Molecular Dynamics of DNA origami nanostructures

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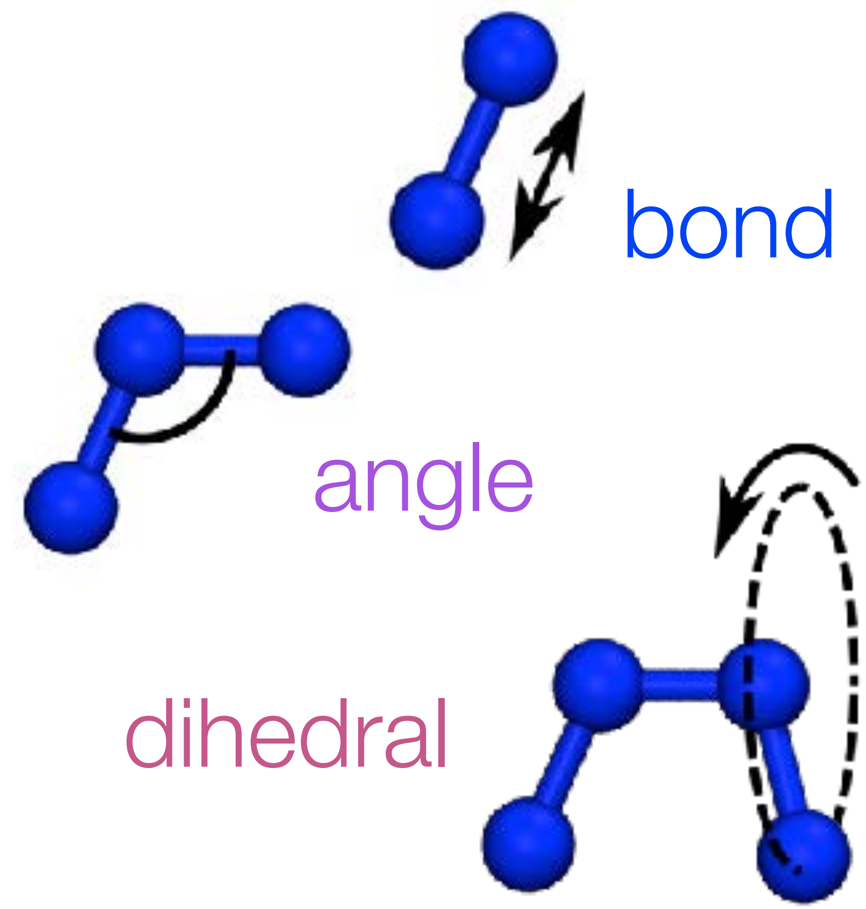
All-atom Molecular Dynamics (MD)

Atoms modeled as classical point particles

Interactions prescribed by CHARMM36 force field with CUFIX corrections

Simulations run using NAMD† on Blue Waters

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

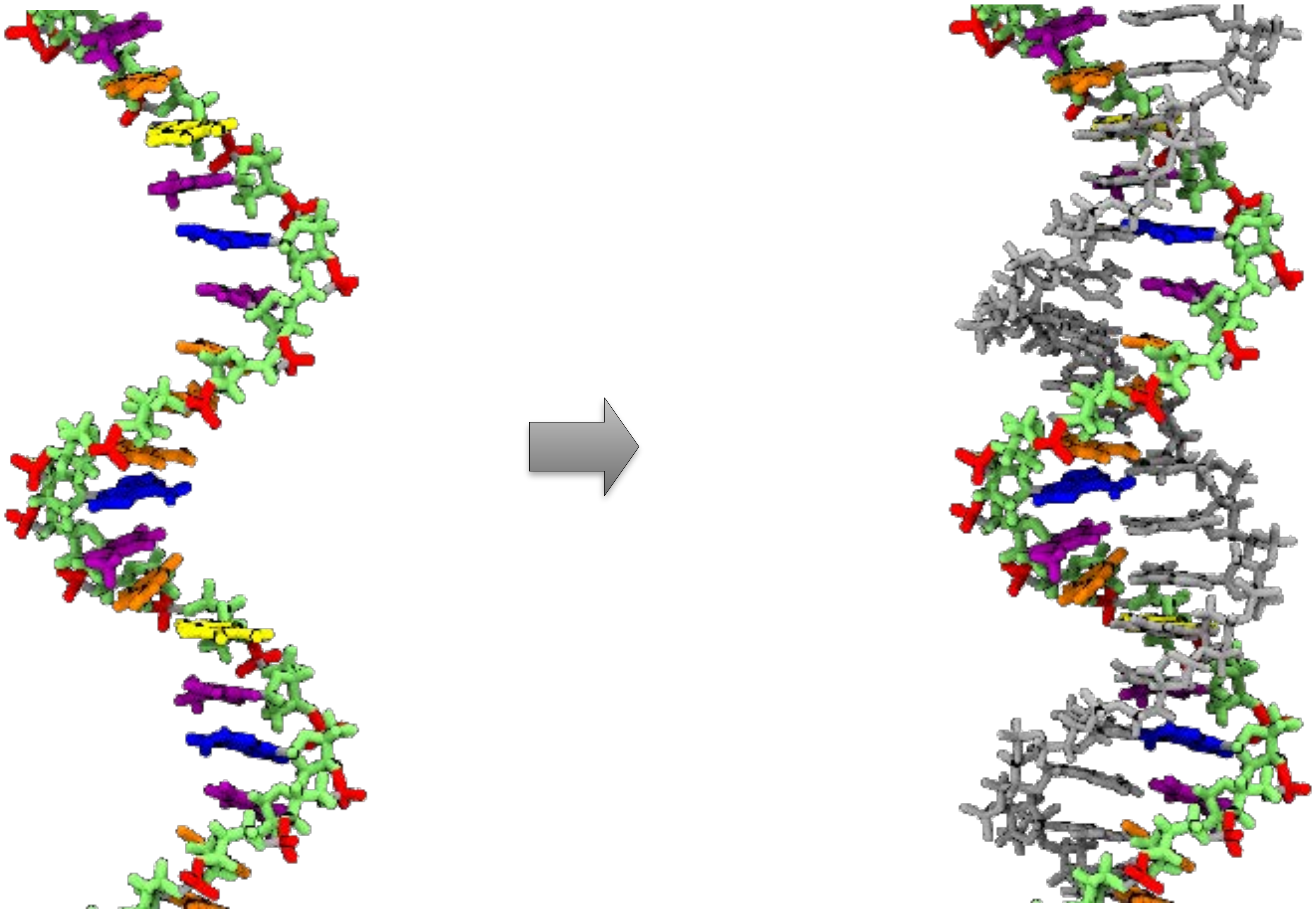


Lennard-Jones (van der Waals)

electrostatic

† Phillips *et.al.* J. Com. Chem. 26:1781

Single-stranded DNA hybridizes with sequence specificity



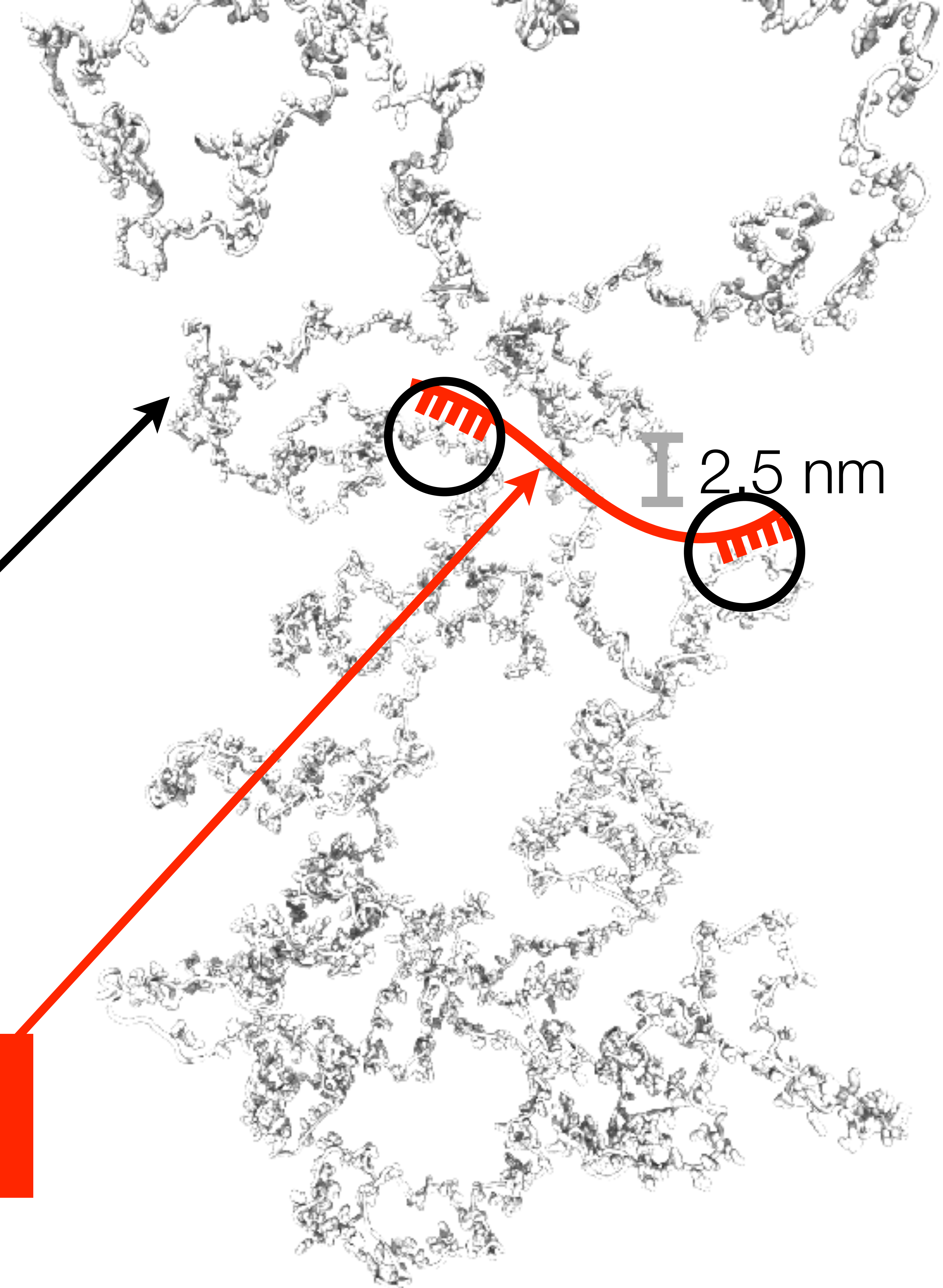
phosphate   sugar   adenine • thymine   guanine • cytosine

DNA origami

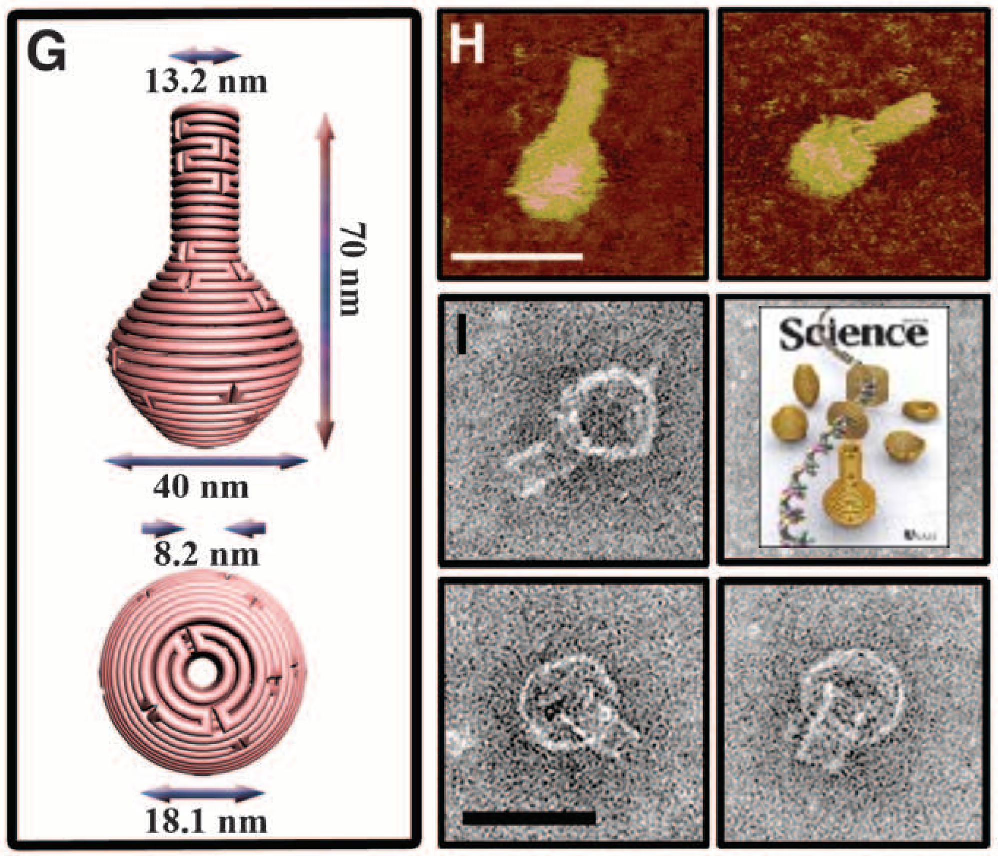
Building a structure with nanoscale precision by **folding** DNA

Viral D… …old)

Synthetic… …(staples)
~30-… …tides

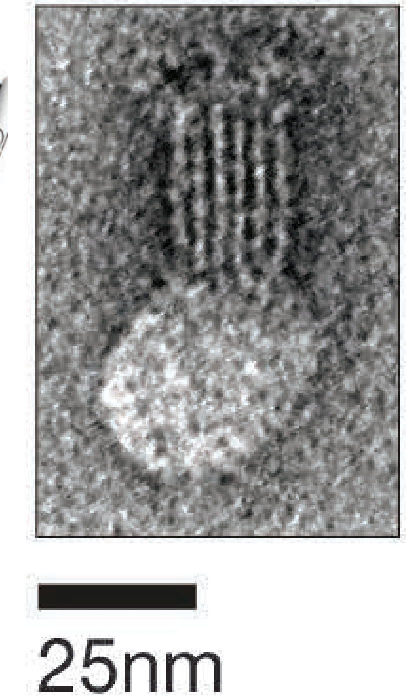


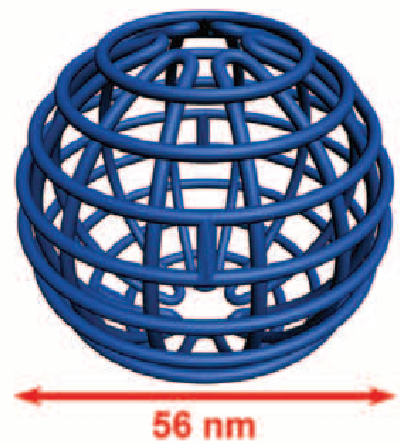
DNA origami structures

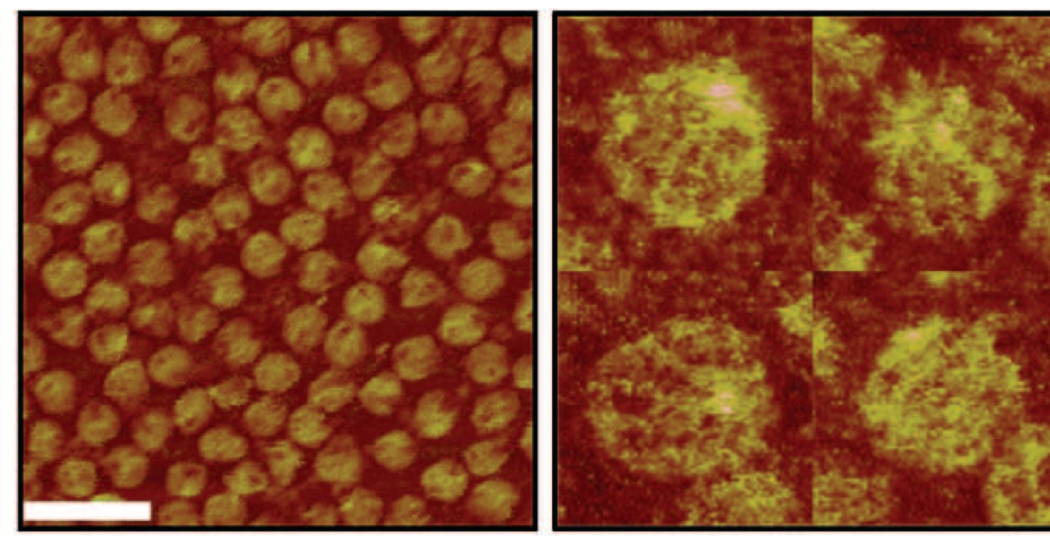


Yan and coworkers, Science (2011)

