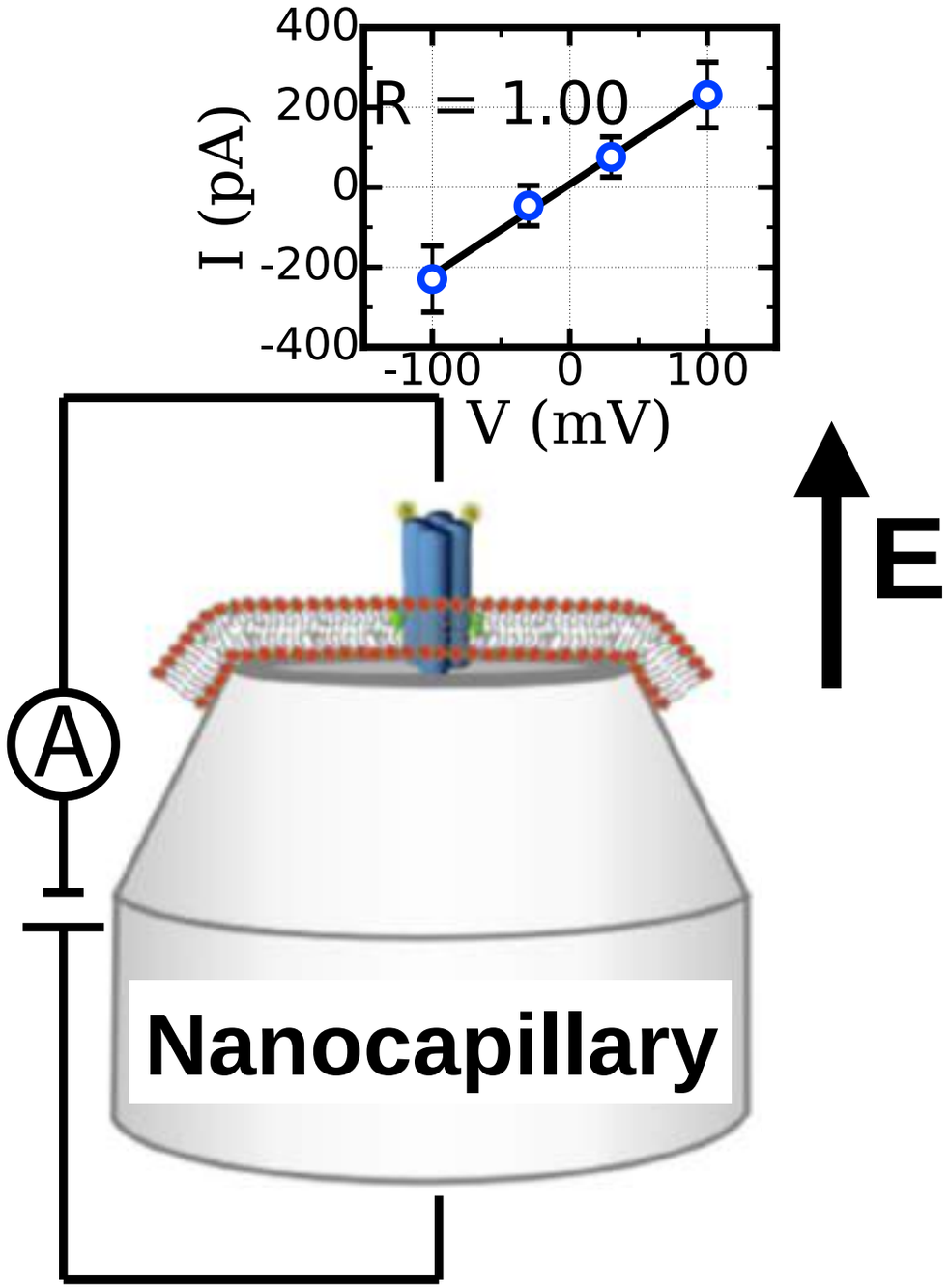
Cl^-

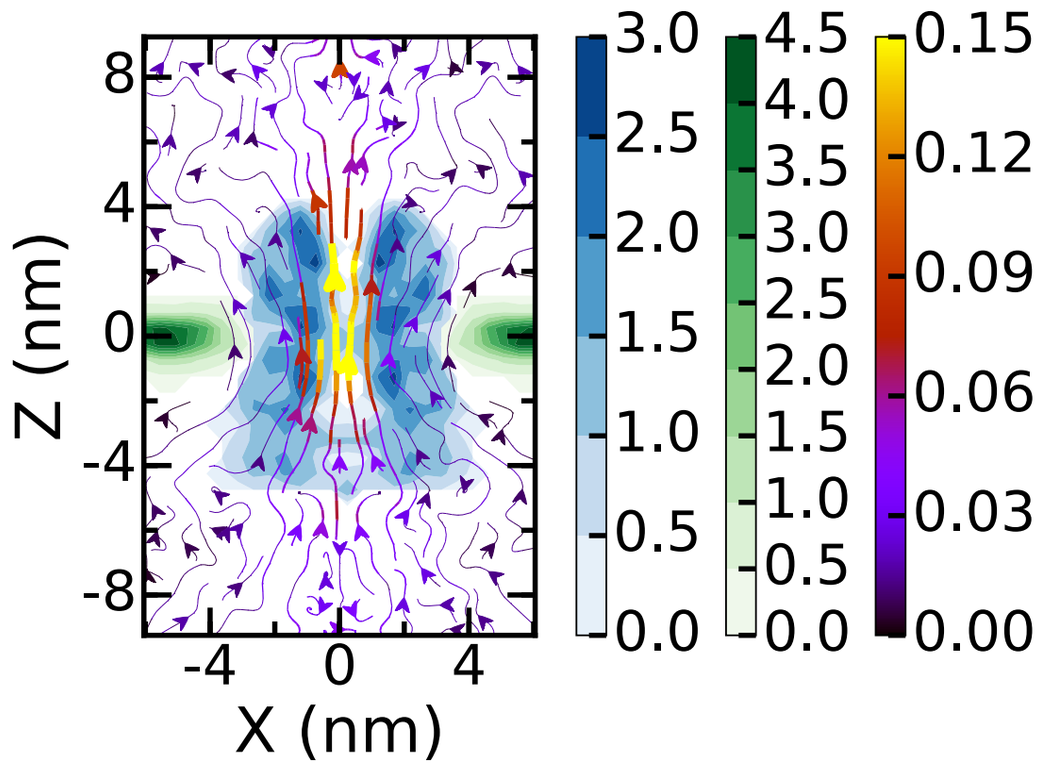
Instantaneous current:

