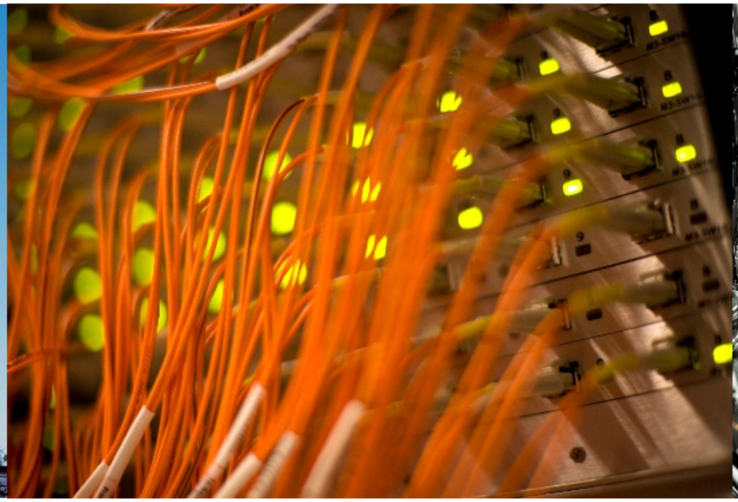
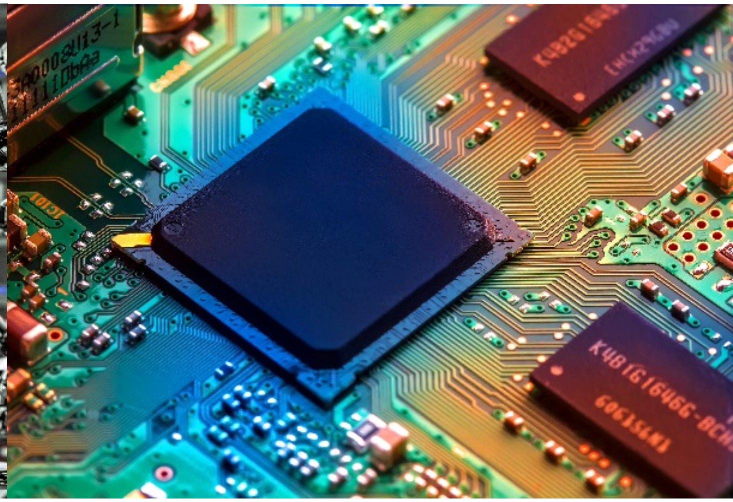
Electronic Detection of DNA-nicks Using 2D Solid-state Nanopore Transistor

I use Blue Waters to devise novel 2D nanopore systems for genetic and epigenetic detection