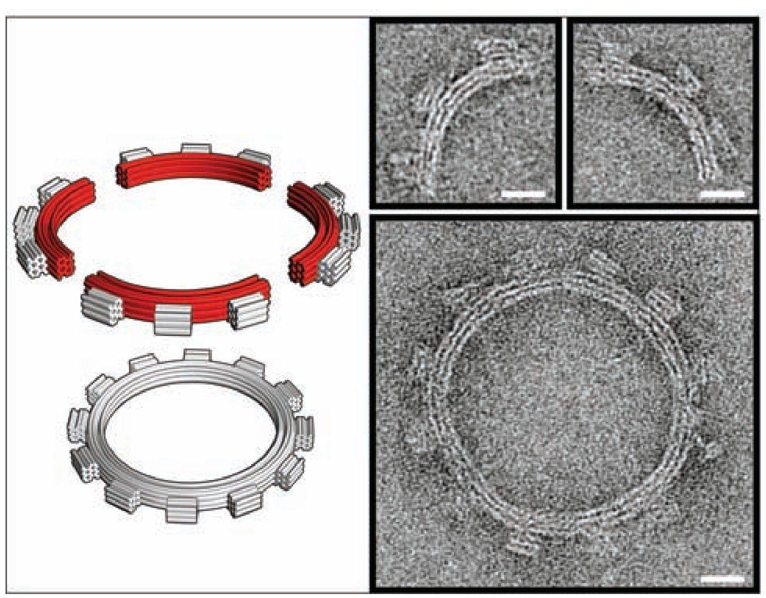
Dietz and coworkers, Science (2012)



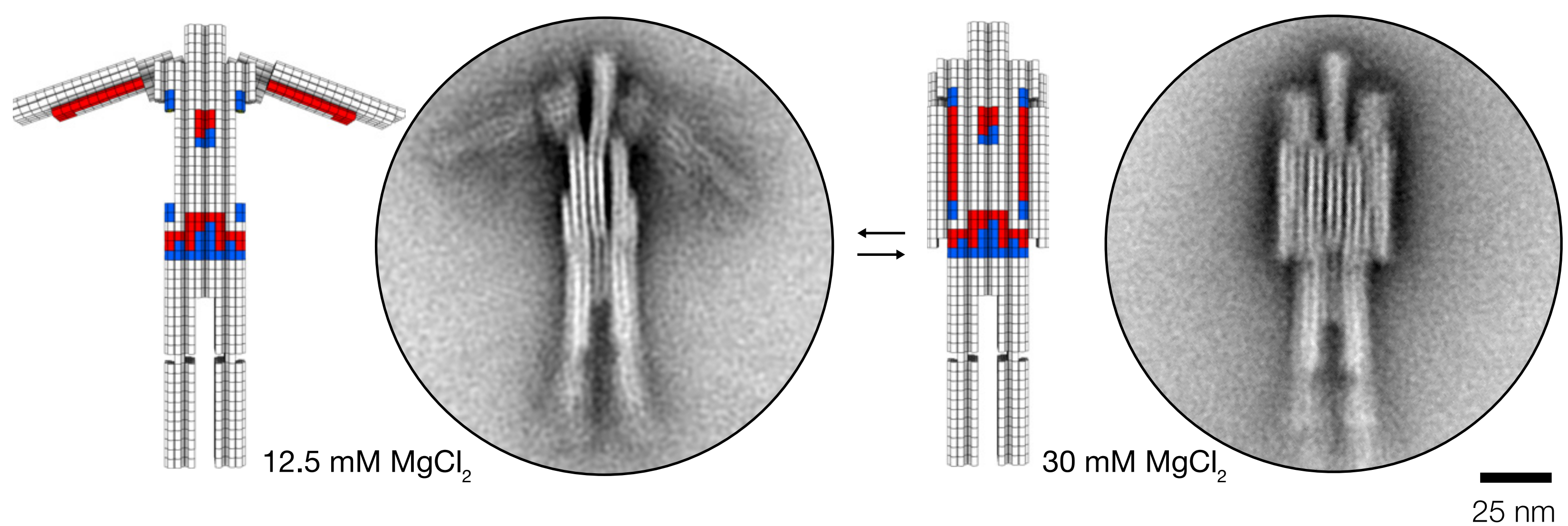




Yan and coworkers, Science (2013)

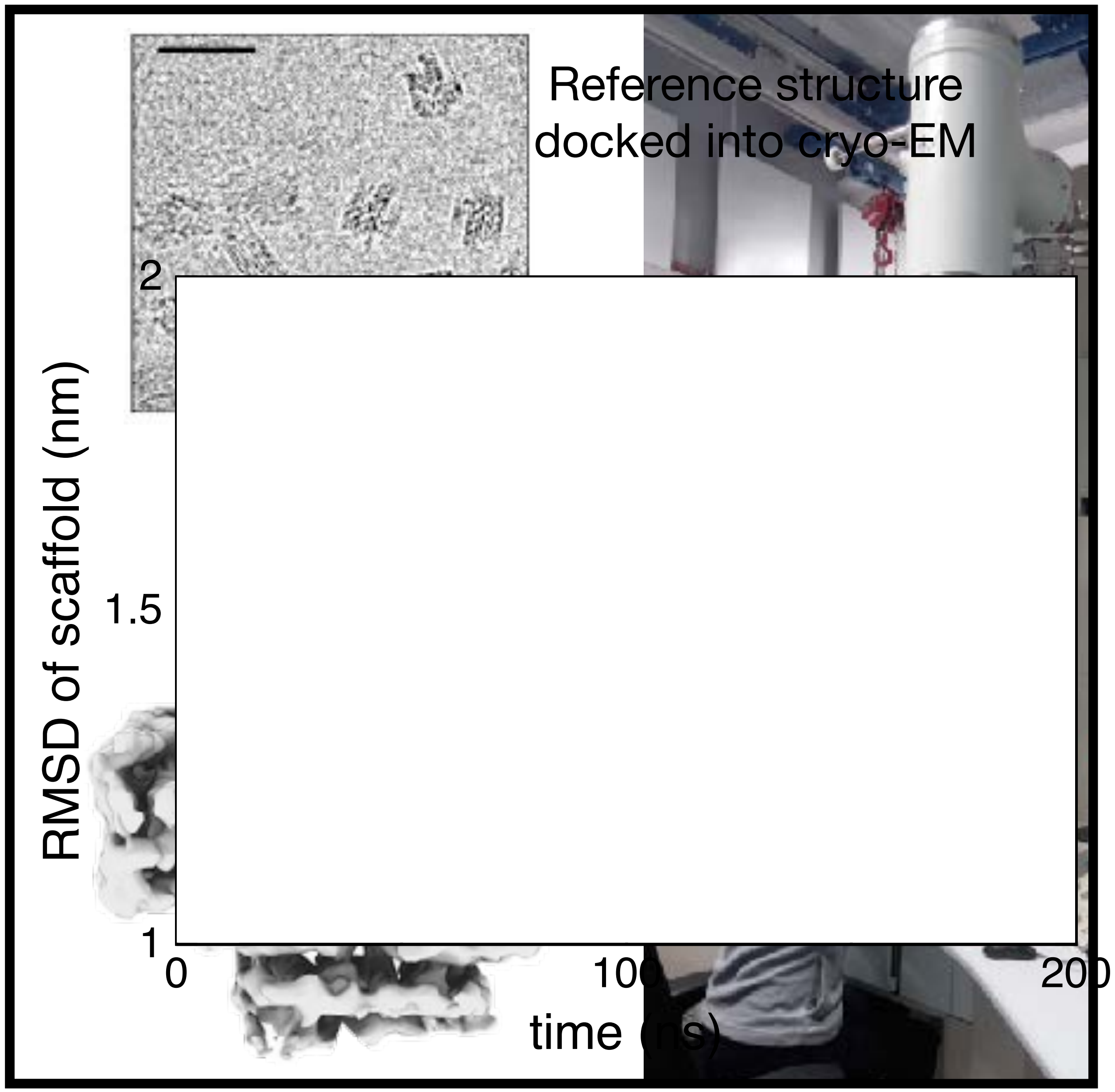


Shih and coworkers, Science (2009)



Dietz and coworkers, Science (2015)

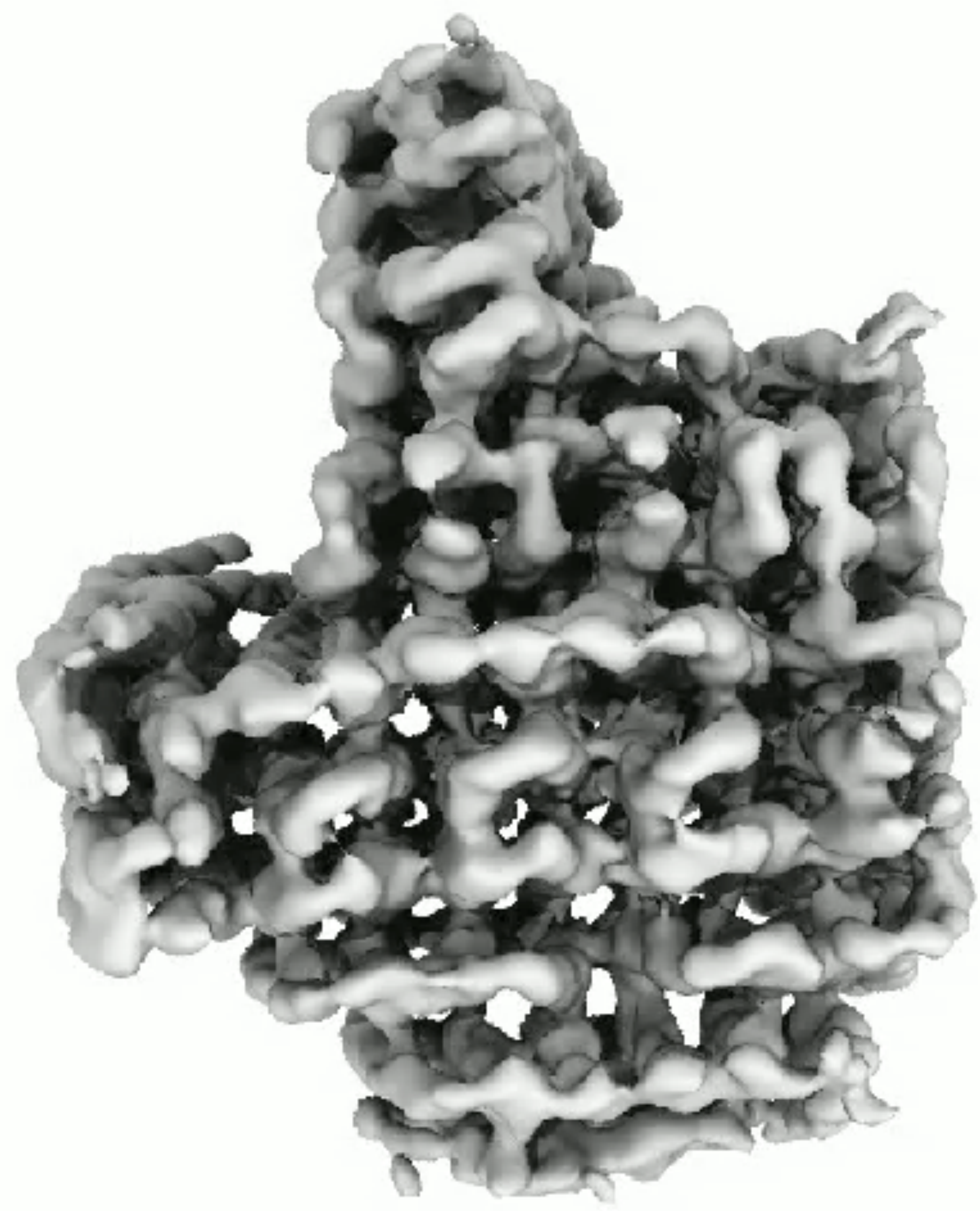
Cryo-electron microscopy and all-atom simulation for DNA origami structure prediction