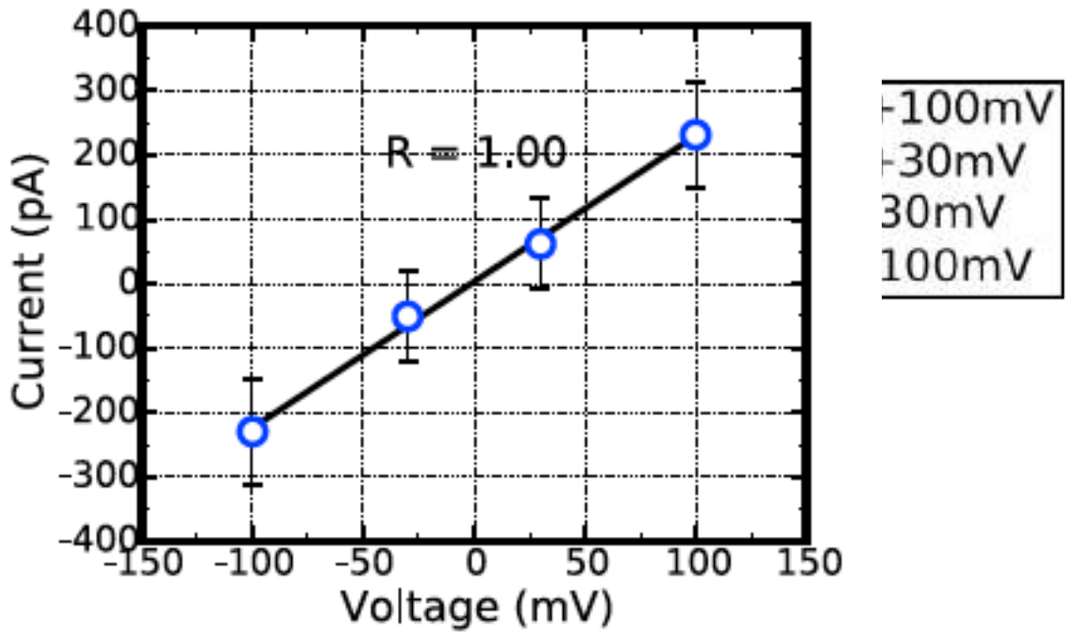
$$I(t) = \frac{1}{\Delta t L_z} \sum_{i=1}^{N} q_i (z_i(t + \Delta t) - z_i(t))$$

Göpfrich, Kerstin *et al*.,
Nano Lett., 2015, 15(5), 3134−3138.

MD simulation of DNA channel conductivity

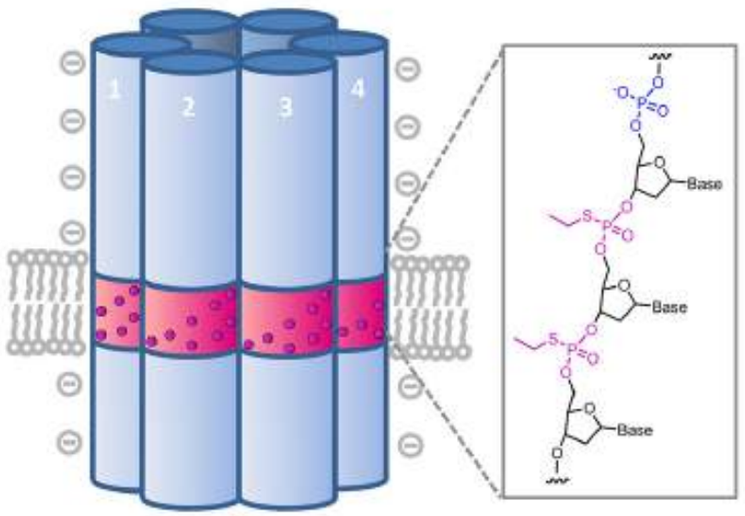




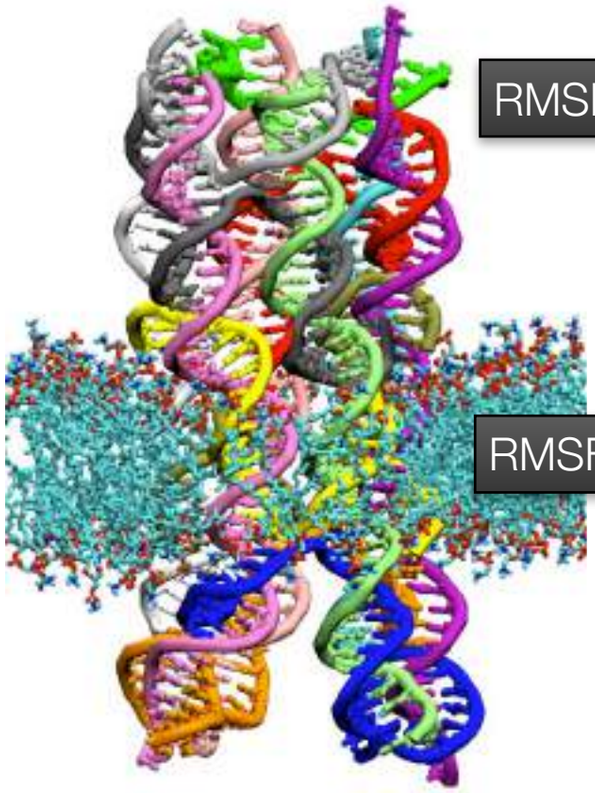


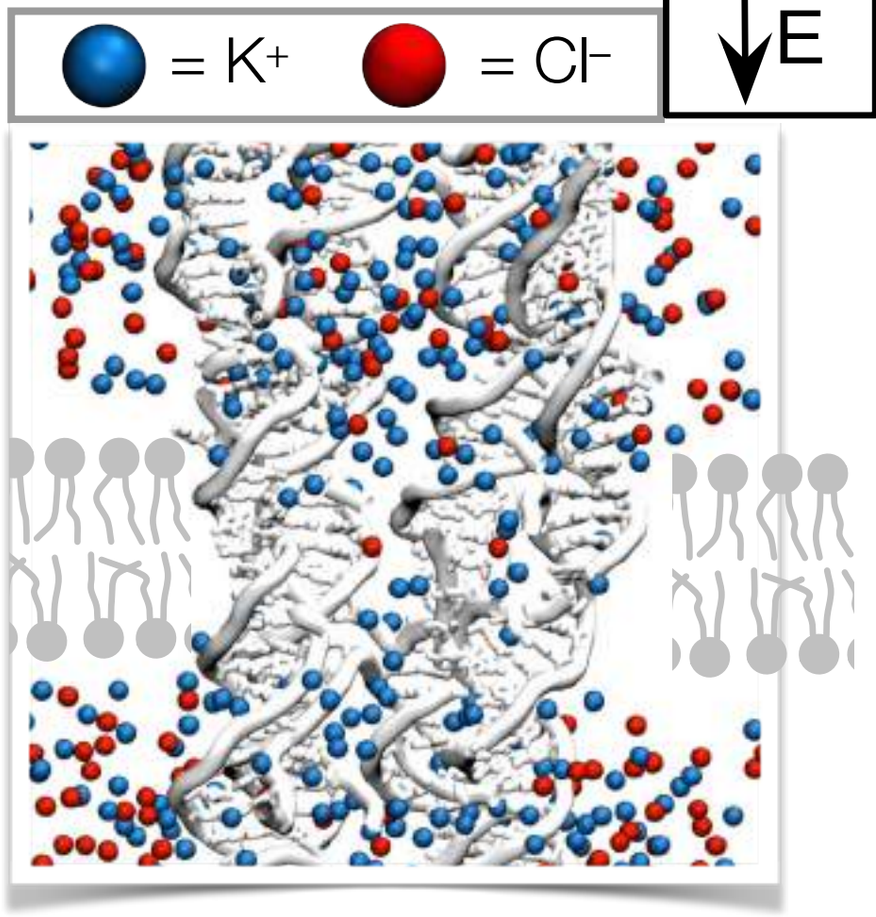
Göpfrich, Kerstin *et al*.,
Nano Lett., 2015, 15(5), 3134−3138.