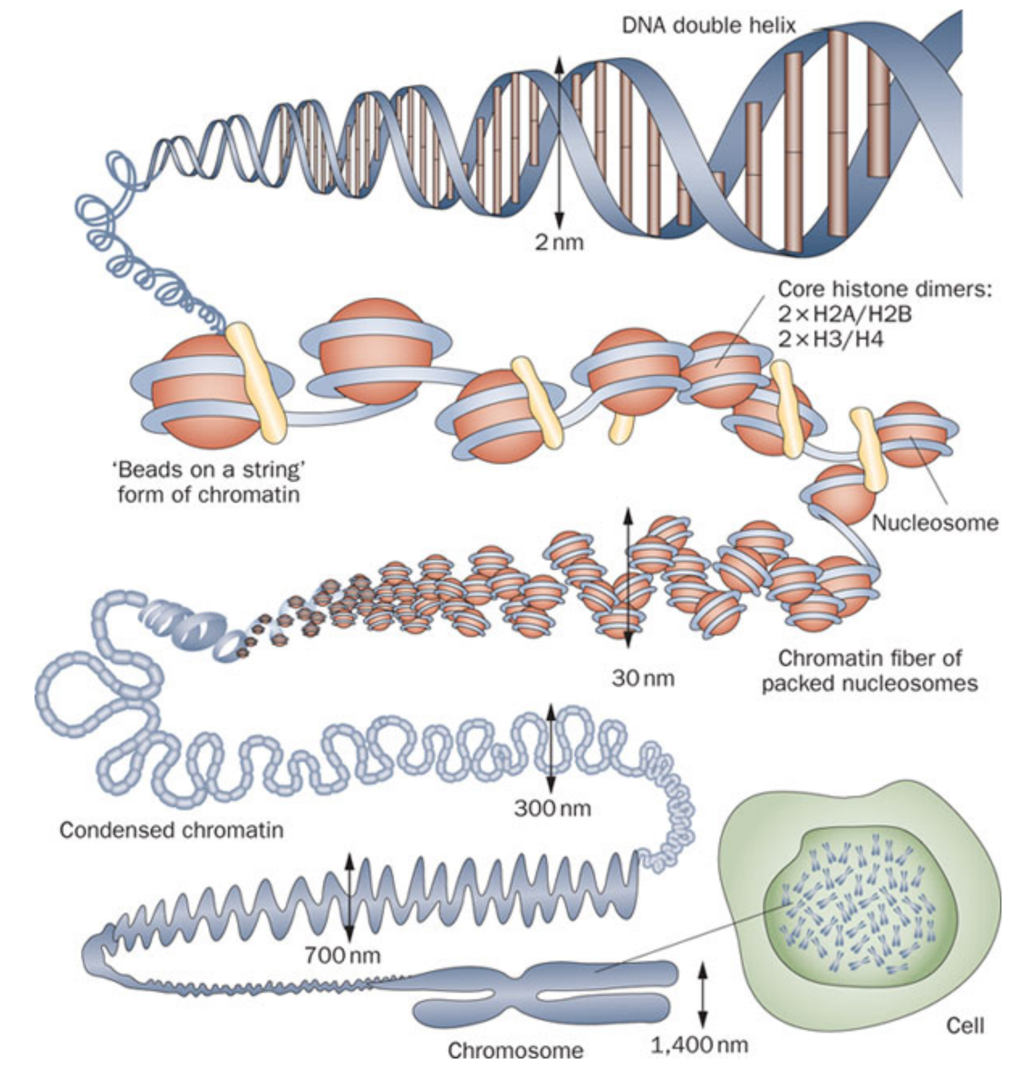


Presented by Nagendra Athreya

PI: Jean-Pierre Leburton

ILLINOIS
Electrical & Computer Engineering
COLLEGE OF ENGINEERING

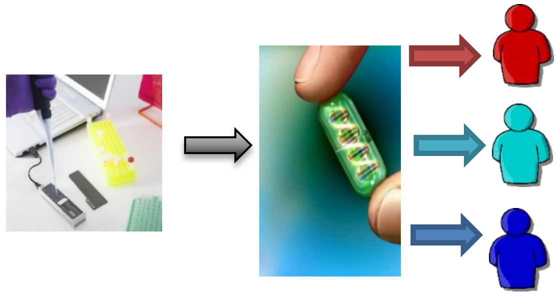
DNA: The Blue Print of Life



Tonna, Stephen, Assam El-Osta, Mark E. Cooper, and Chris Tikellis. *Nature Reviews Nephrology* (2010)