PNAS 109:20012

Nucleic Acids Research 44:3013

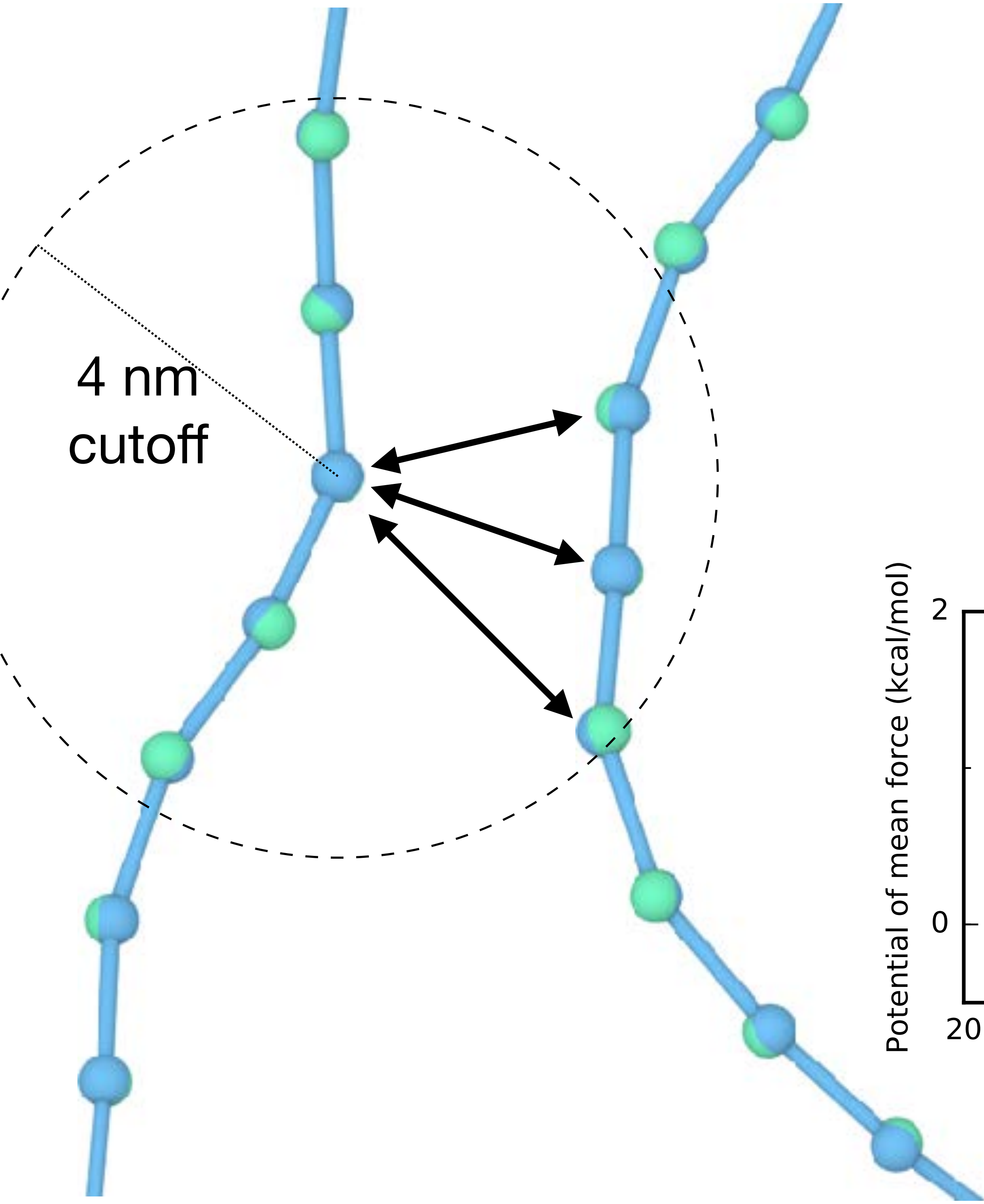
Comparison between simulation and experiment