Chemistry matters

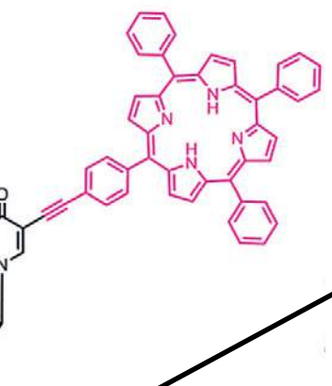


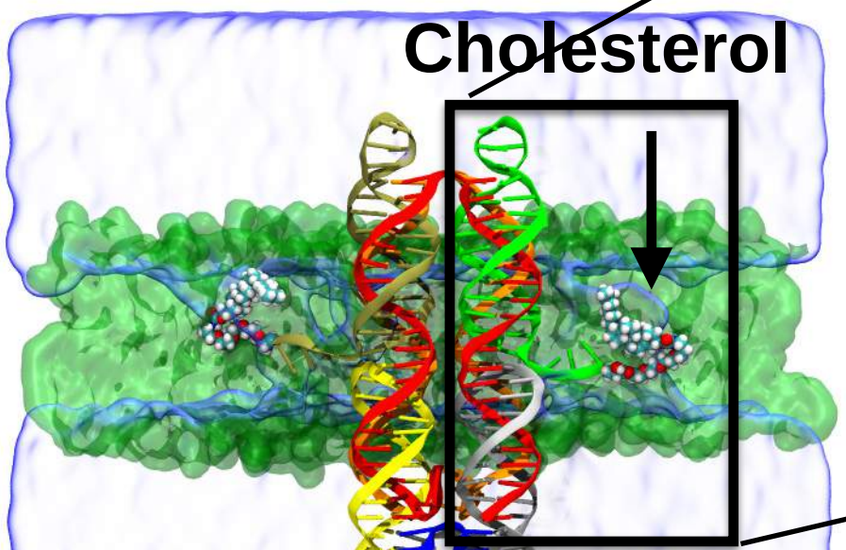
Nano Letters, 13: 2351

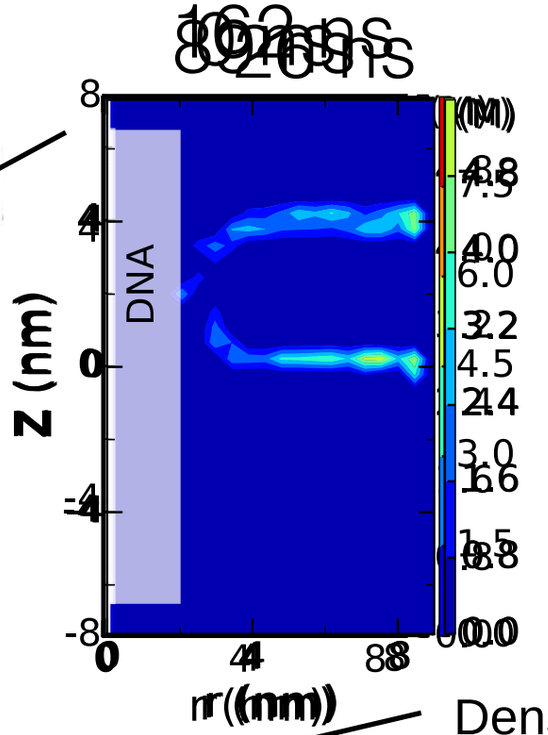




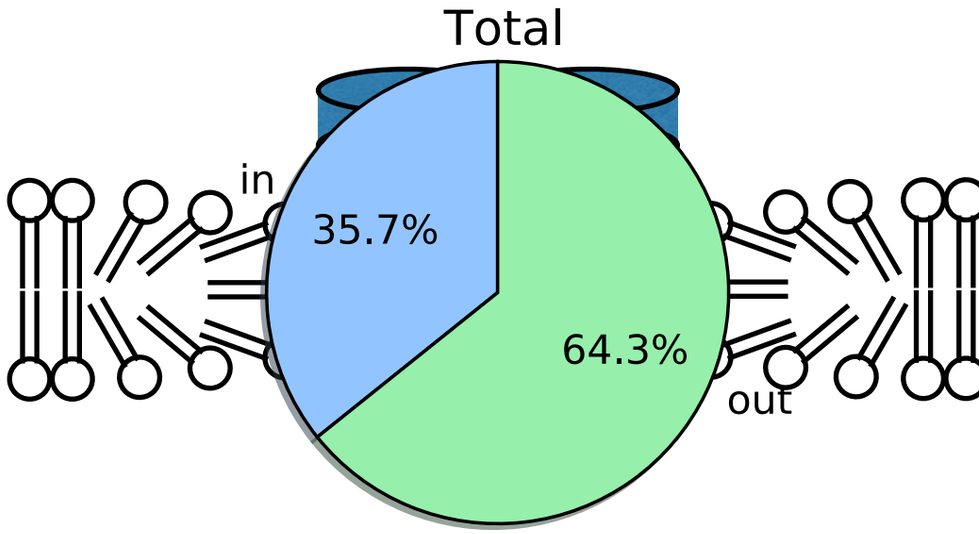
Angewandte Chemie
10.1002/anie.201305765