Applications of Decoding the Genome

Personalized Medicine

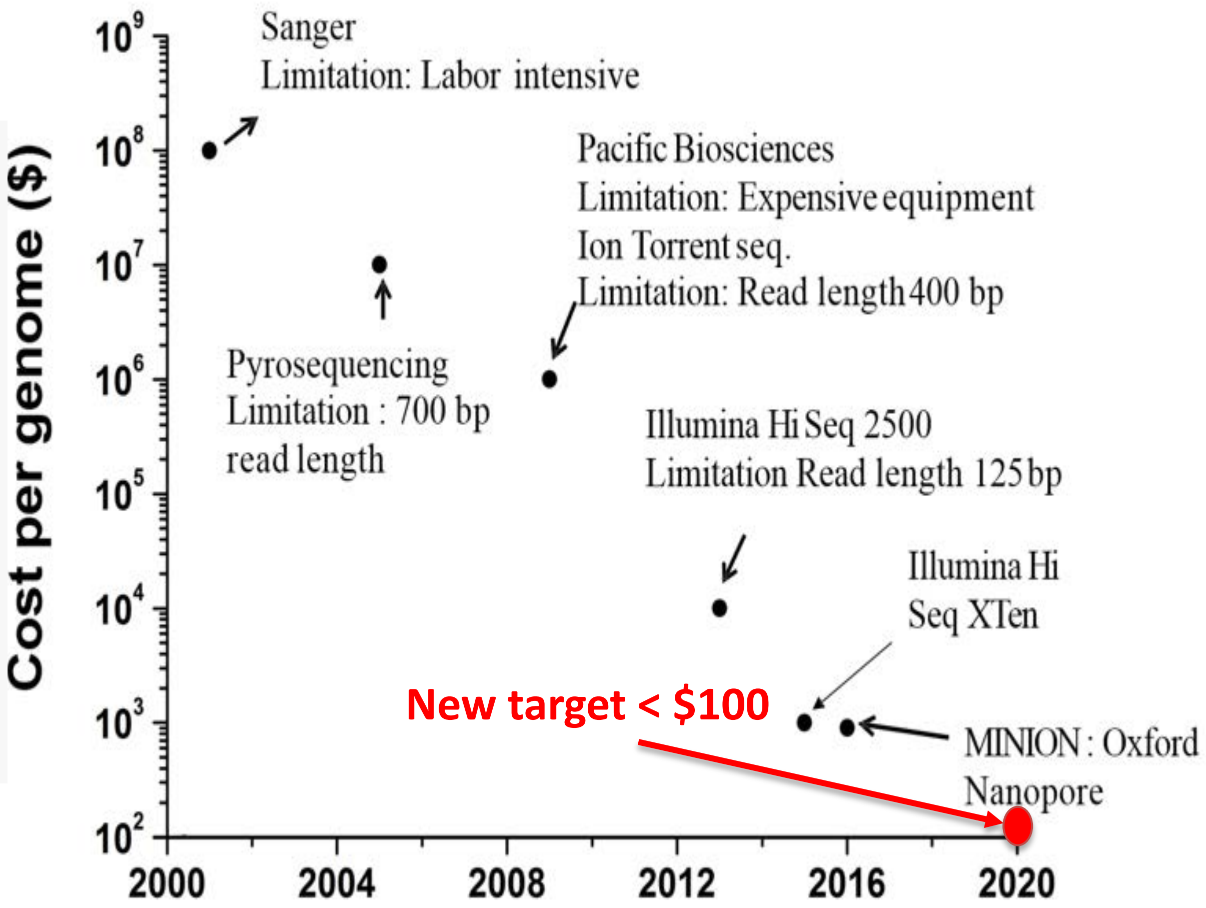


Pharmaceutical Research

Nelson MR et. al., *Nature Genetics*, 47(8):856-60. 2015

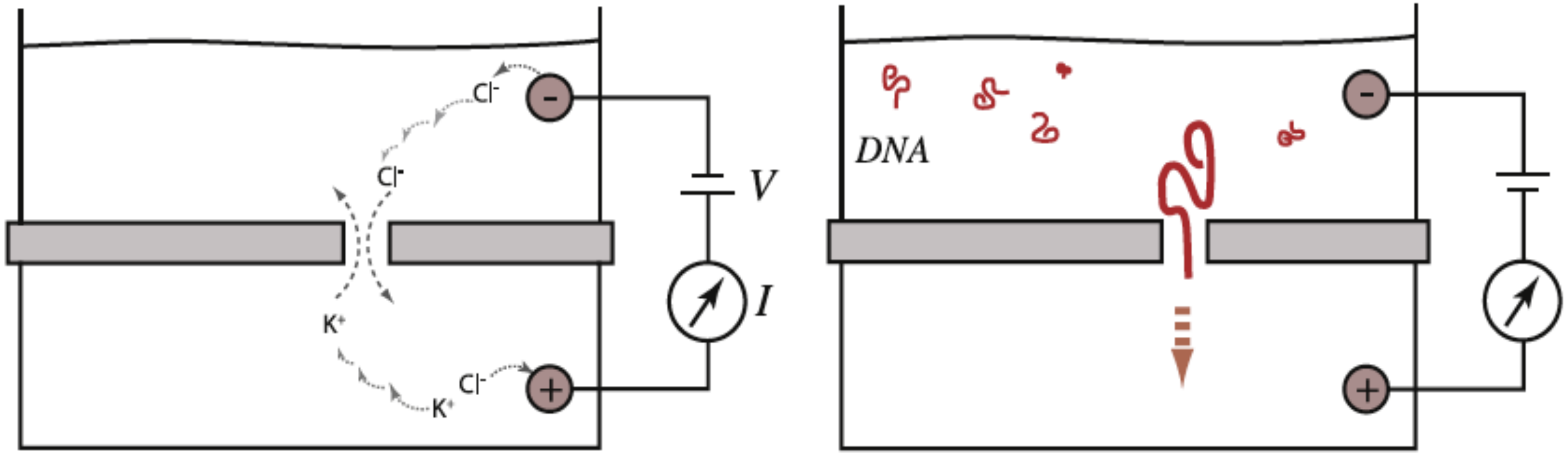
Point-of-care Genomic Testing