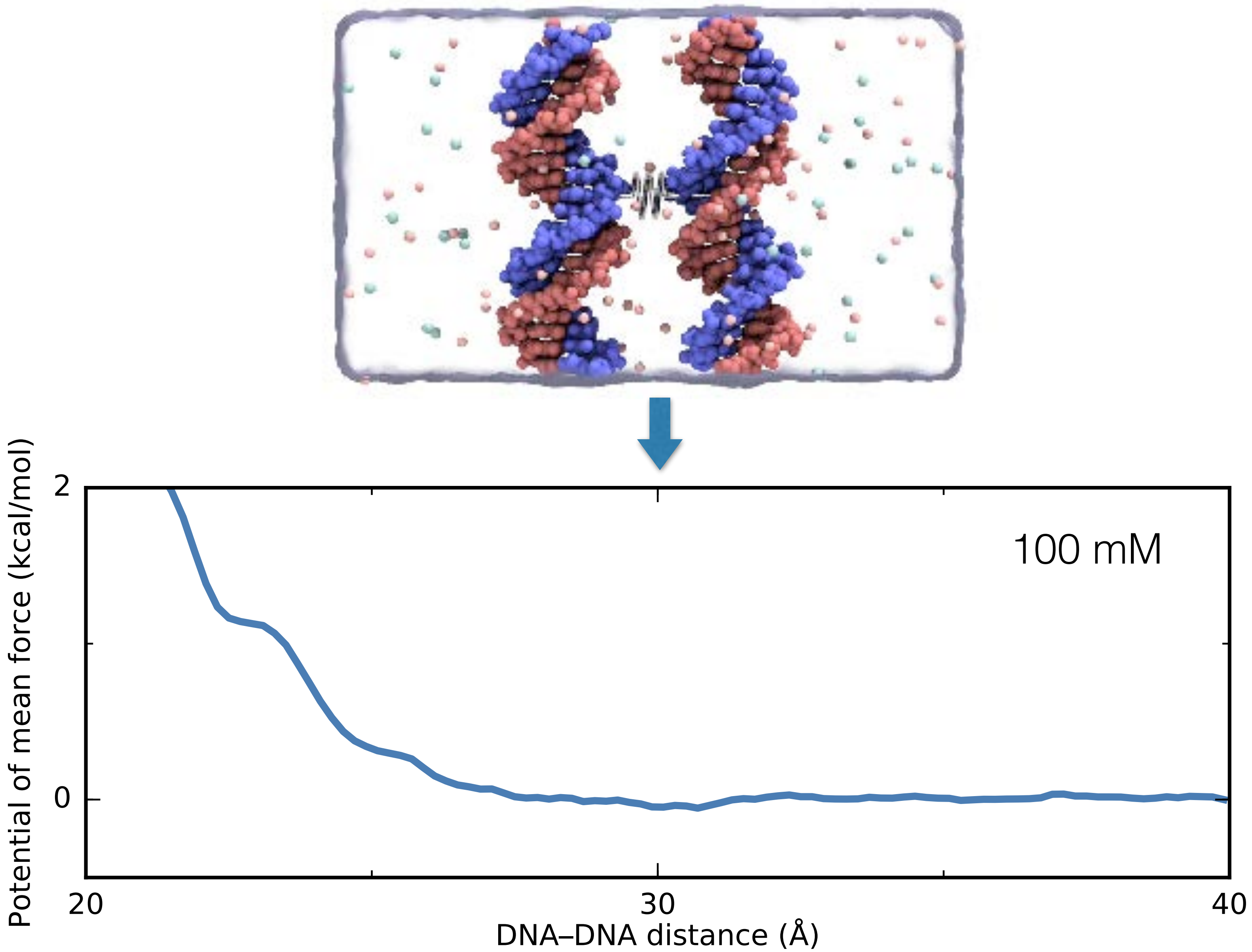


EM density psuedo-atomic model simulation

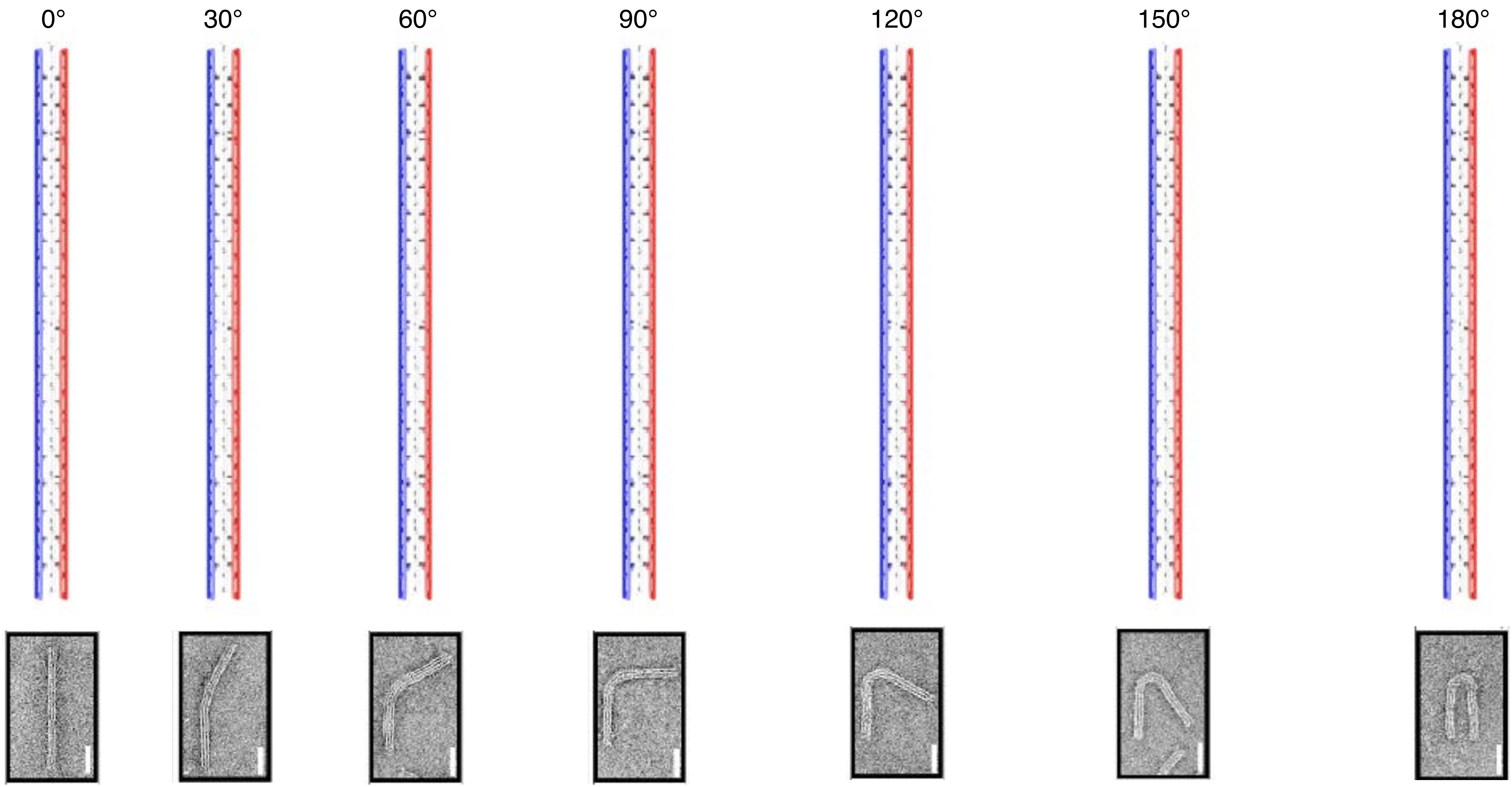
Nucleic Acids Research 44:3013

Interactions in a simple coarse-grained DNA model



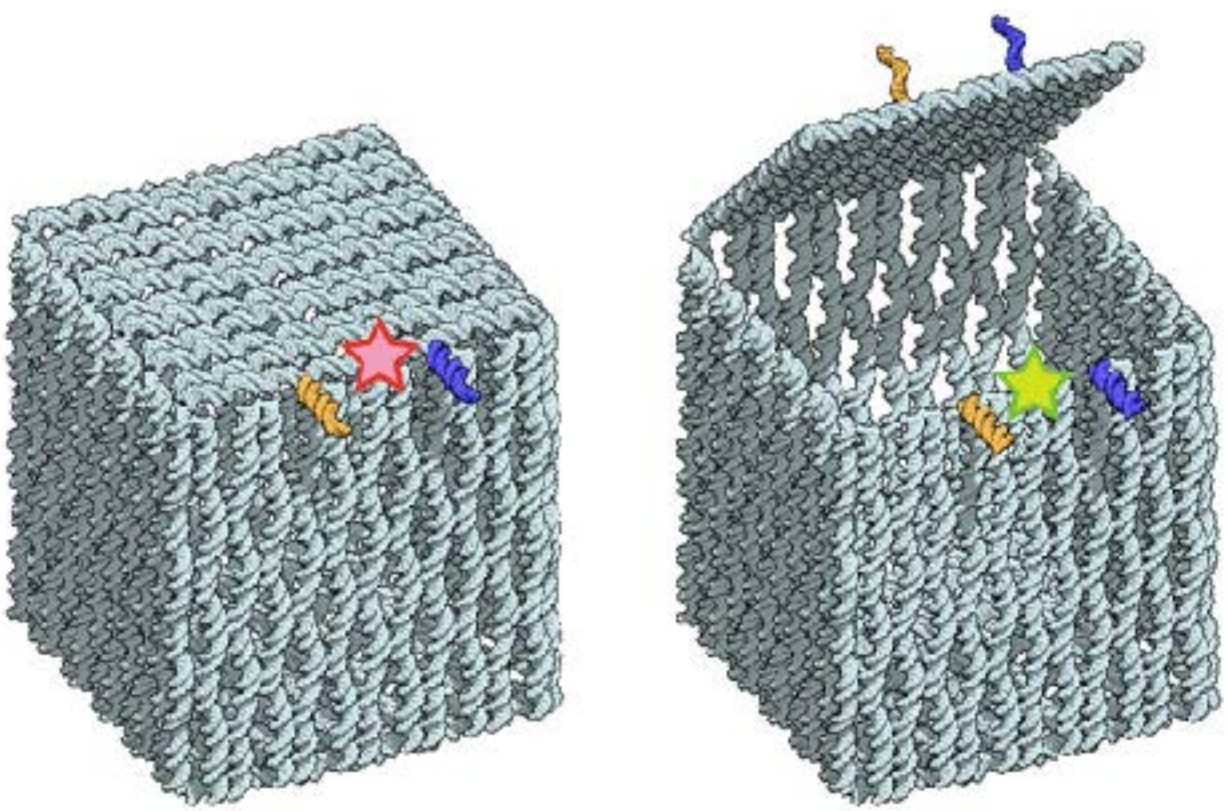


Coarse-grained model captures programmed curvature



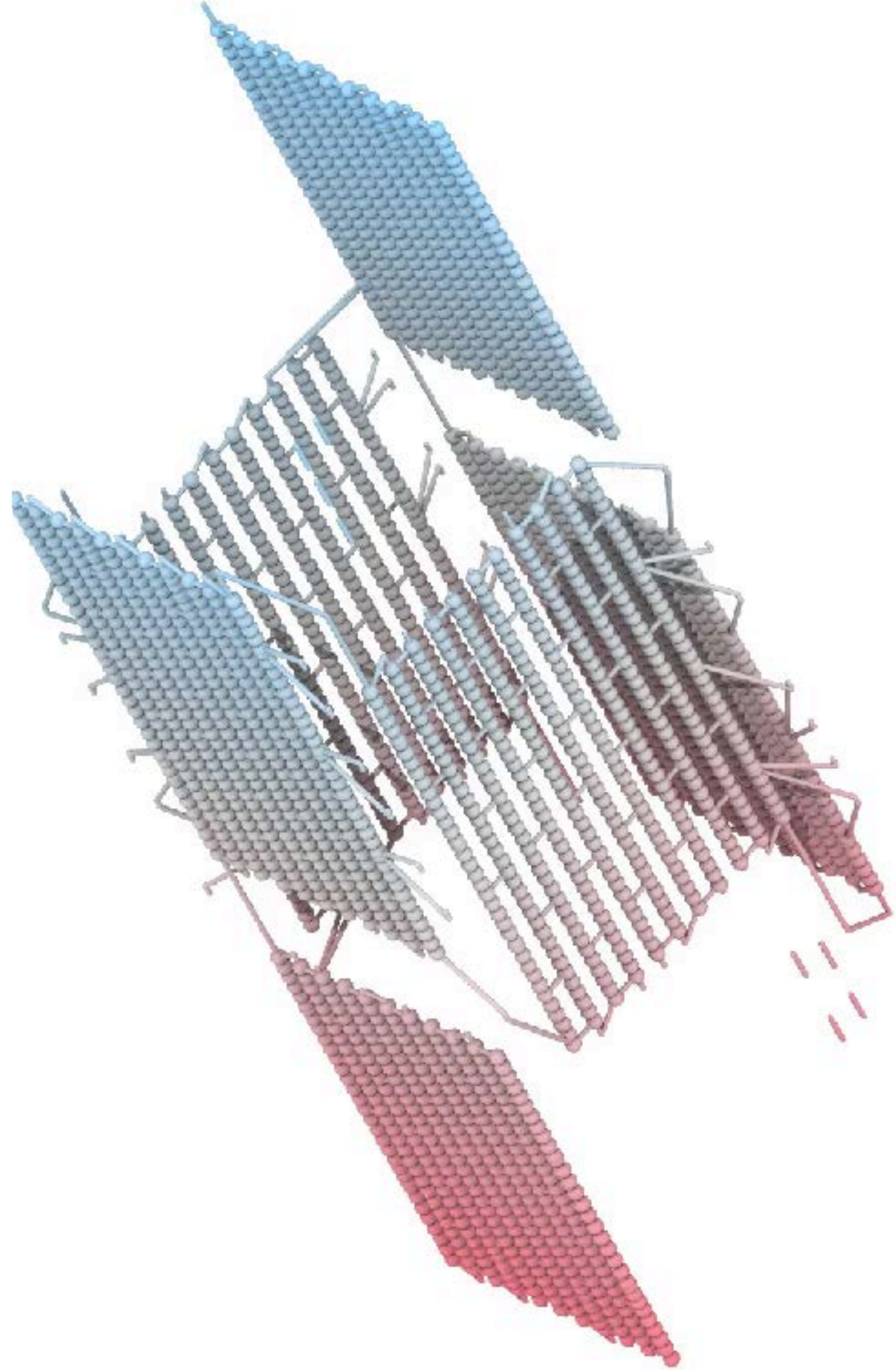
Design and TEM: Science 325:725

Adaptive resolution simulation of DNA origami systems



Andersen et al., Nature 2009

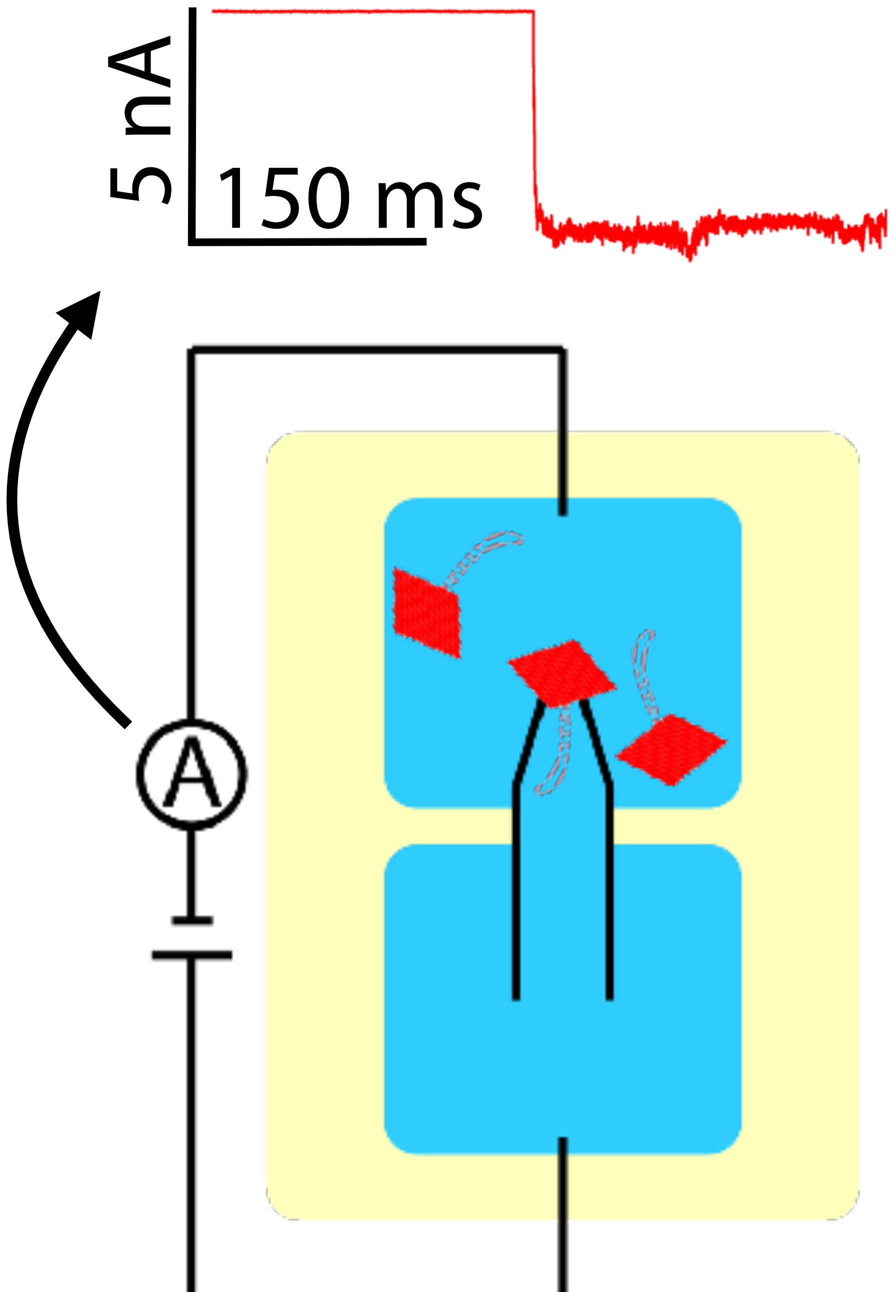
Birkedal Group



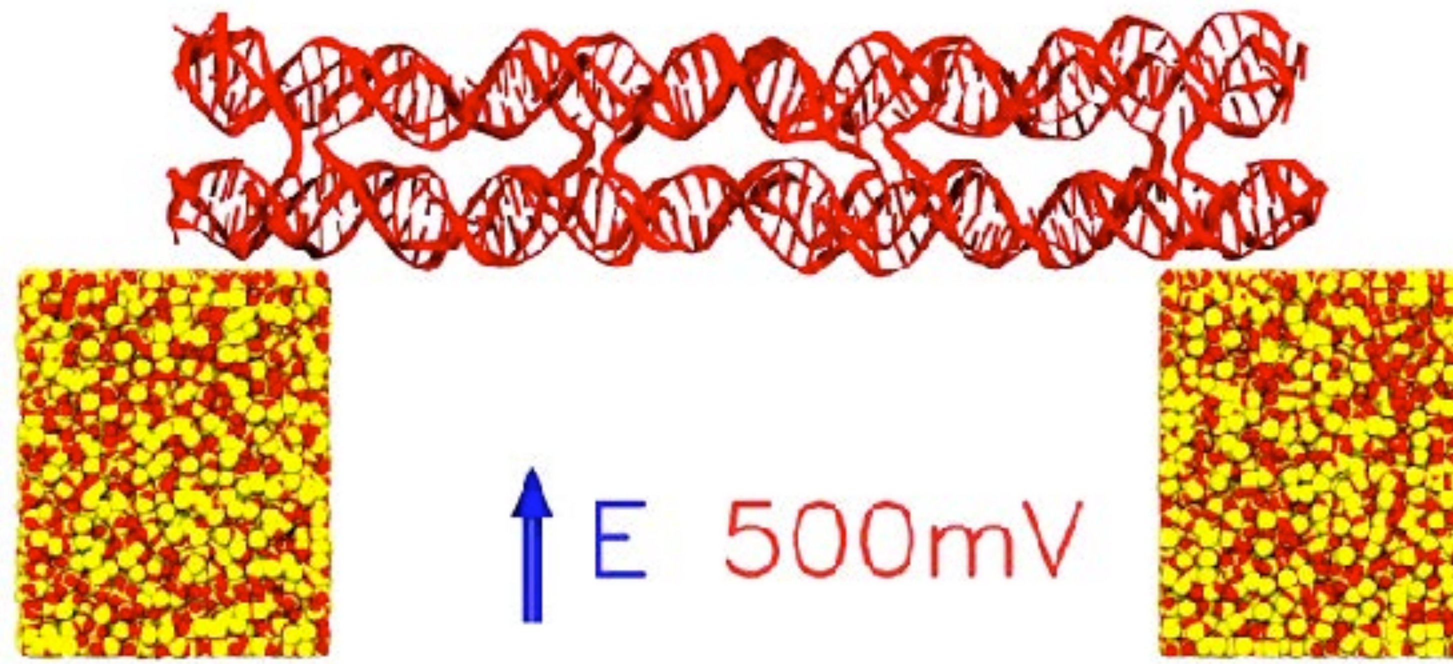
DNA-based Voltage sensing

Keyser Group

Experimental setup

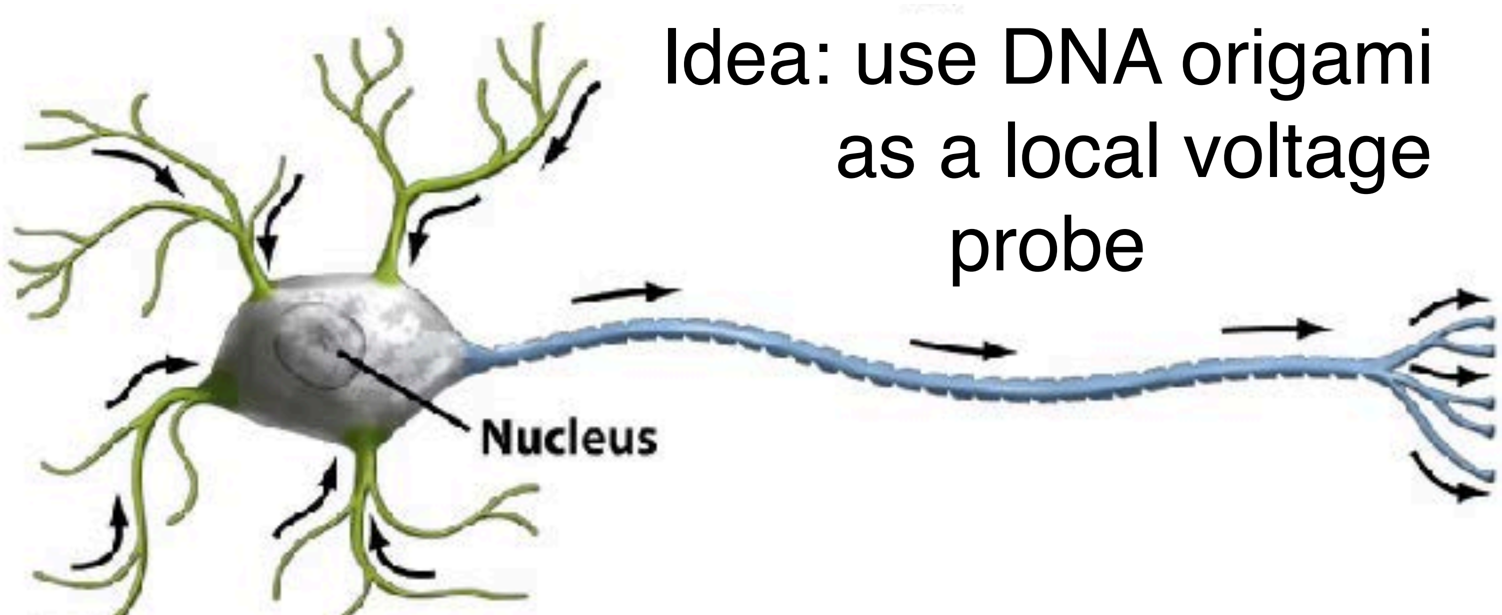


All-atom MD simulation



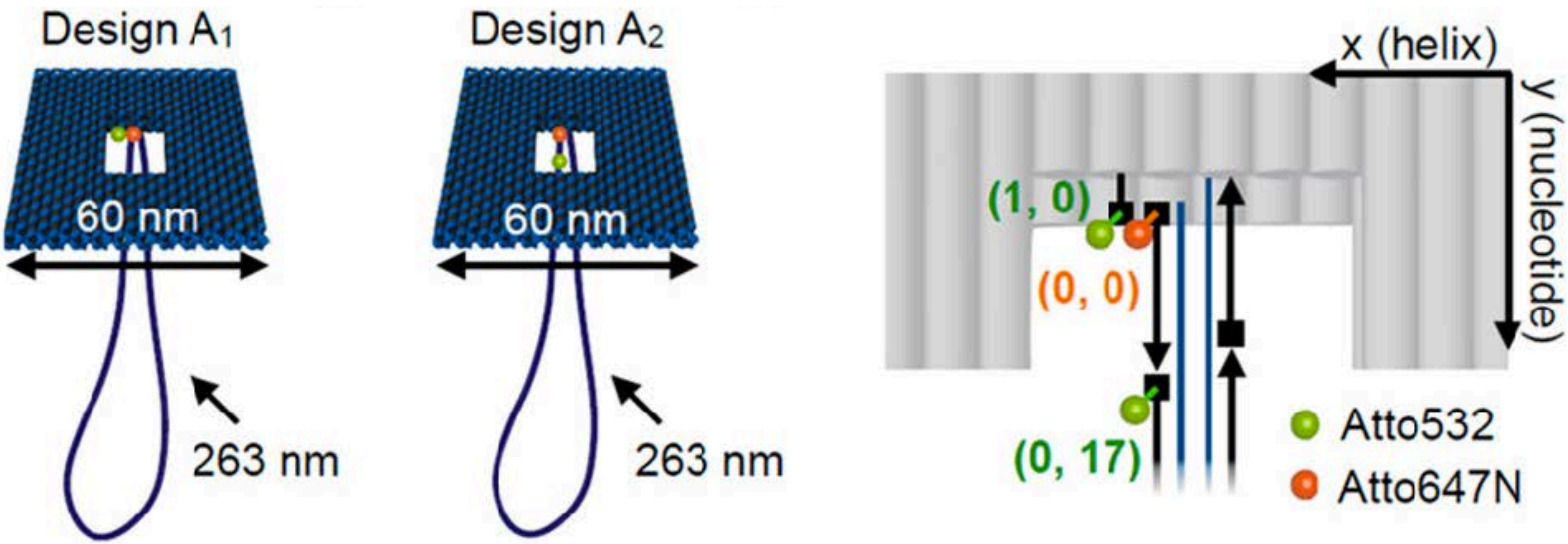
ACS Nano 9:1420-1433 (2015)