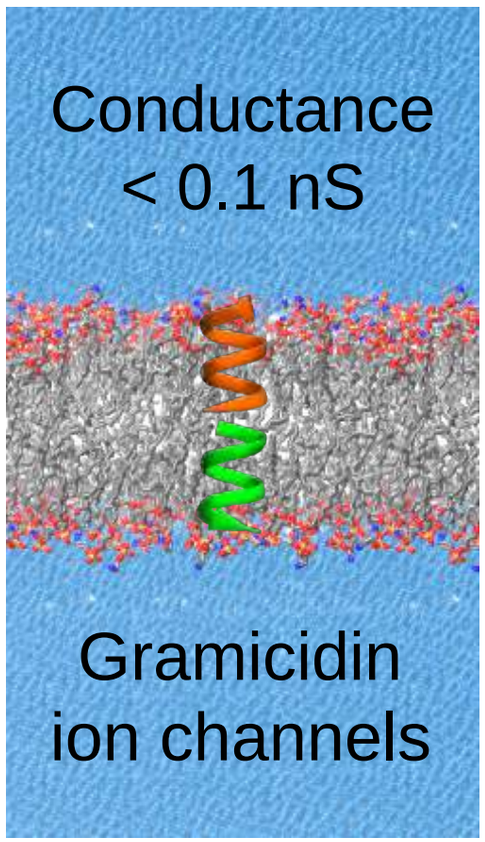


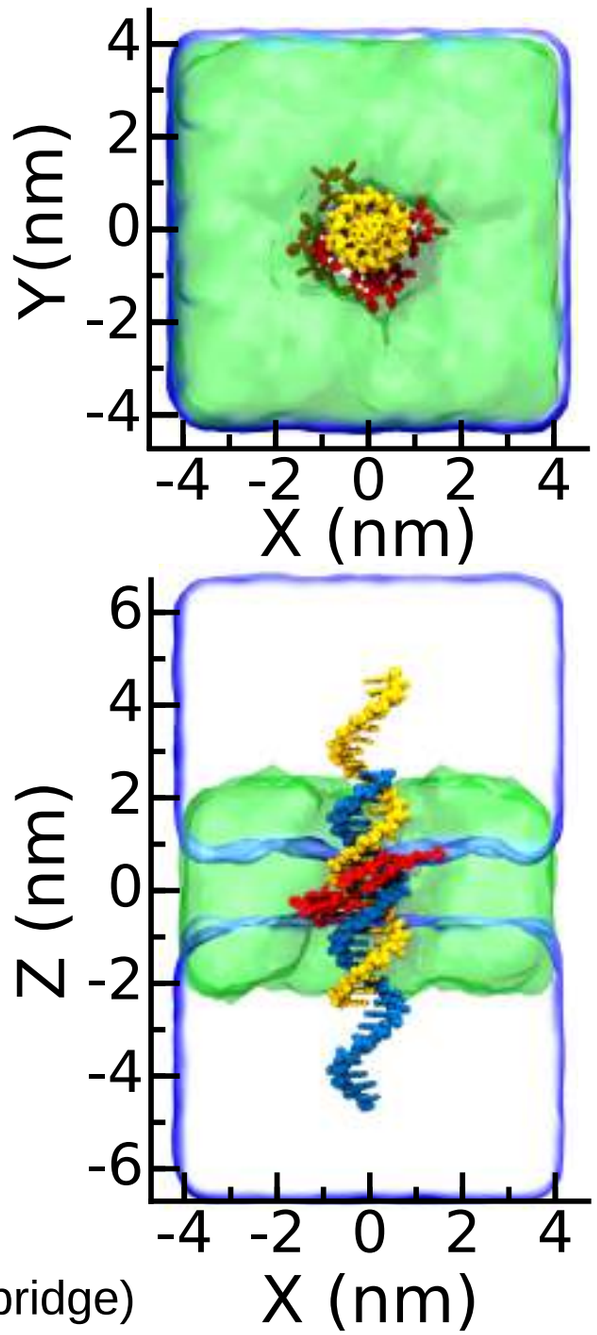


Density of lipid head groups

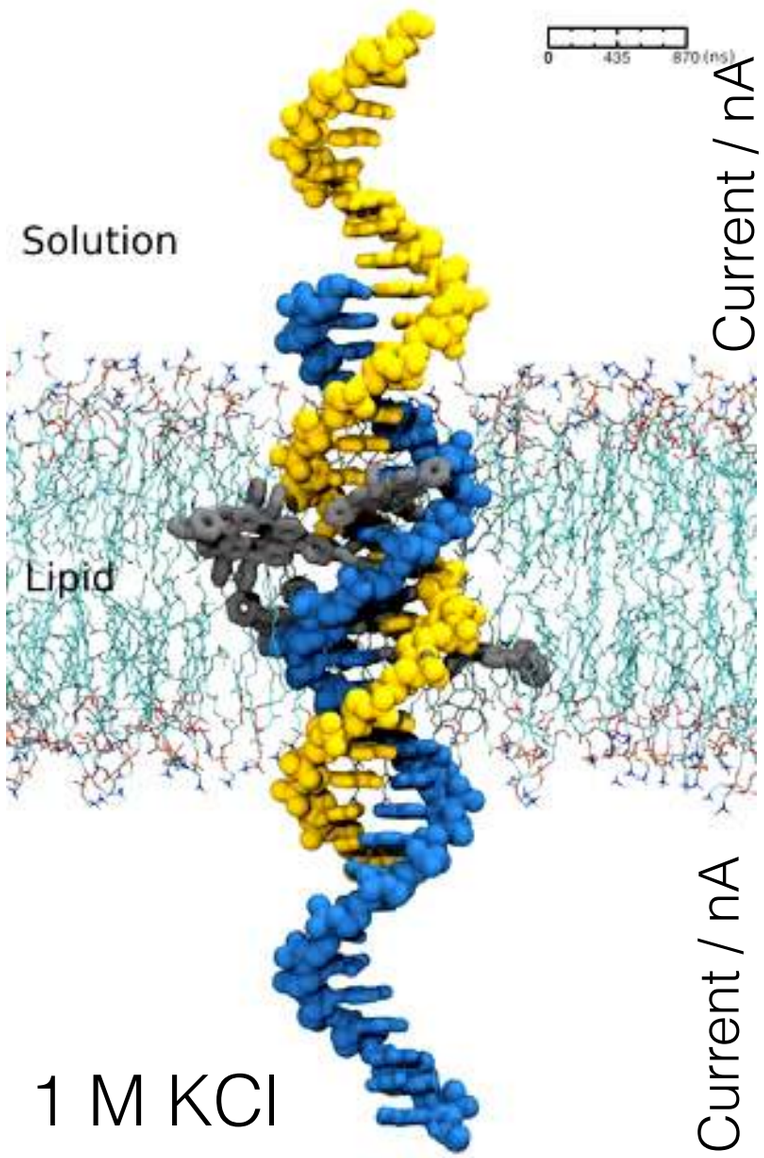


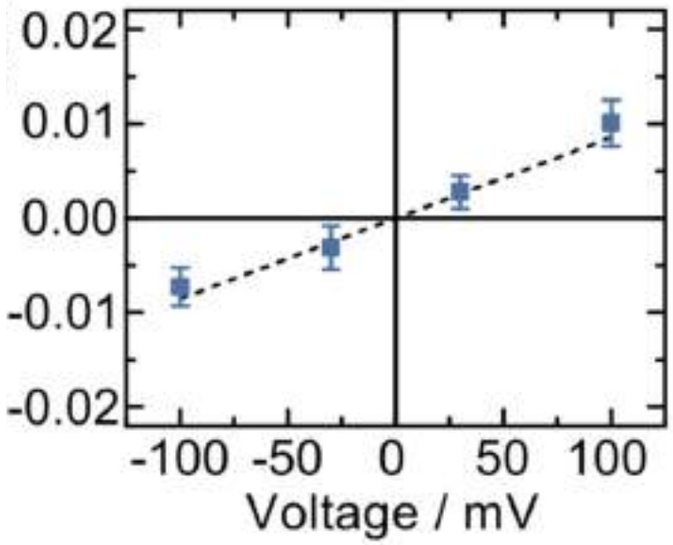
Small conductance DNA channel



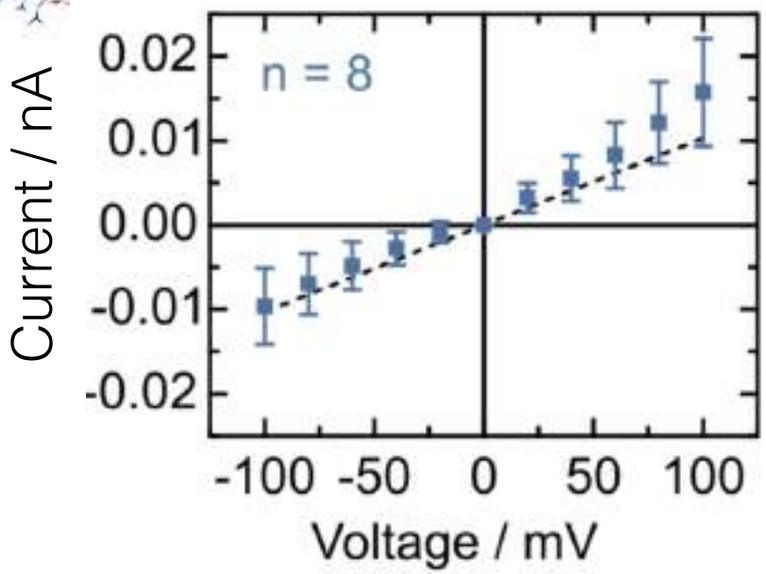