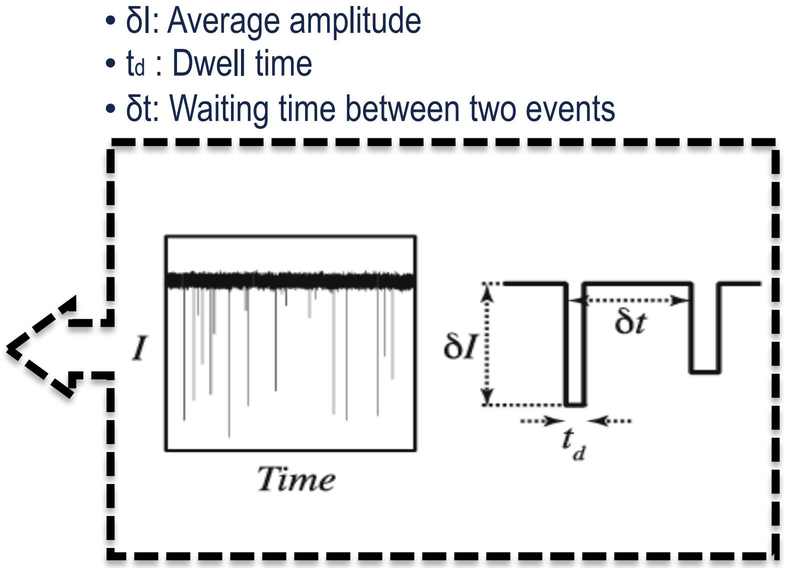
Sequencing Technologies



Nanopore Sequencing is a potential solution

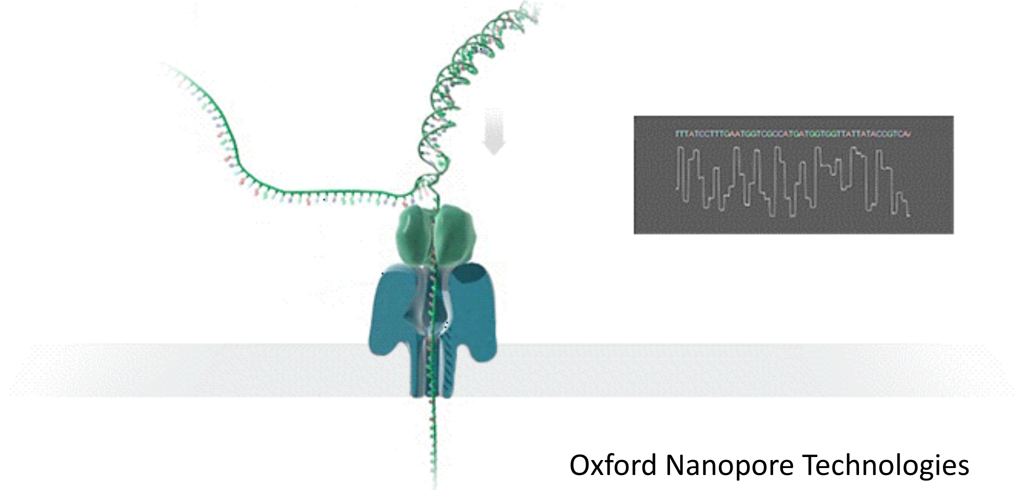
Principle of Nanopore Sensing





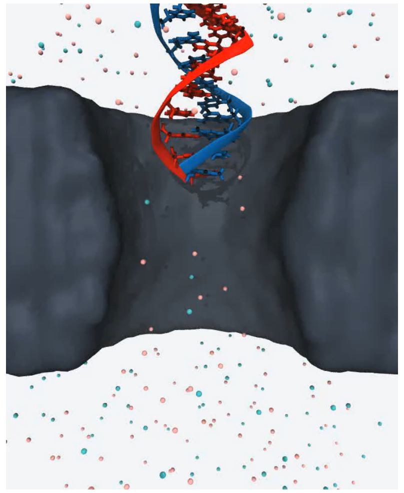
Wanunu, M. (2012, June). *Physics of Life Reviews*.