Idea: use DNA origami as a local voltage probe



Design of a nanoscale voltage sensor

Keyser and Tinnefeld Groups

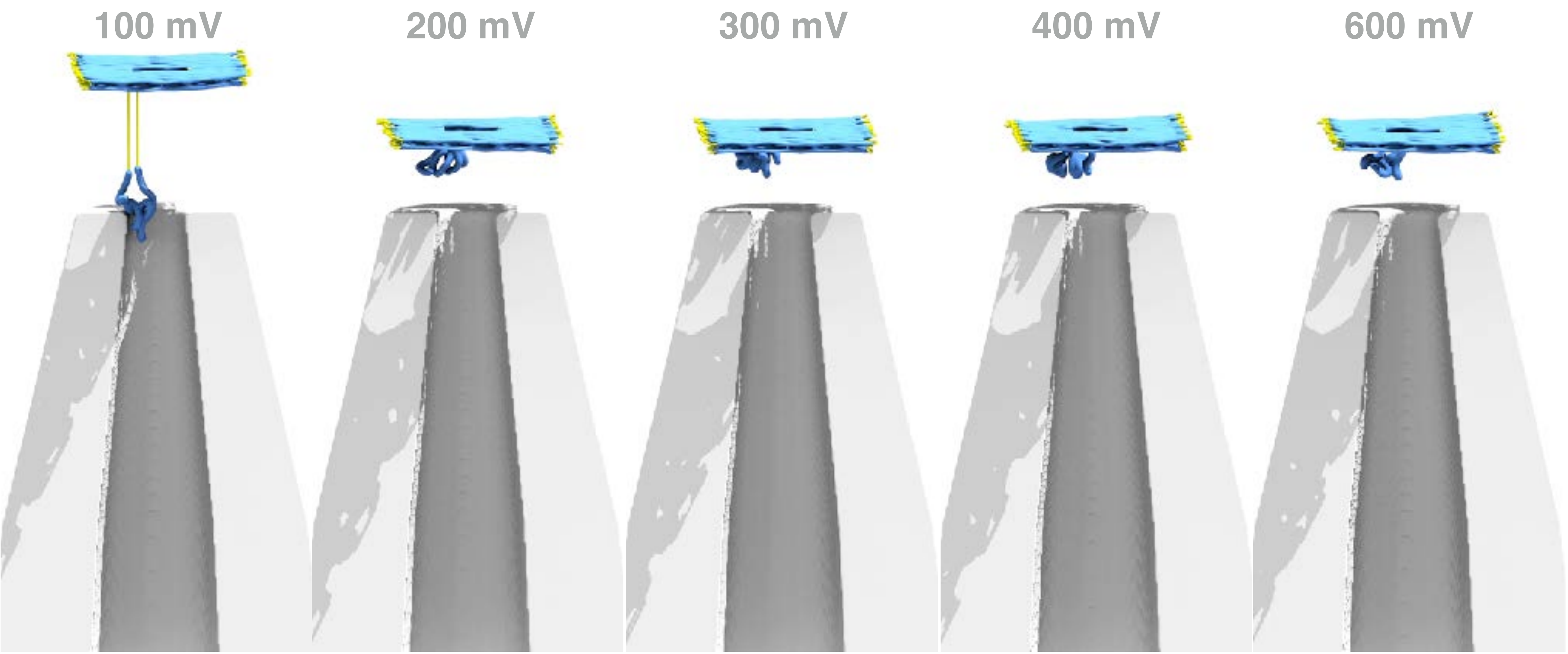


Nano Lett., doi: 10.1021/acs.nanolett.7b05354 (2018)

Coarse-grained simulations of a FRET plate capture

~5 bp/bead CG model

40 μs simulations



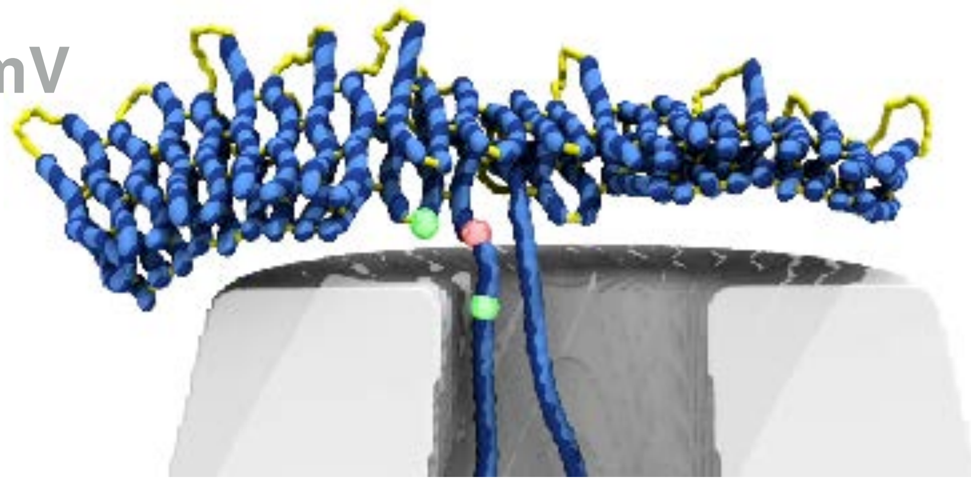
Nano Lett., doi: 10.1021/acs.nanolett.7b05354 (2018)

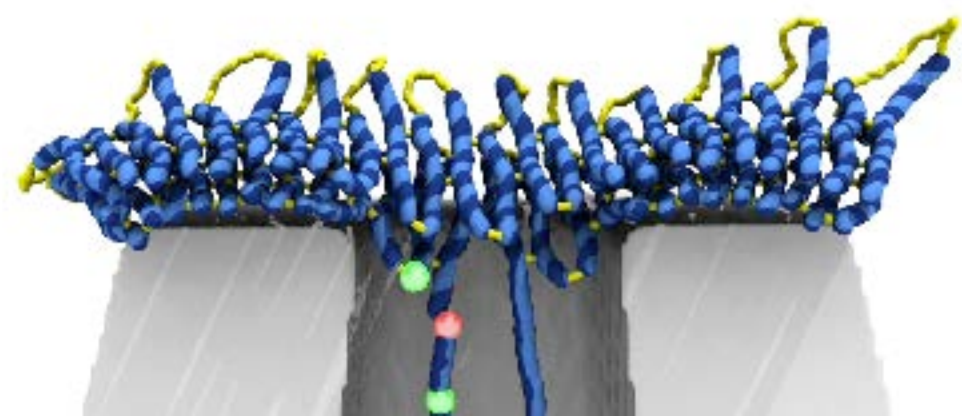
CG simulation of FRET efficiency

2 beads/bp CG model

1 μs simulations

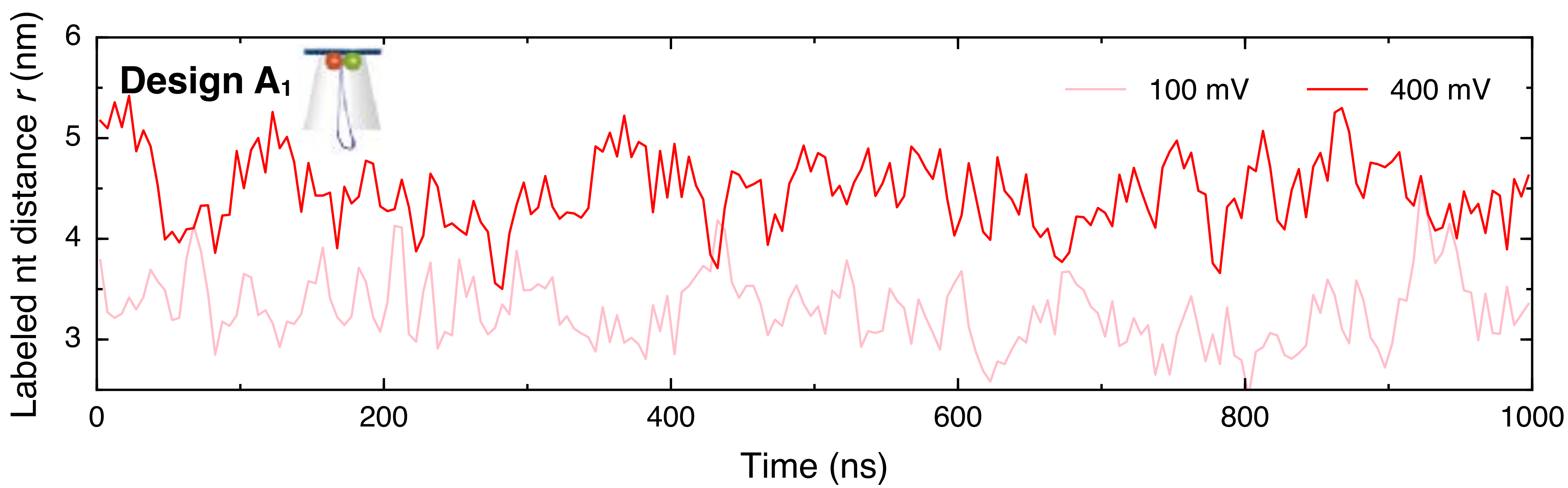
100 mV





400 mV

200 m

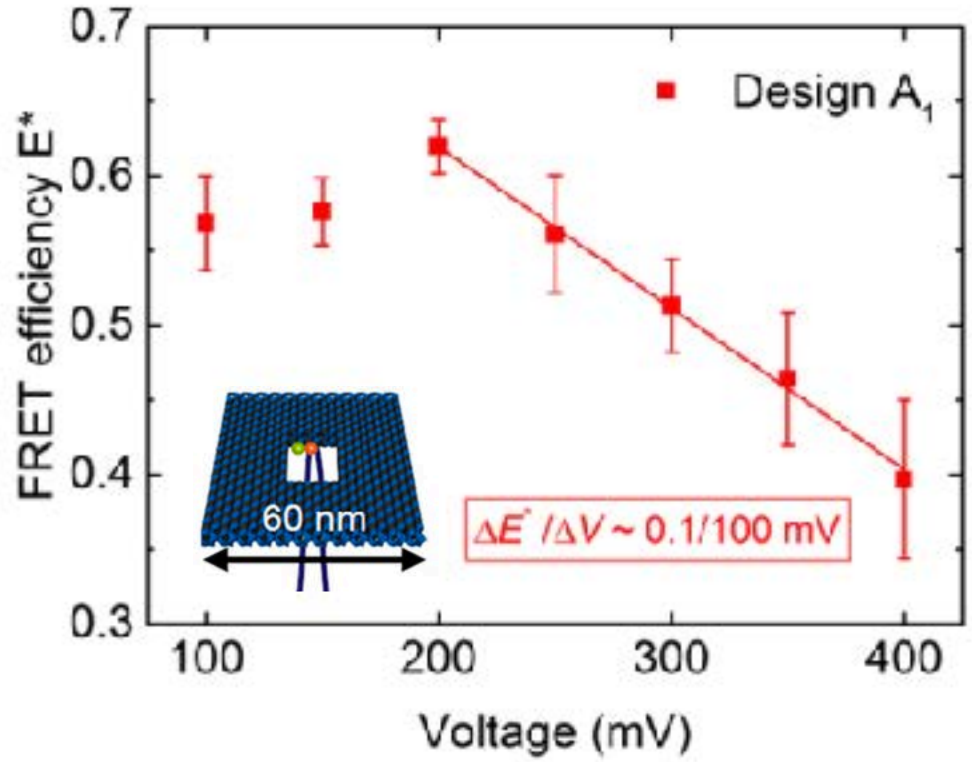


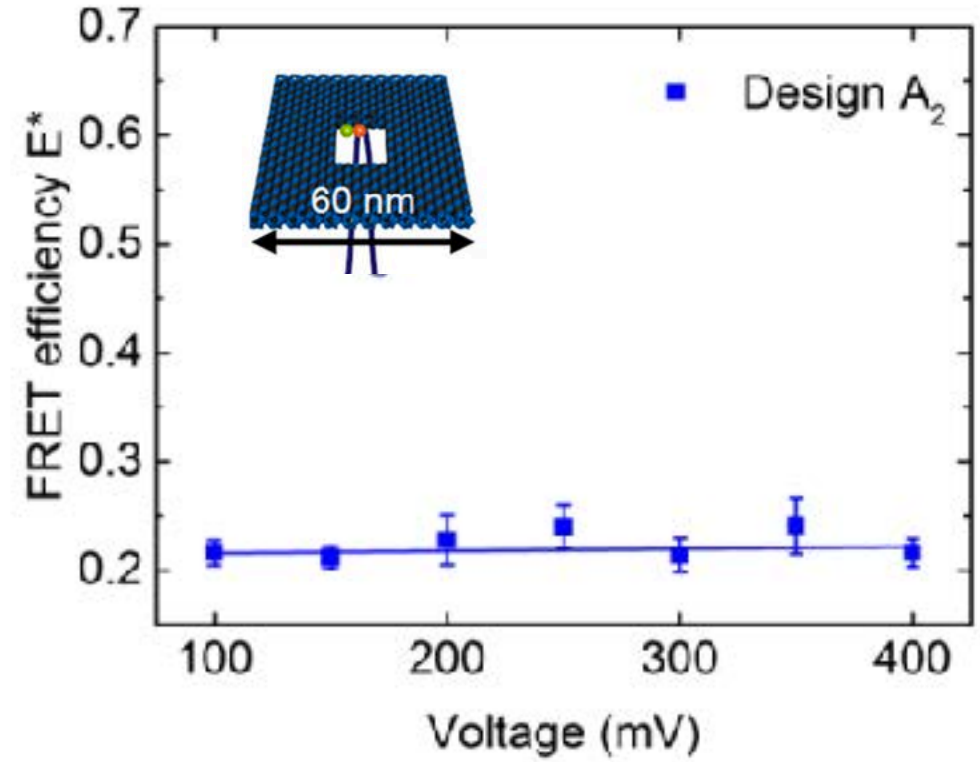
00 mV

Nano Lett., doi: 10.1021/acs.nanolett.7b05354 (2018)

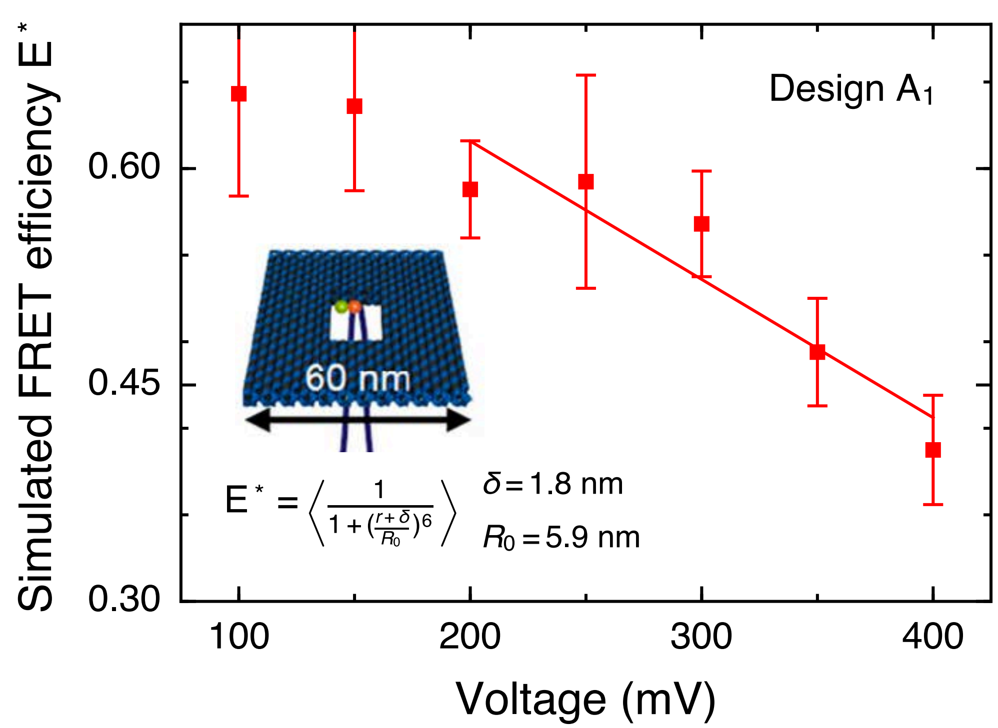
Voltage sensing with DNA origami

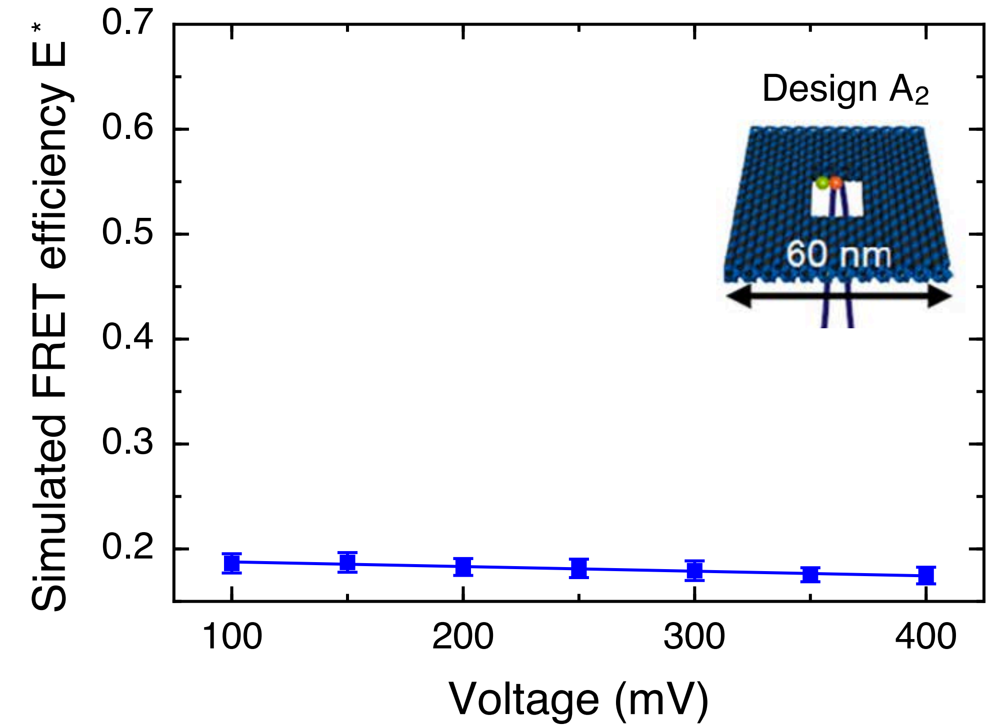
Experiment:





Simulation:

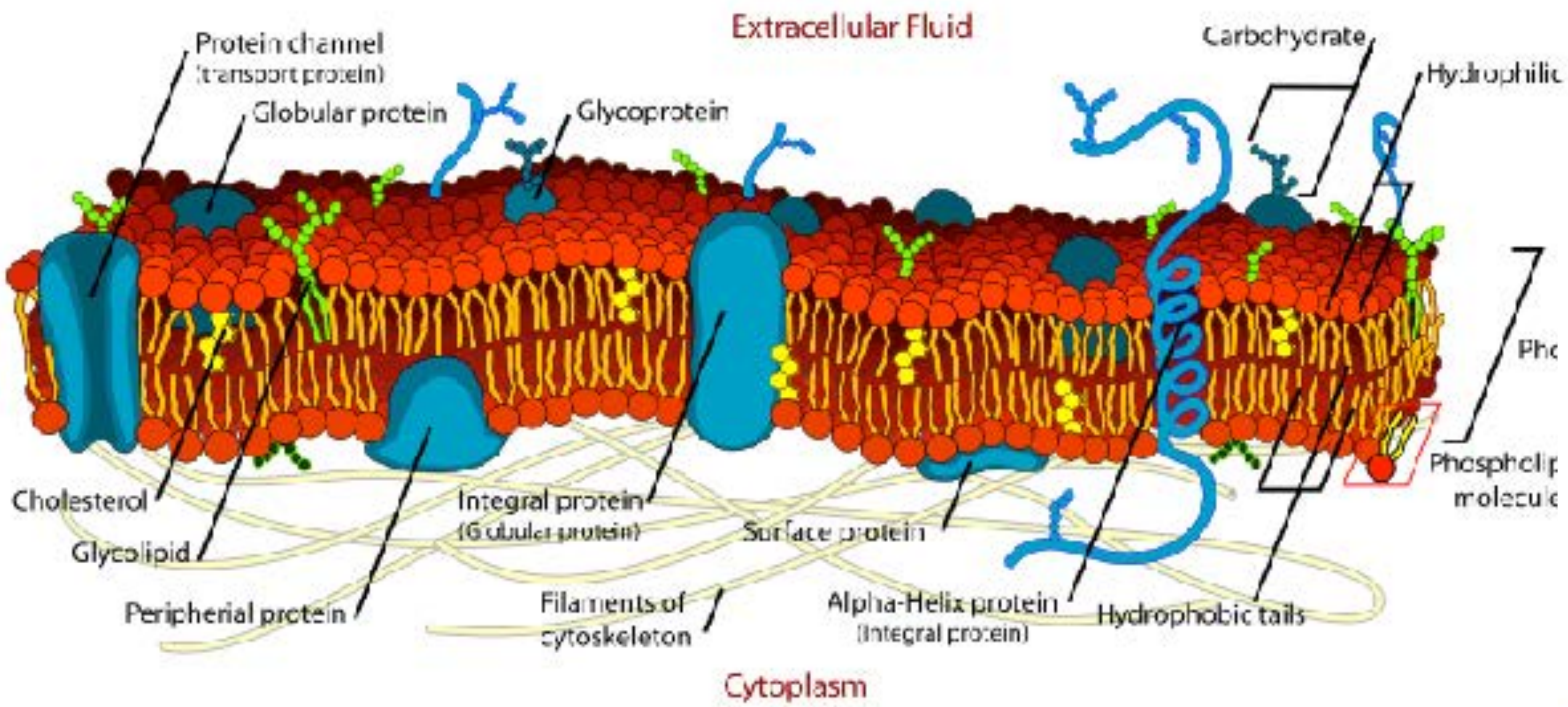




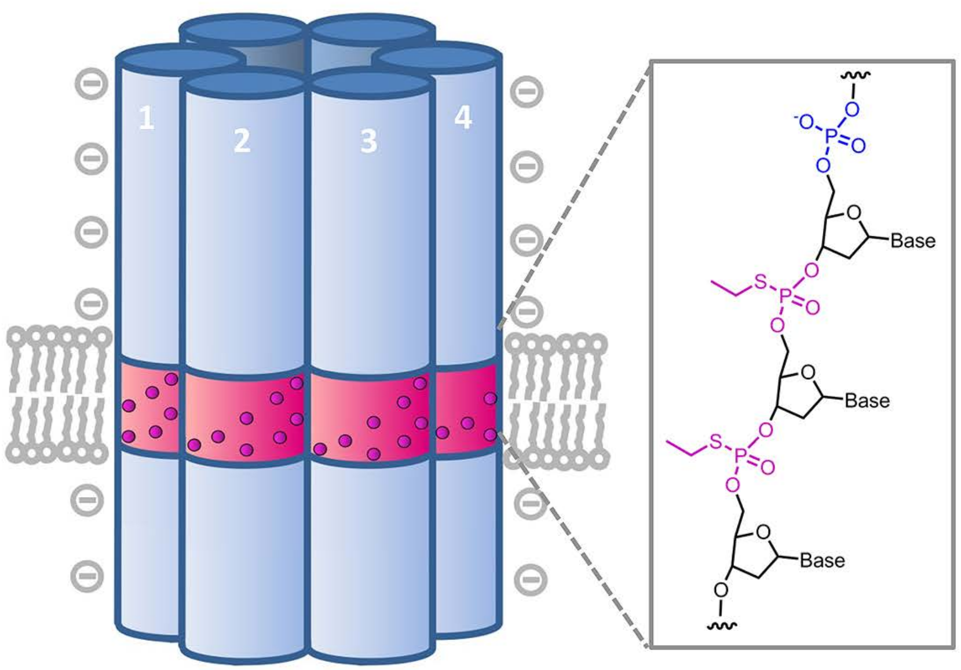
Nano Lett., doi: 10.1021/acs.nanolett.7b05354 (2018)

DNA Ion Channels

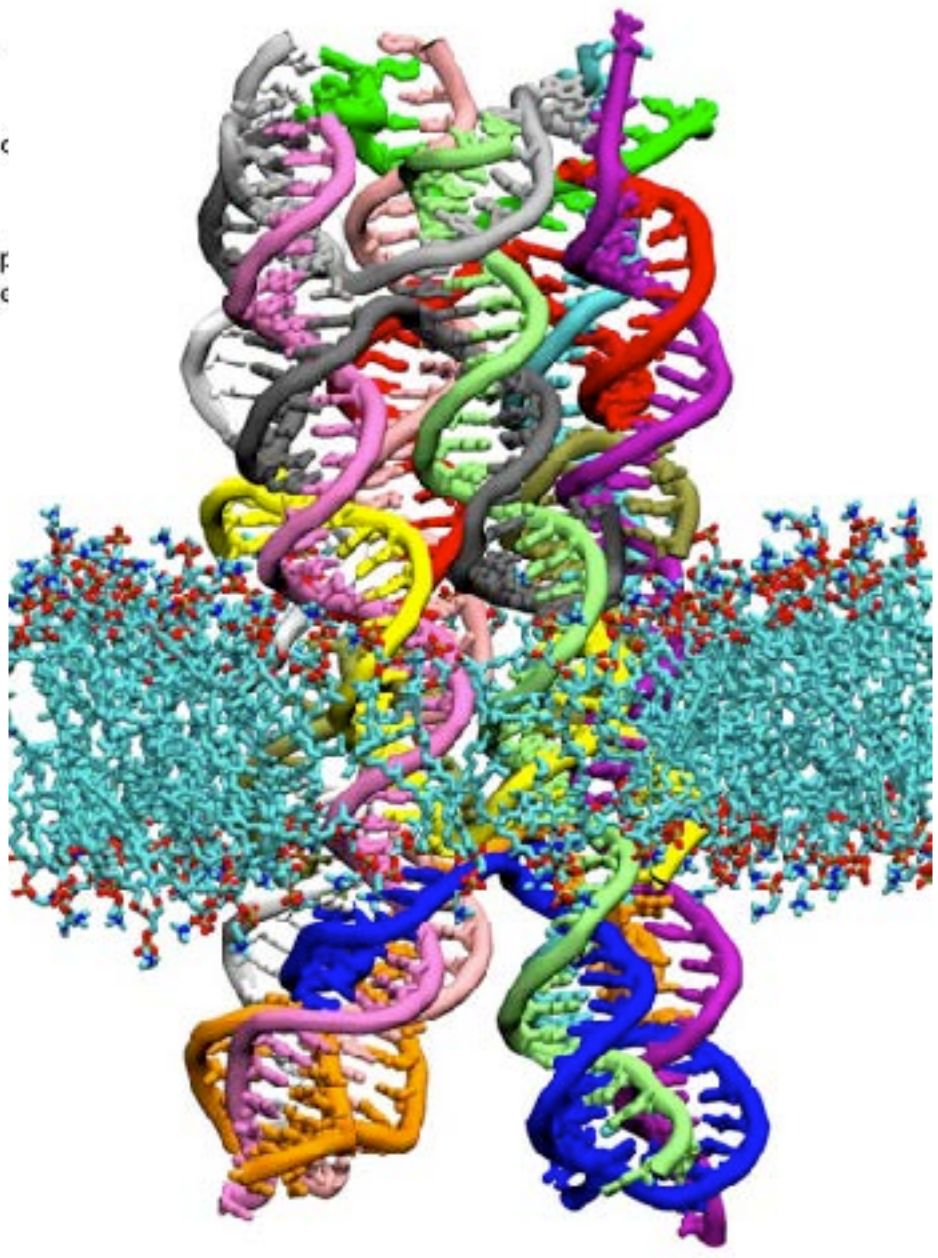
Jejoong Yoo



Nano Letters, *13*: 2351

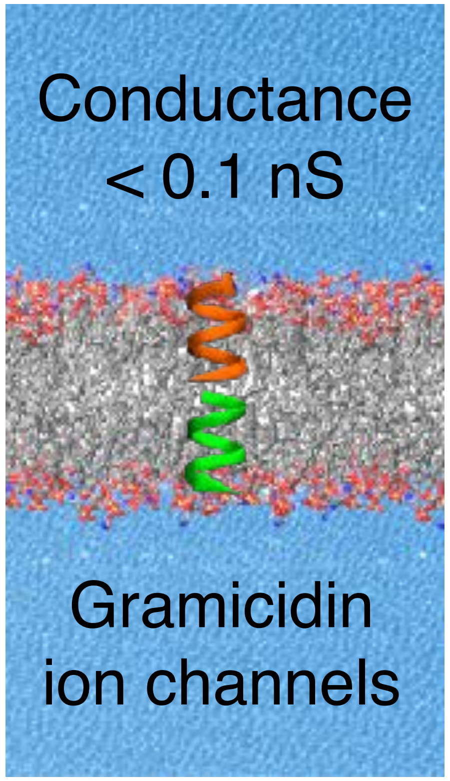


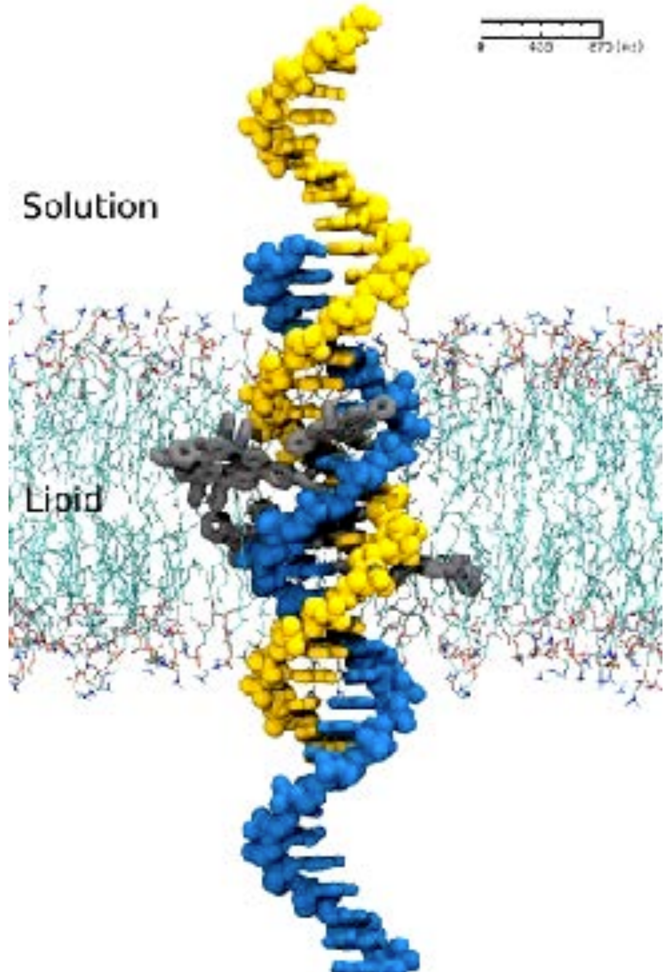
Porins, 1 nS conductance



Yoo & Aksimentiev, JPCL 6, 4680 (2015)