1 helix
140,000 atoms





Conductance: ~ 0.1 nS



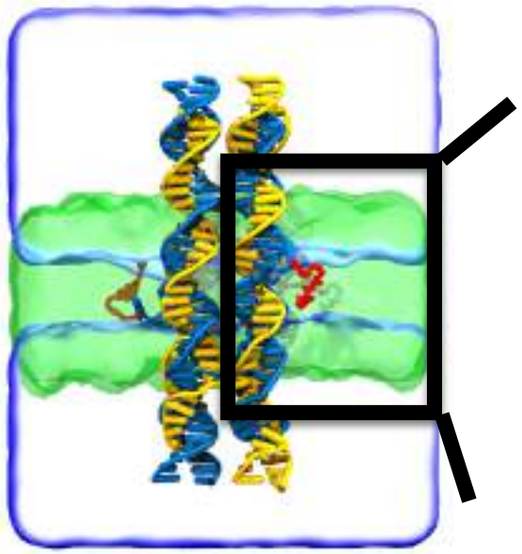
Experiment:
Ulrich Keyser (Cambridge)
Eugen Stulz (Southampton)
Mathias Winterhalter (Jacobs U)

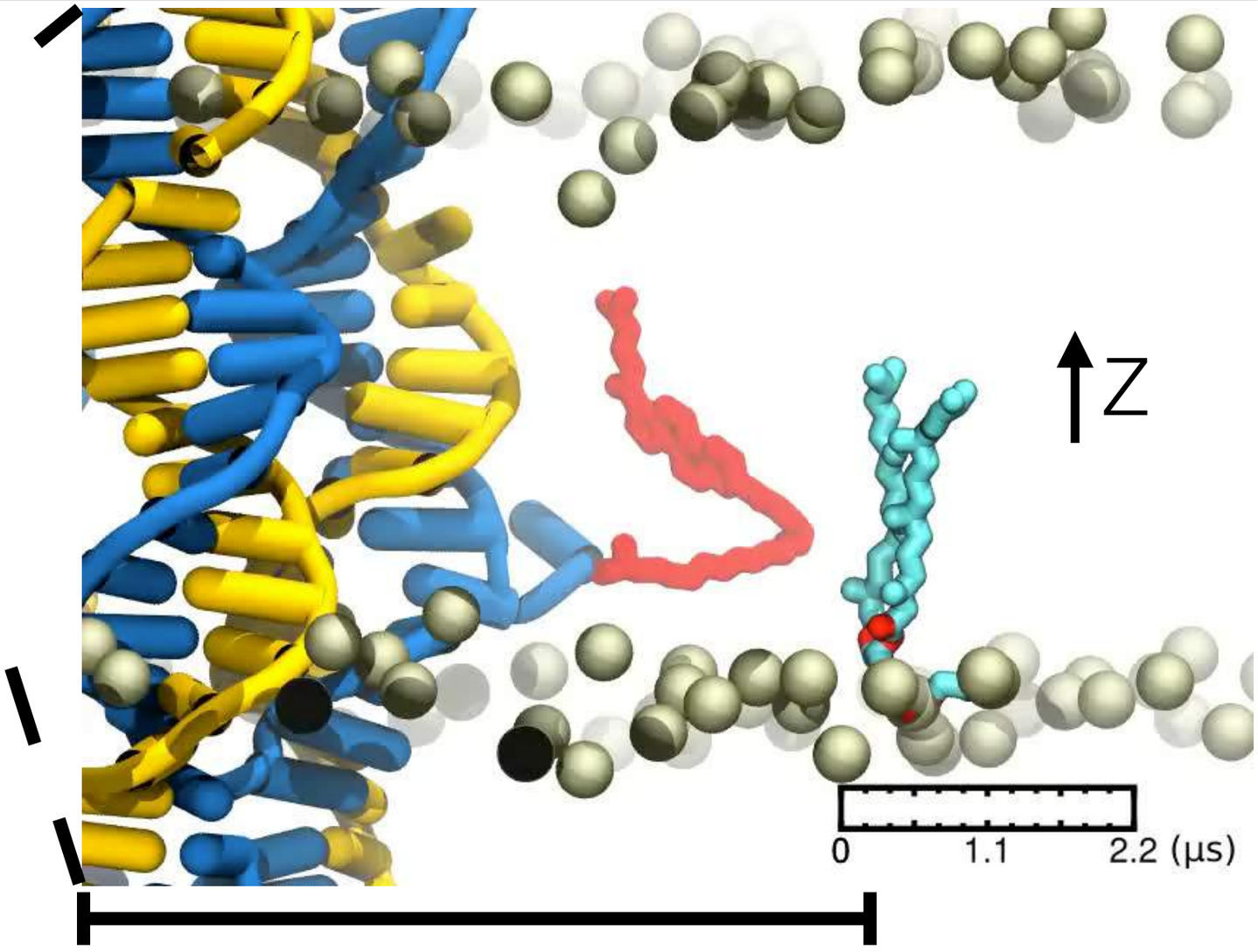
Goepfrich, et al., Nano Lett 16: 4665 (2016)