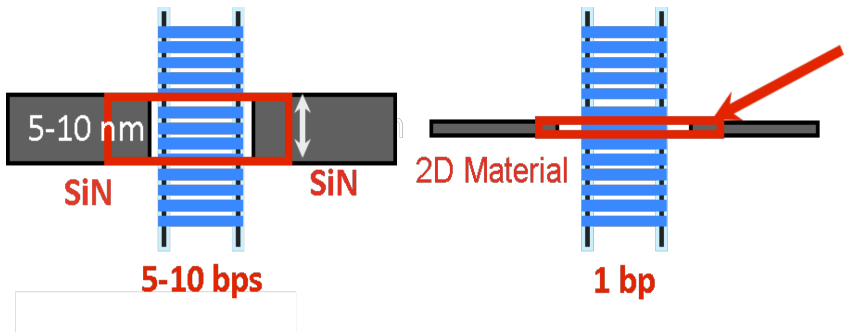
Biological Nanopores



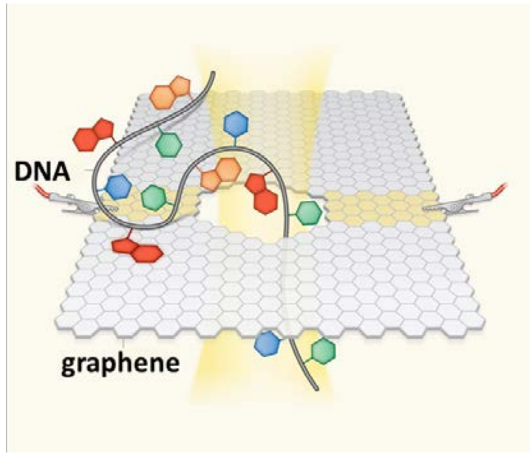
Oxford Nanopore Technologies

Solid-state Nanopores





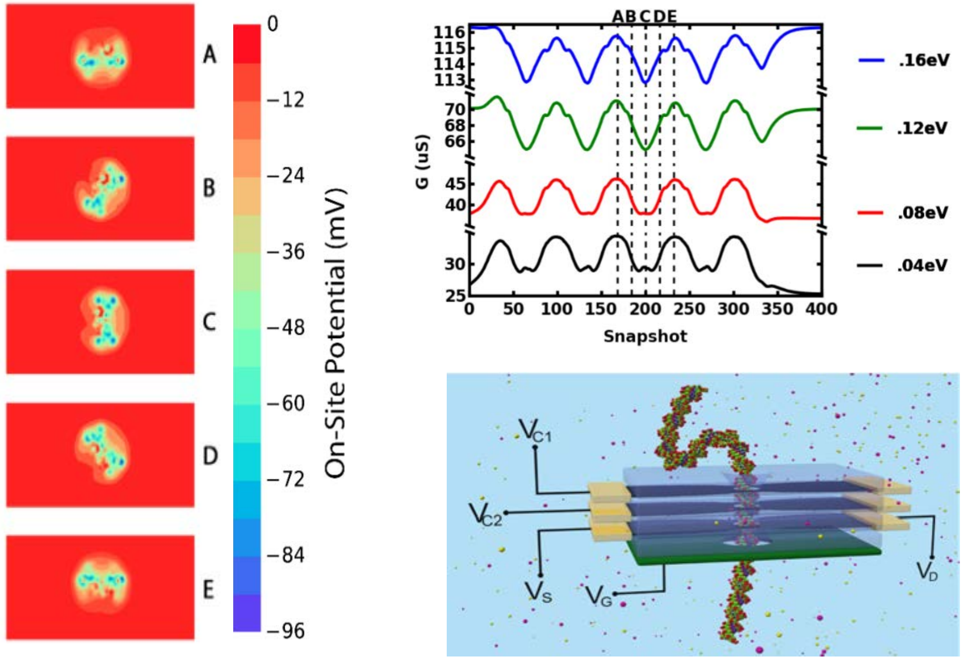
Towards Electronic Detection of Bio-molecules