DNA Ion Channels



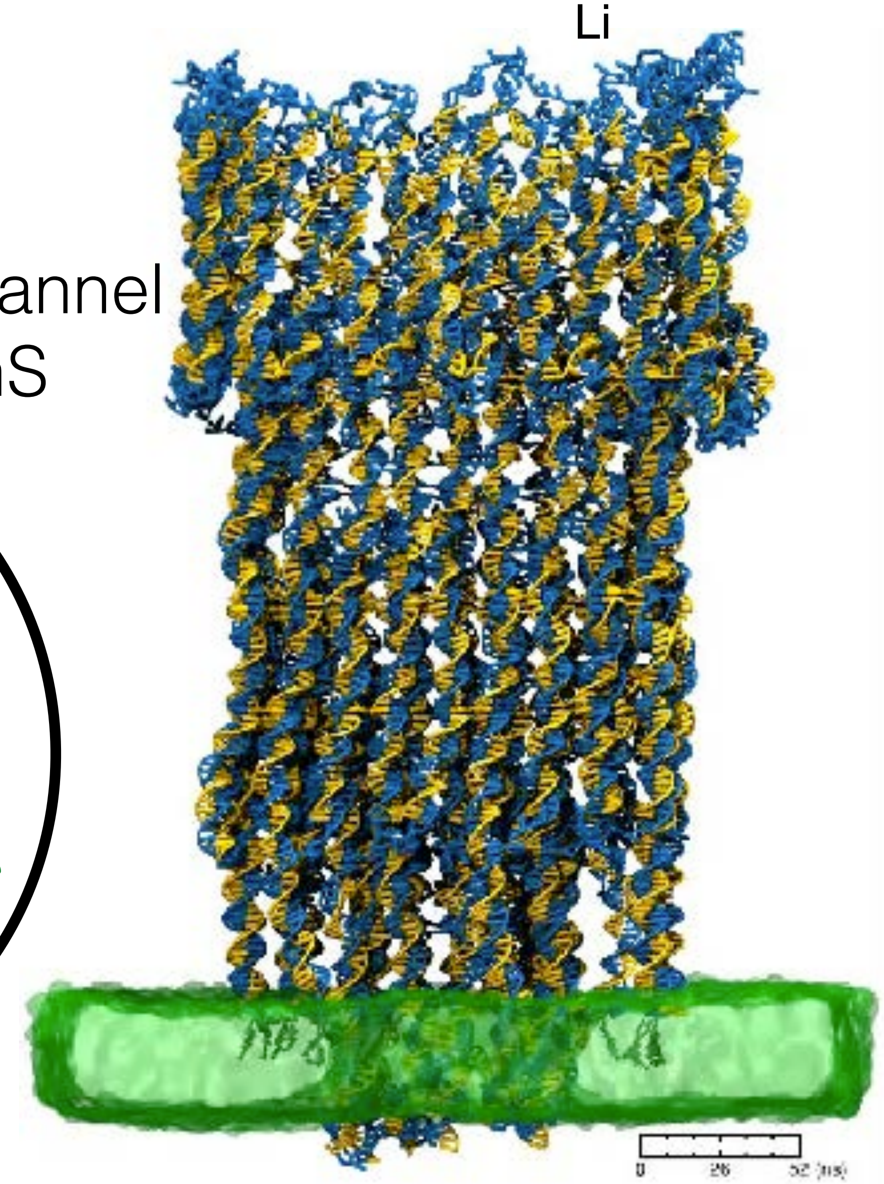


Membrane channel made of a single DNA duplex (0.1 nS)

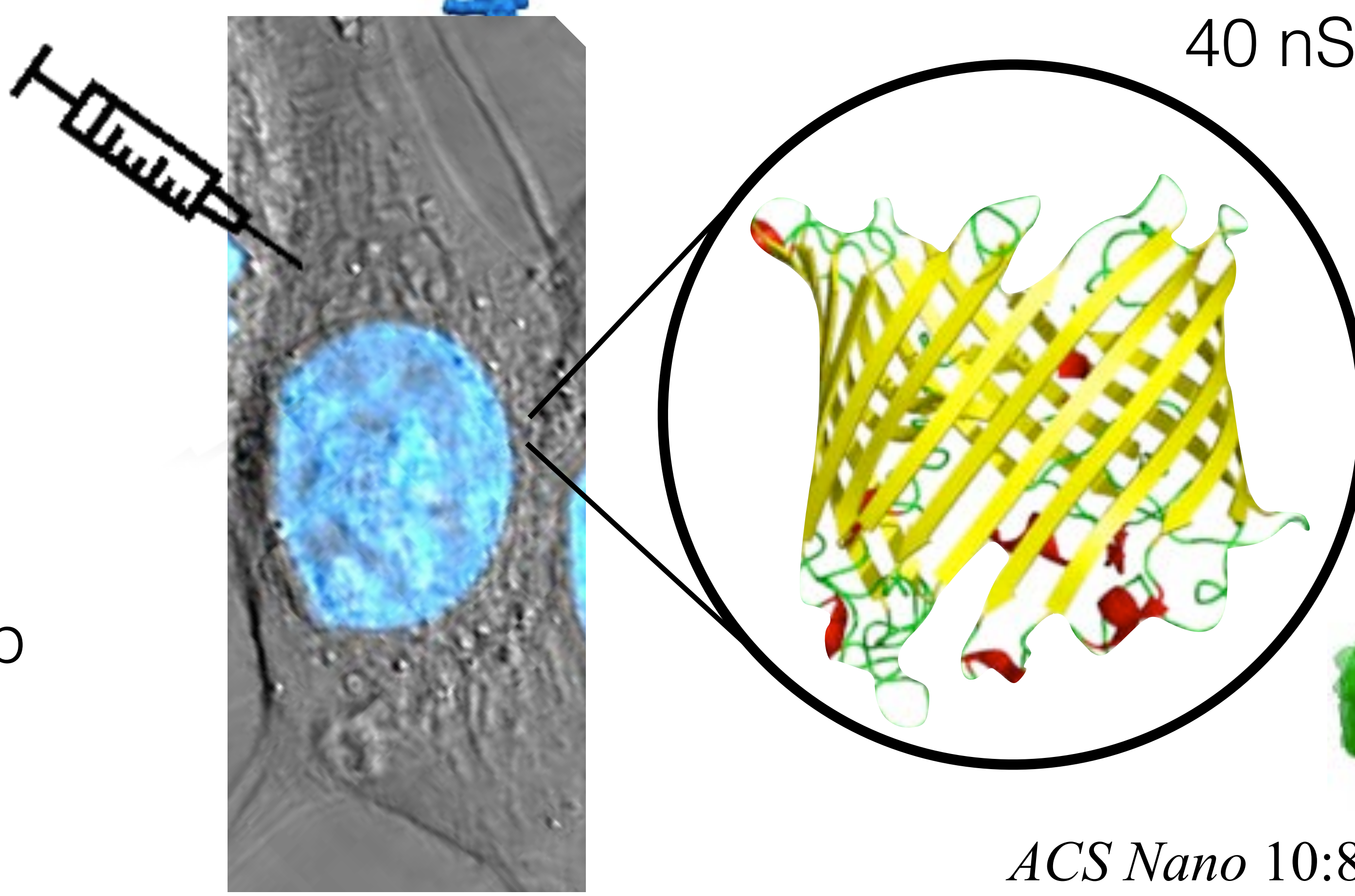
Nano Letters 16:4665 (2016)

Chen-Yu Li

Porin-like DNA channel 40 nS



Keyser Group

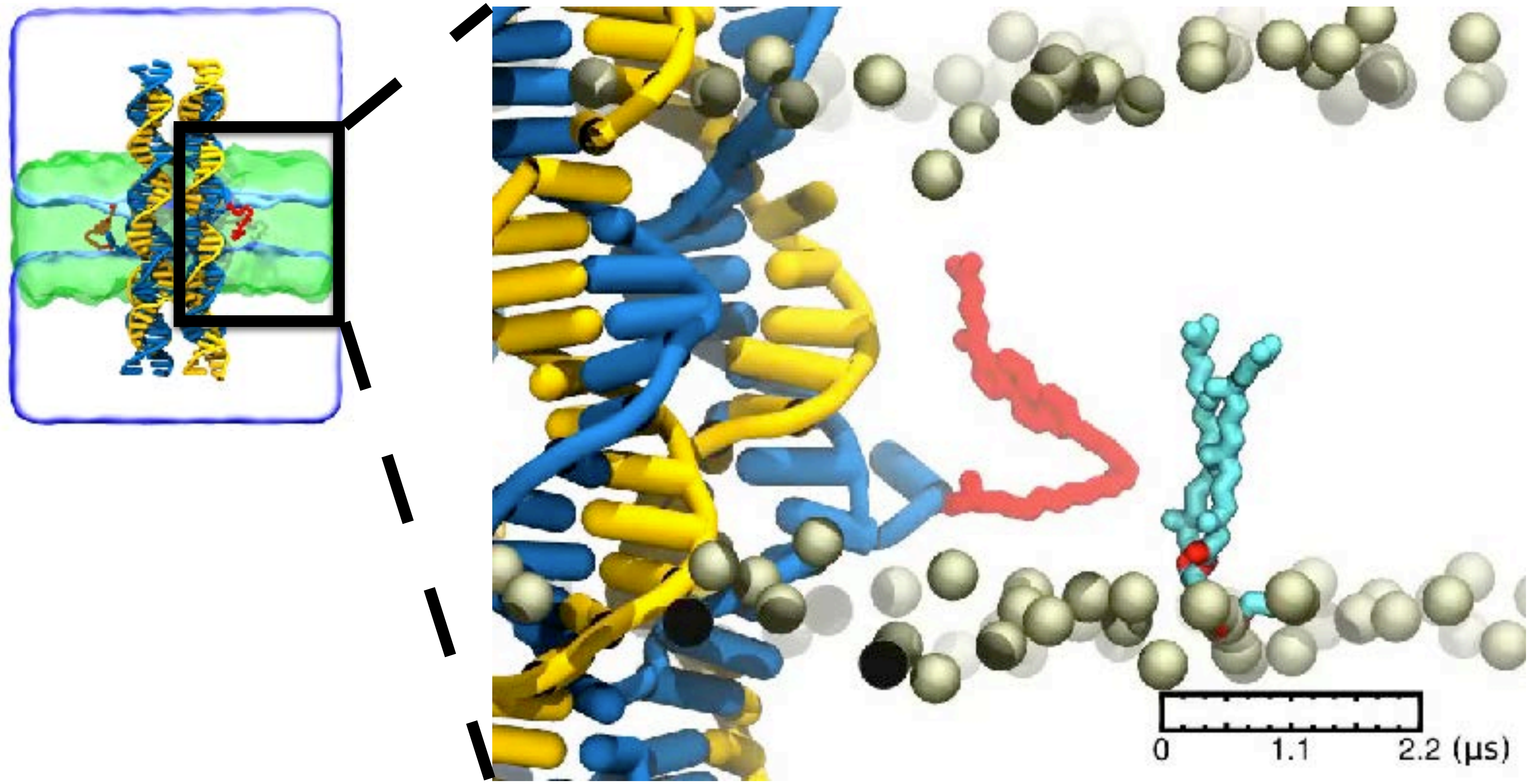


ACS Nano 10:8207 (2016)

All-atom MD simulation of lipid-DNA interface

Chen Yu Li

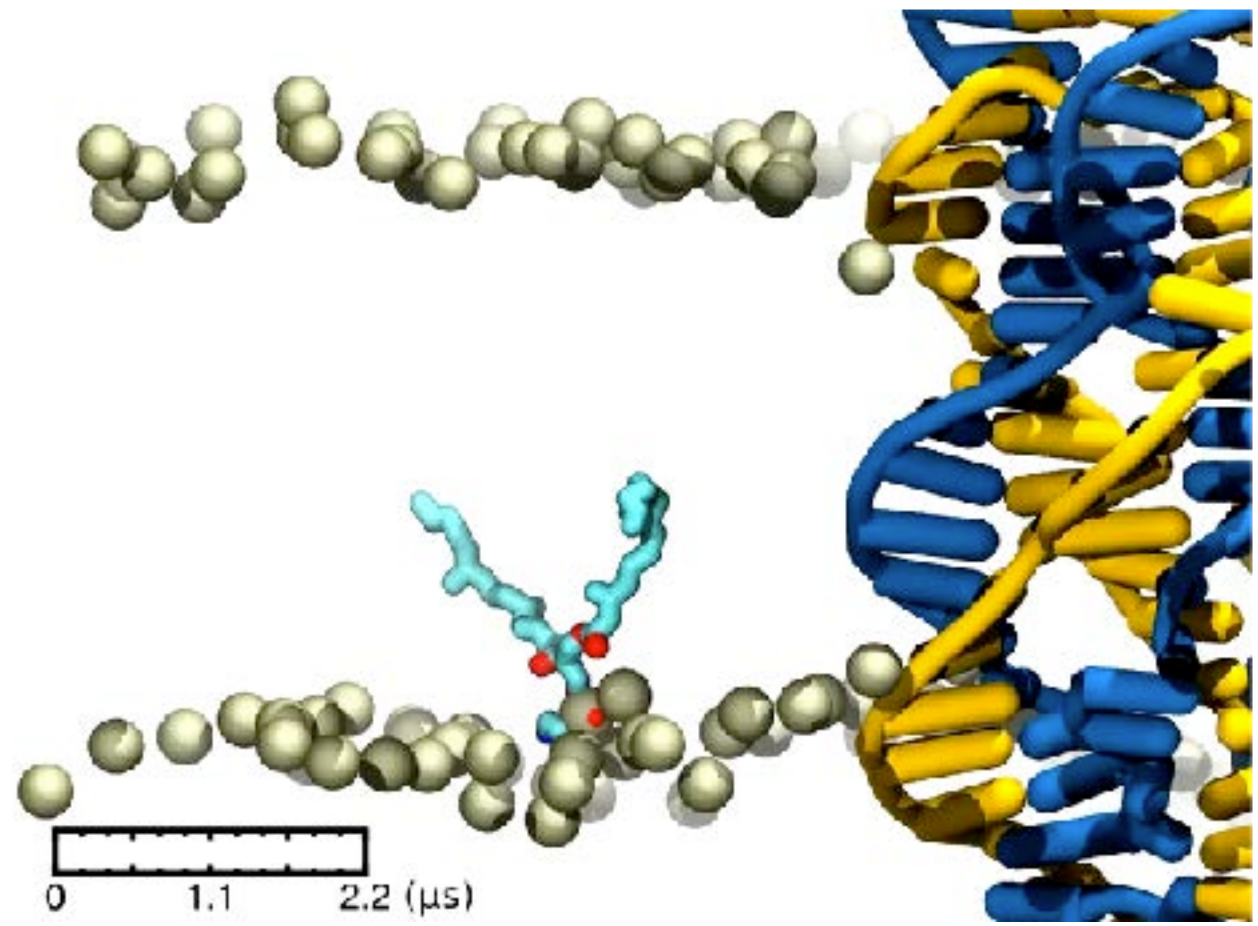
No applied electric field



Lipid molecule around the DNA channel can translocate to the other leaflet.