All-atom MD simulation of lipid-DNA interface

Chen Yu Li

No applied electric field

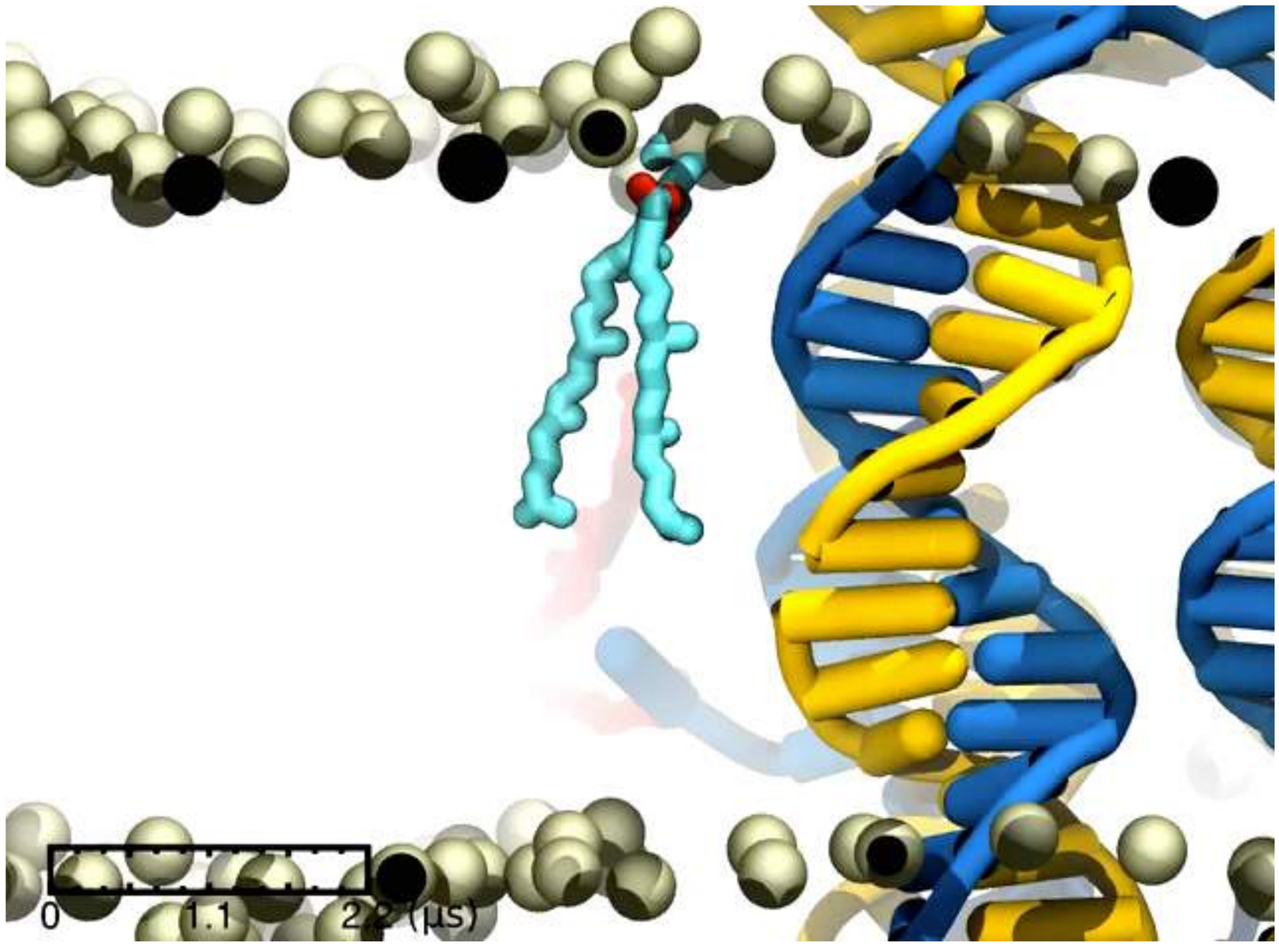




Lipid molecules can translocate to the other leaflet through the toroidal pore made by DNA

Nature Communications 9: 2426 (2018)

Lipid translocation through toroidal pores is **very common** and **very fast**



Lipid translocation in cells is catalyzed by enzyme

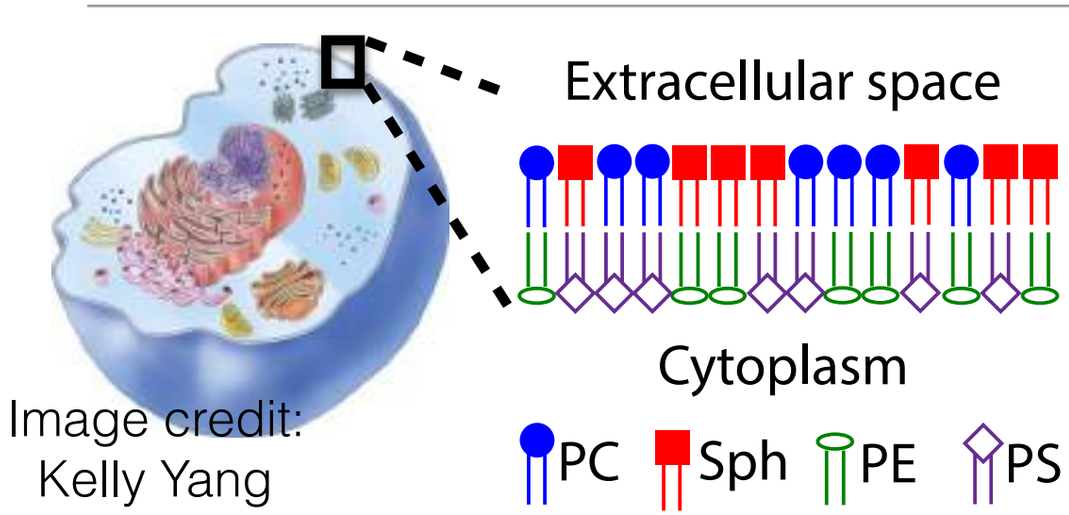
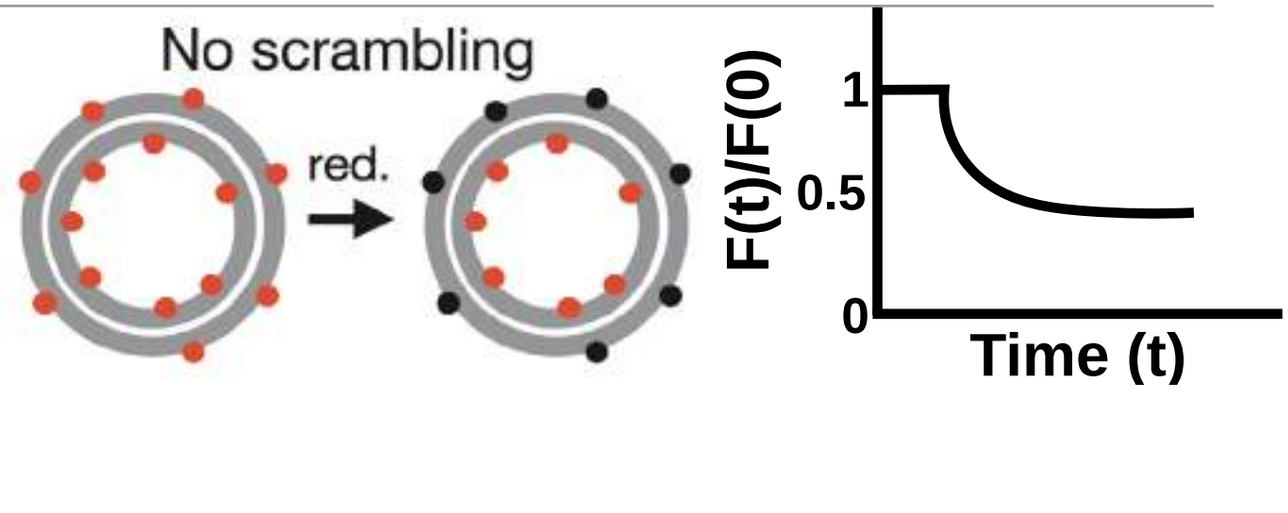
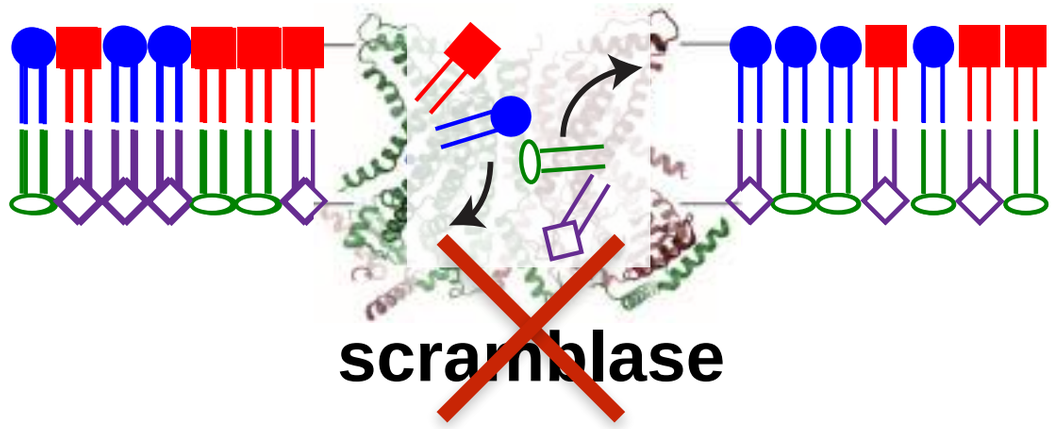