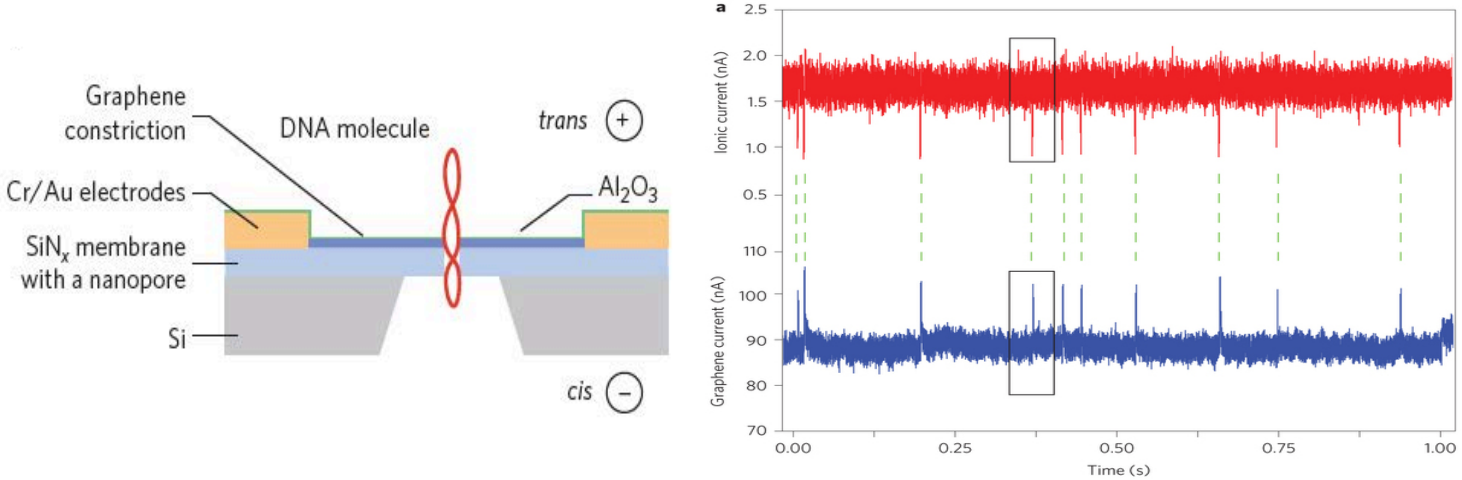
Sheet Current
1. Tunable sensitivity of detection. 2. Easily integrated into semiconductor 3. Massively parallel detection.