http://dx.doi.org/10.1101/241166

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



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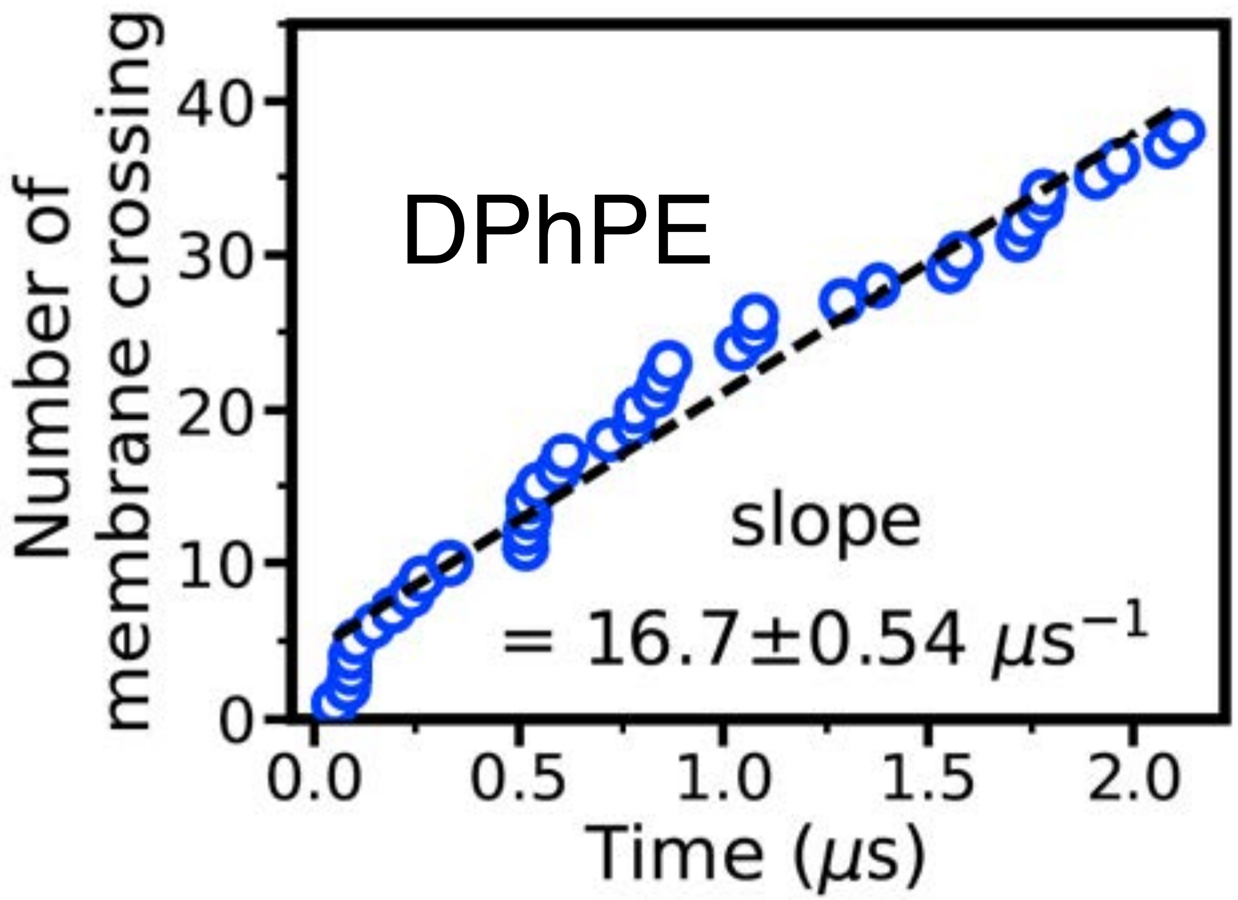
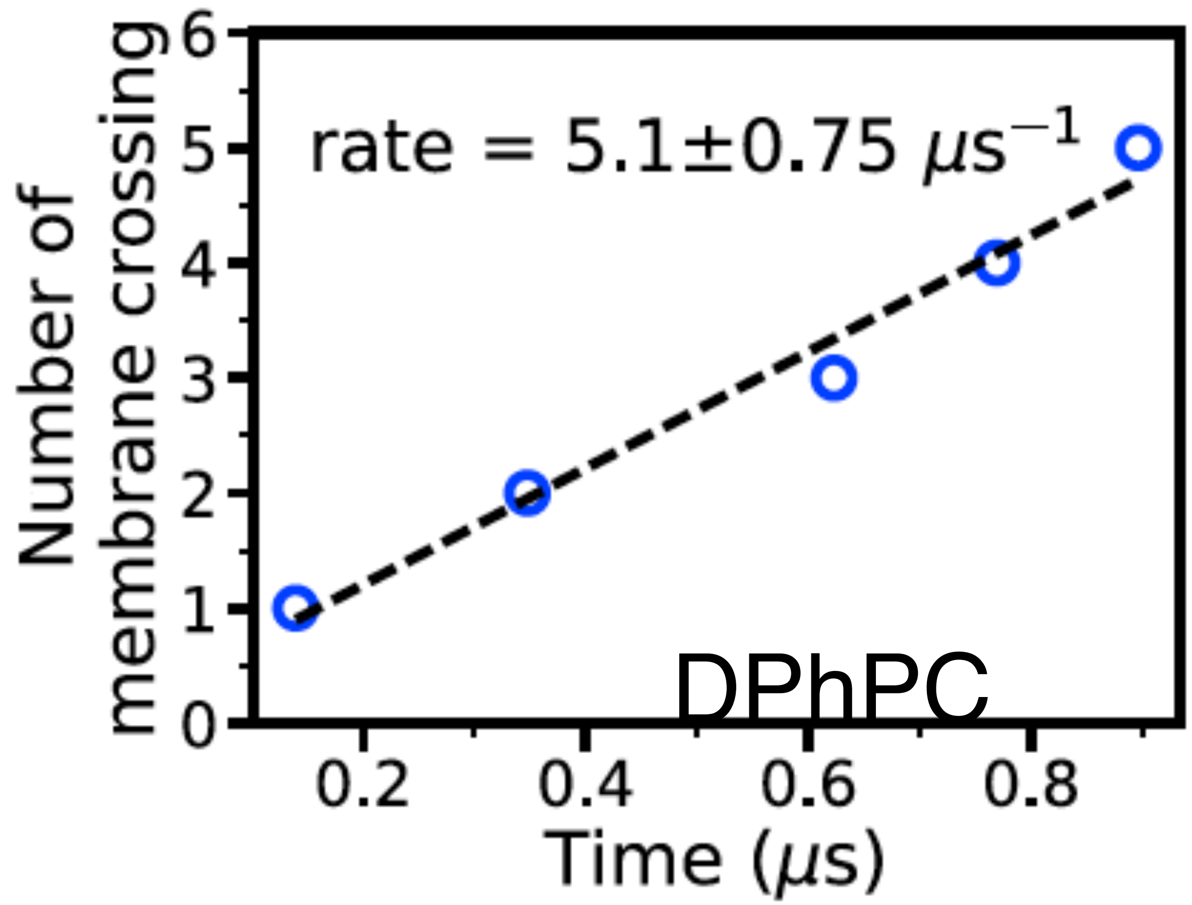
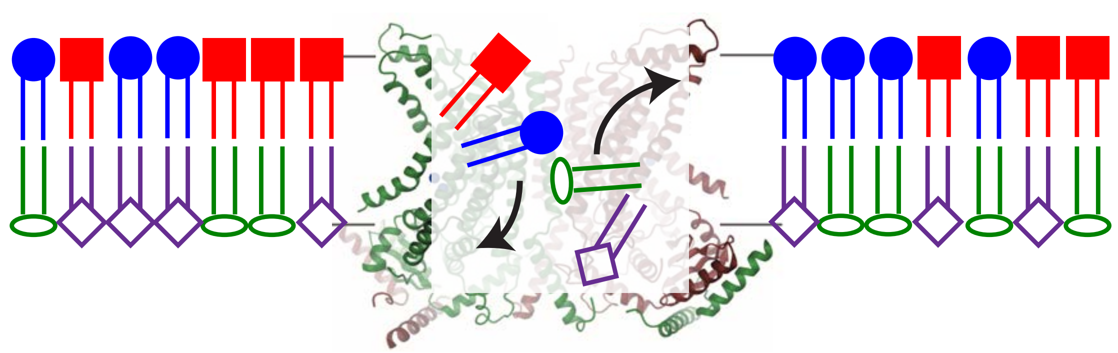




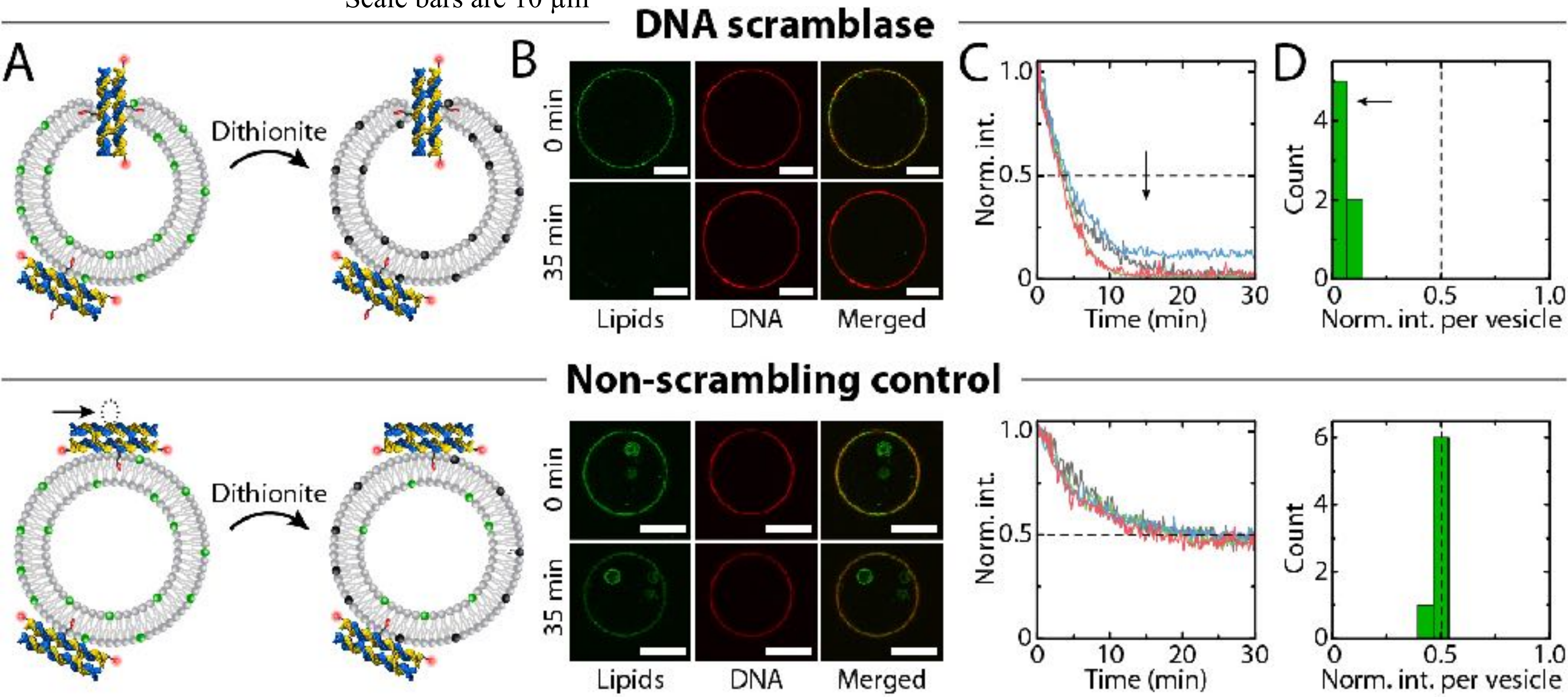
3-5 orders of magnitude faster than natural scramblases



Experimental verification

Keyser Group

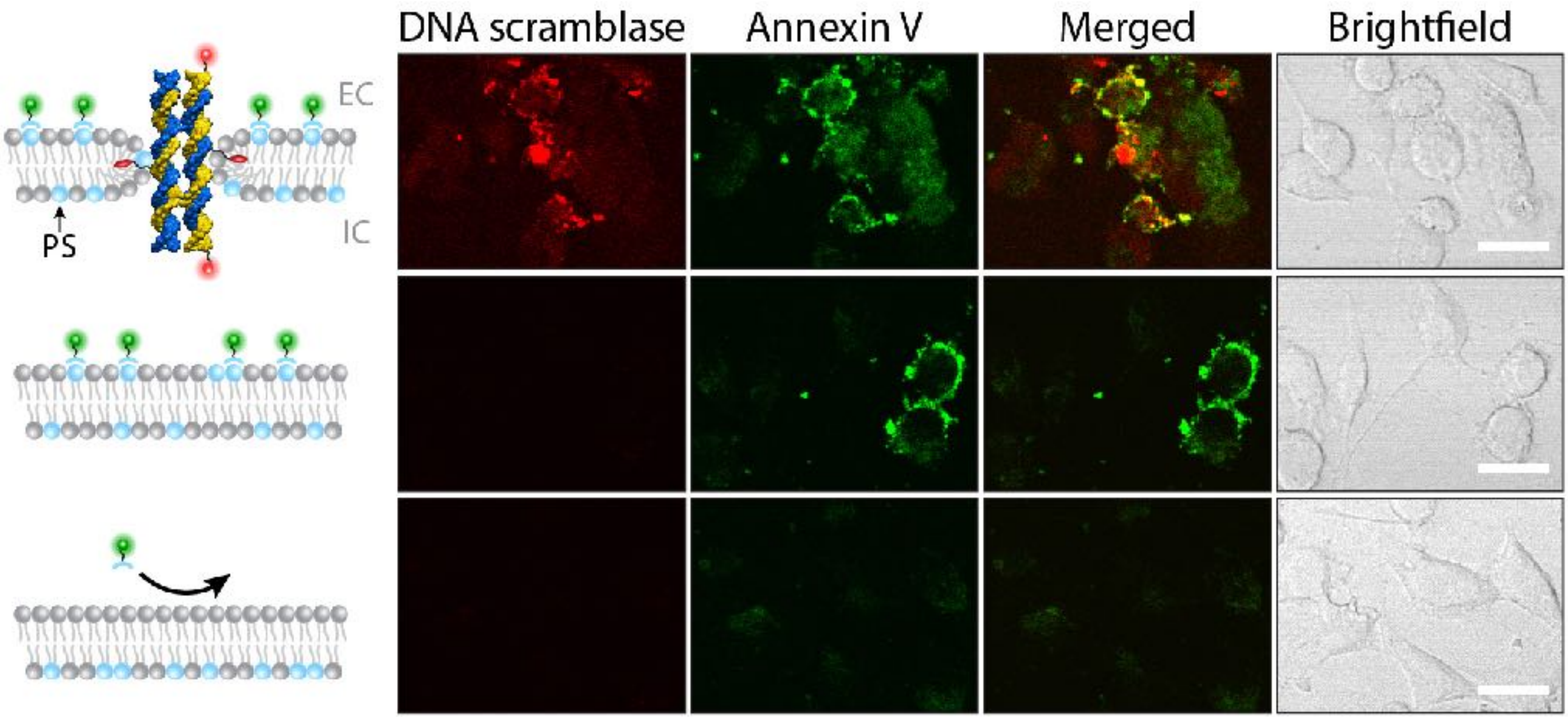
Scale bars are 10 μm



Ohmann, Li, … Ulrich F. Keyser, Aksimentiev, http://dx.doi.org/10.1101/241166

Works in human cells

Annexin V binds specifically to PS lipids found in inner leaflet of human cells



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

Scale bar is 20 μm

Positive control: apoptosis-inducing microbial alkaloid staurosporine

Negative control: DNA folding buffer

http://dx.doi.org/10.1101/241166

Acknowledgements

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BLUE WATERS

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Victoria Birkedal

Ulrich Keyser

Philip Tinnefeld