Image credit:
Kelly Yang



Lipid molecules are asymmetricall distributed in the cell membrane.

apoptosis or thrombin formation:



scramblase

Deficiency in lipid scrambling could result in autoimmune response or Scott syndrome.

$$\frac{F(t)}{F(0)} = x_{in}e^{-k_s t} + (1-x_{in})e^{-k_q t}$$

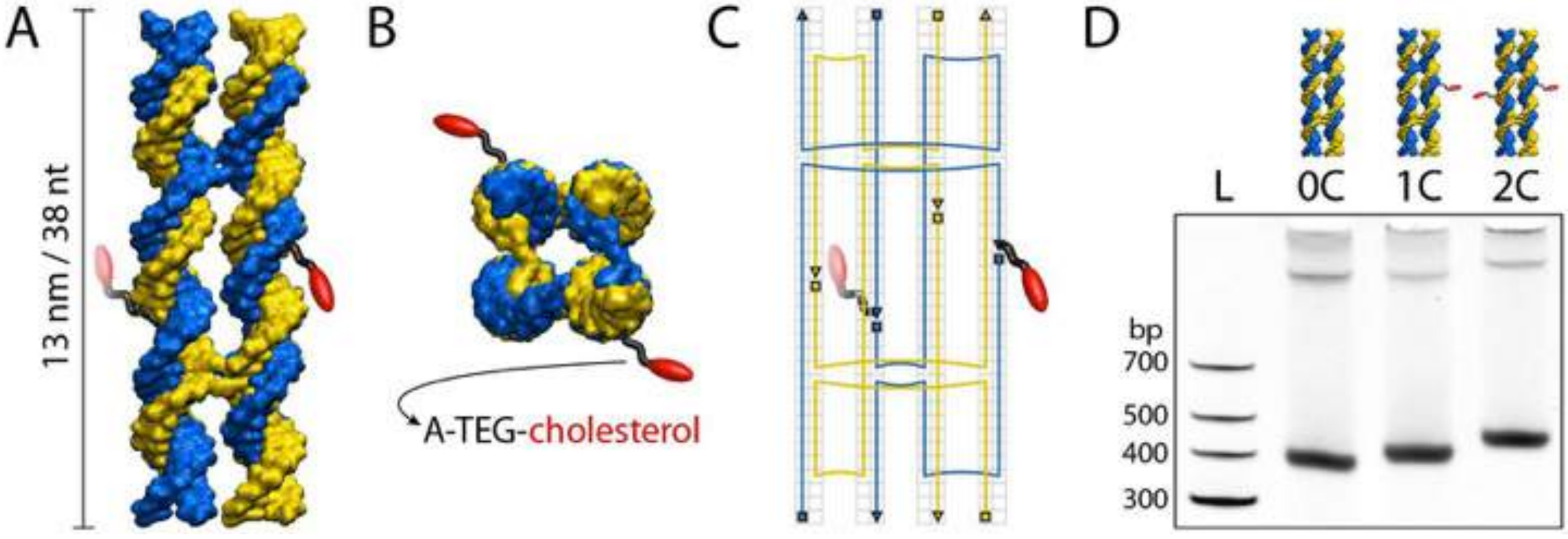
x_{in}: ratio of labeled lipid in the inner leaflet

k_q and k_s: rate constant for quenching and scrambling

Brunner *et al*, *Nature* 516, 207–212, 2014

Experimental verification

Alex Ohmann

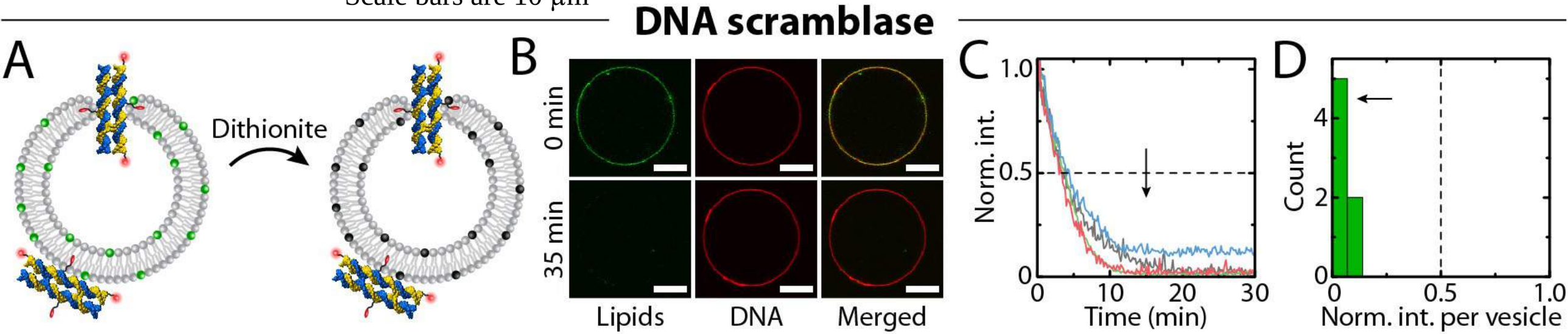


Ohmann, Li, … Ulrich F. Keyser, Aksimentiev, Nature Communications 9: 2426 (2018)

Experimental verification

Alex Ohmann

Scale bars are 10 μm



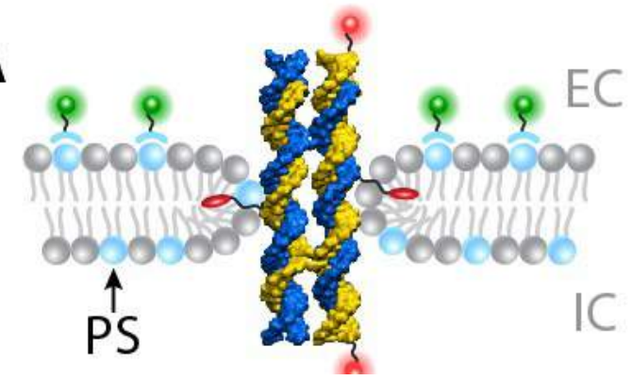
Ohmann, Li, … Ulrich F. Keyser, Aksimentiev, Nature Communications 9: 2426 (2018)