Image Courtesy: Bayley, *Nature*, **467**,164-65, 2010

Previous Work



Leburton Group, UIUC, 2013



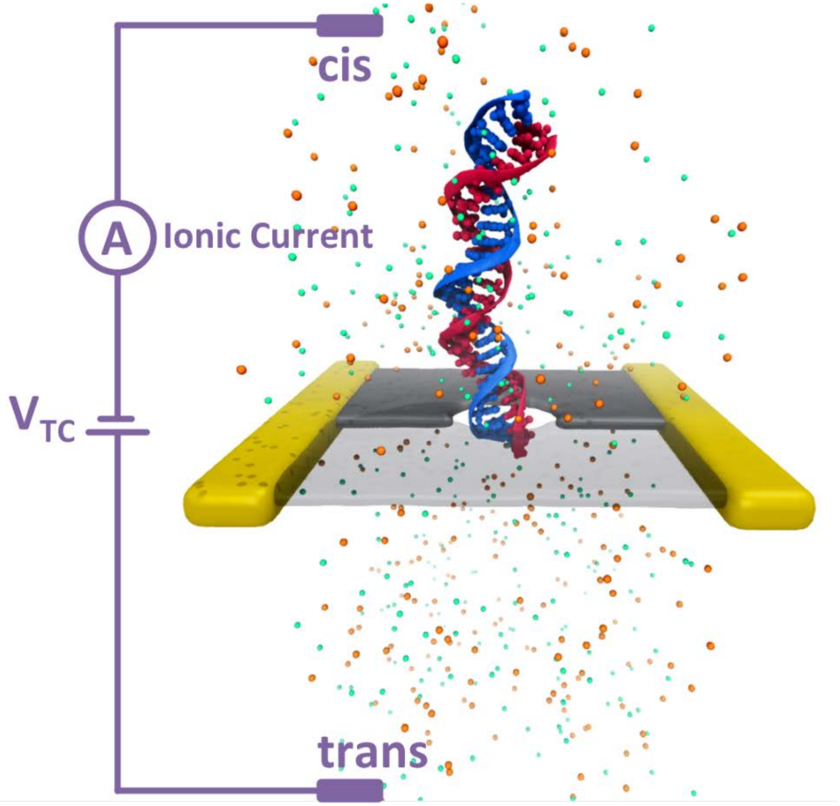
Radenovic Group, EPFL, 2013

Modeling Ionic Currents using BW Nodes

System Model
↓
Molecular Dynamics Simulation (NAMD)
↓
DNA Trajectory
↓
Ionic Current

- ~500k atoms
- 5-10 Nodes/simulation
- 2-4 weeks/simulation

MD System Setup



Ionic Current Calculations

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

summed over all K^+, Cl^- ions

Give atoms initial positions $\boldsymbol{r}^{(t=0)}$, choose short Δt
↓
Get forces $\boldsymbol{F} = -\nabla V(\boldsymbol{r}^{(i)})$ and $\boldsymbol{a} = \boldsymbol{F}/m$
↓
Move atoms: $\boldsymbol{r}^{(i+1)} = \boldsymbol{r}^{(i)} + \boldsymbol{v}^{(i)} \Delta t + {}^{1}/_{2}\, \boldsymbol{a}\, \Delta t^2 + \ldots$
↓
Move time forward: $t = t + \Delta t$
↓
Repeat as long as you need (loop back to "Get forces")

A. Aksimentiev, et. al, Biophysical Journal, 2004

Modeling Electronic Sheet Currents using BW Nodes

DNA Trajectory

↓

Self-Consistent Poisson Equation Solver

↓

Potentials induced around pore

↓

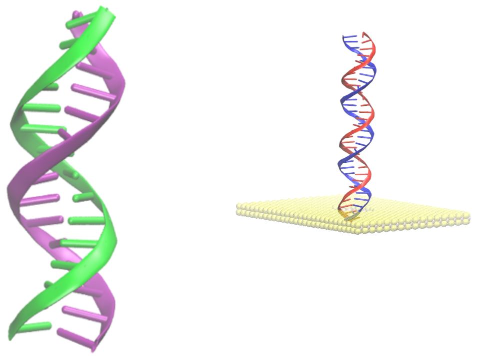
Electronic Transport Calculations using Non-Equilibrium Green's Function Formalism/Boltzmann transport

↓

Electron Current/Conductance

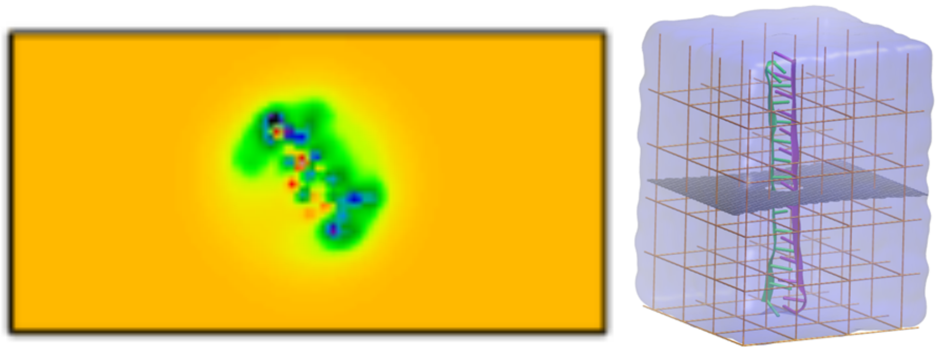
- **Poisson Solver**
  - 50 Nodes/simulation
  - ~6 hours/job
- **Electronic Transport**
  - ~4000 Nodes!!!
  - ~6 hours/job