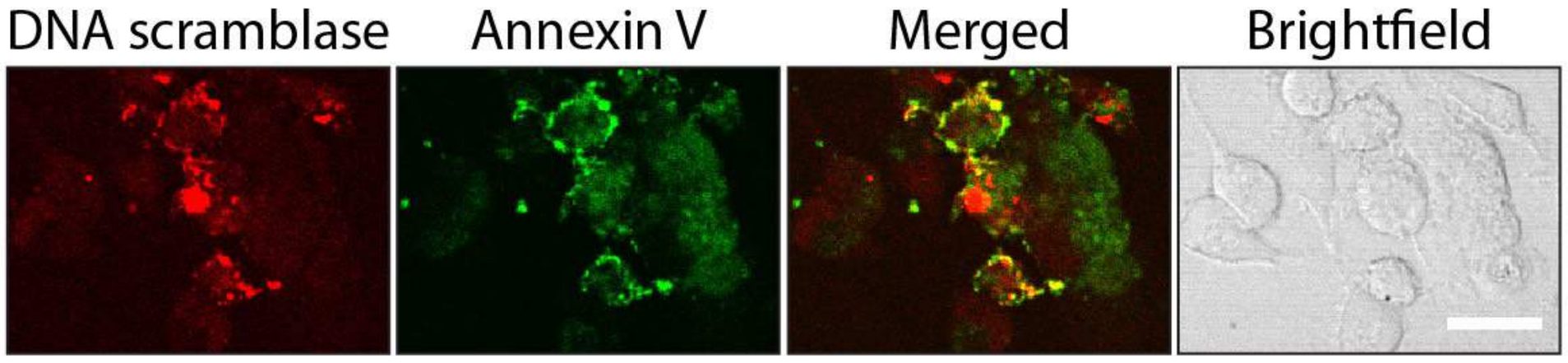
Works in human cells

Human cells contain PS lipids at the inner membrane

Annexin V binds specifically to PS lipids

Scale bar is 20 μm





Breast cancer cells from the cell line MDA-MB-231

Positive control: apoptosis-inducing microbial alkaloid staurosporine

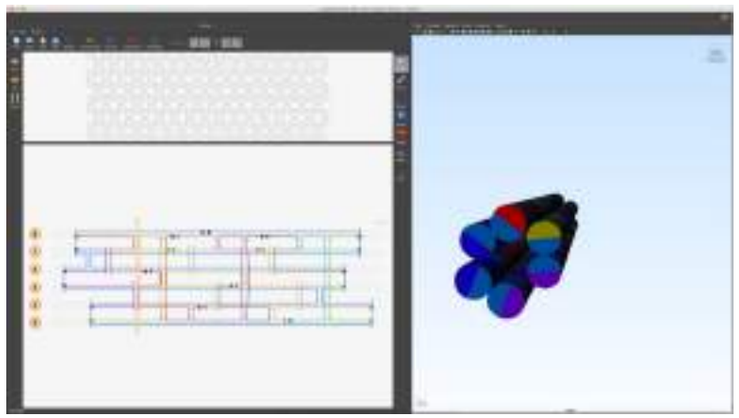
Negative control: DNA folding buffer

Nature Communications 9: 2426 (2018)

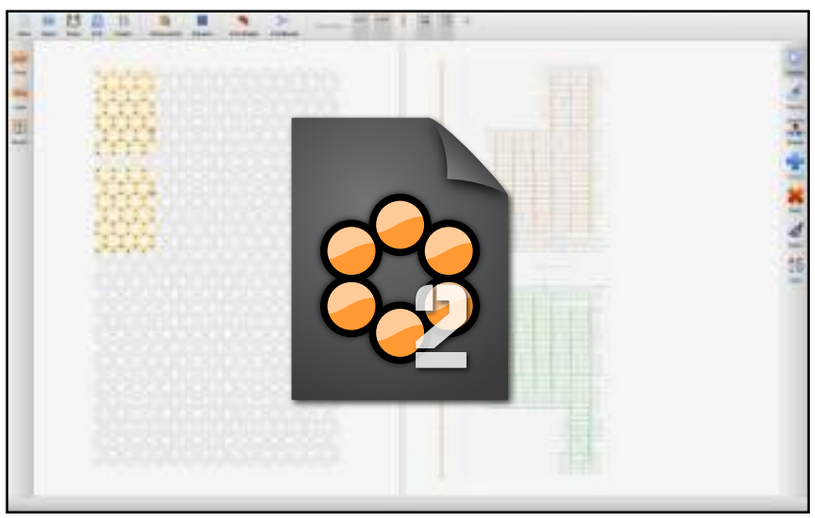
Tutorials overview

Design

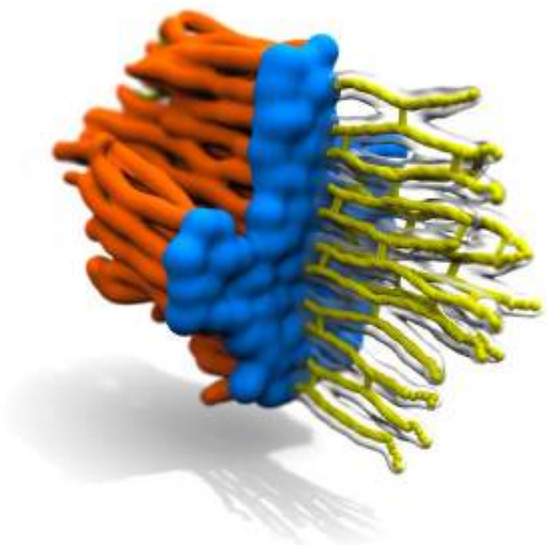
Cadnano (today)



Cadnano toolkit (tomorrow)

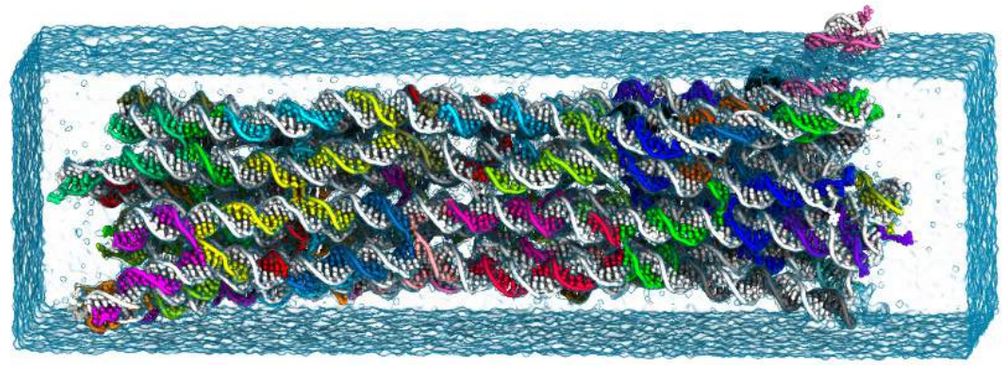


Images and movies with VMD

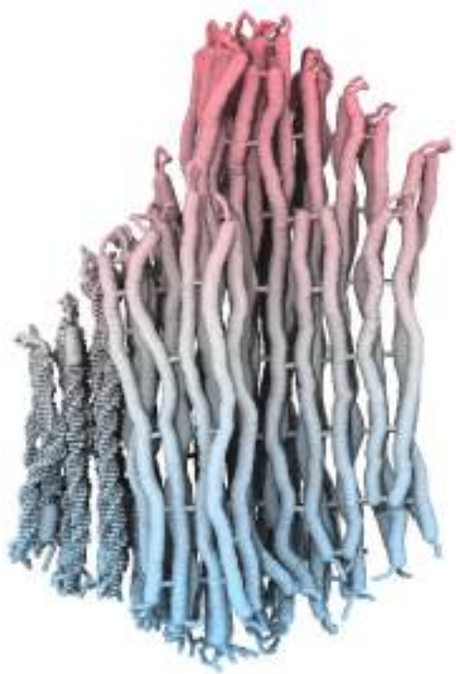


Simulations

All-atom with NAMD (today)



Coarse-grained with ARBD (tomorrow)



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ACS PRF

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TeraGrid™

Center for the Physics of Living Cells

IBM

Oxford NANOPORE Technologies™

US Army Corps of Engineers
Construction Engineering Research Laboratory

ERDC DSRC
DoD Supercomputing Resource Center