DNA charge model

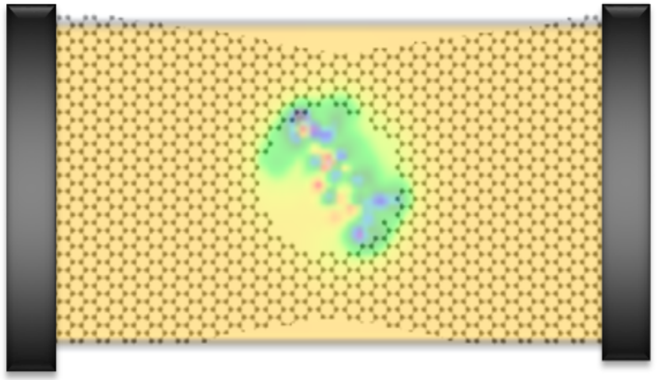


Electrostatics of nanopore system

$$\nabla \cdot [\epsilon(\vec{r})\nabla\phi(\vec{r})] = -e[K^{+}(\vec{r},\phi) - Cl^{-}(\vec{r},\phi)] - \rho_{DNA}(\vec{r})$$

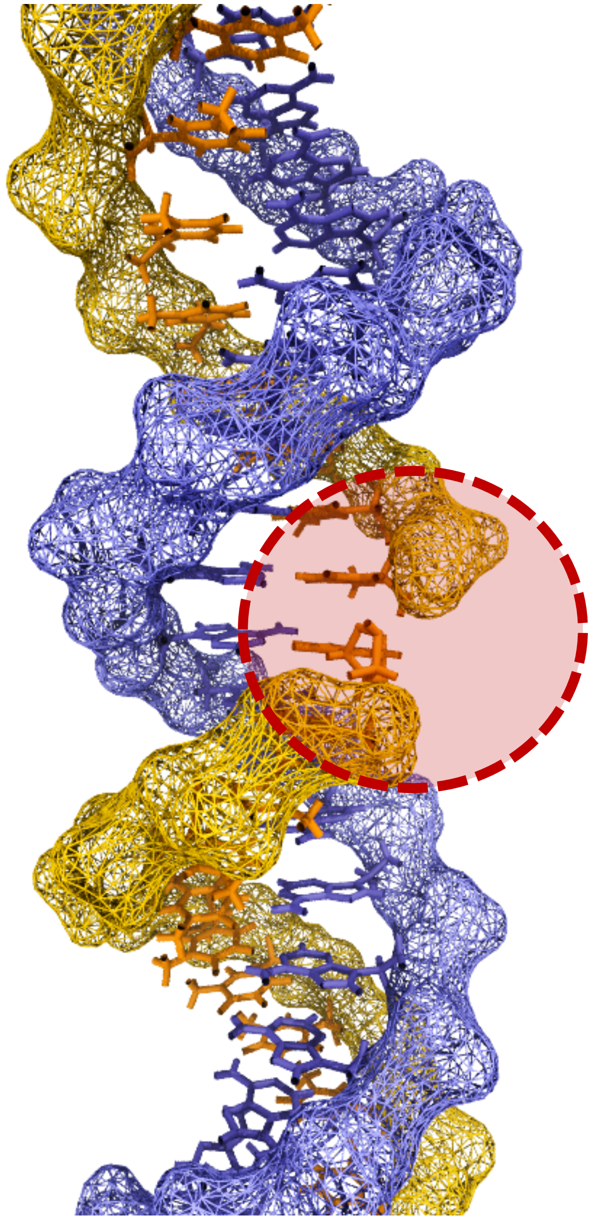


Transverse Electronic Current Response

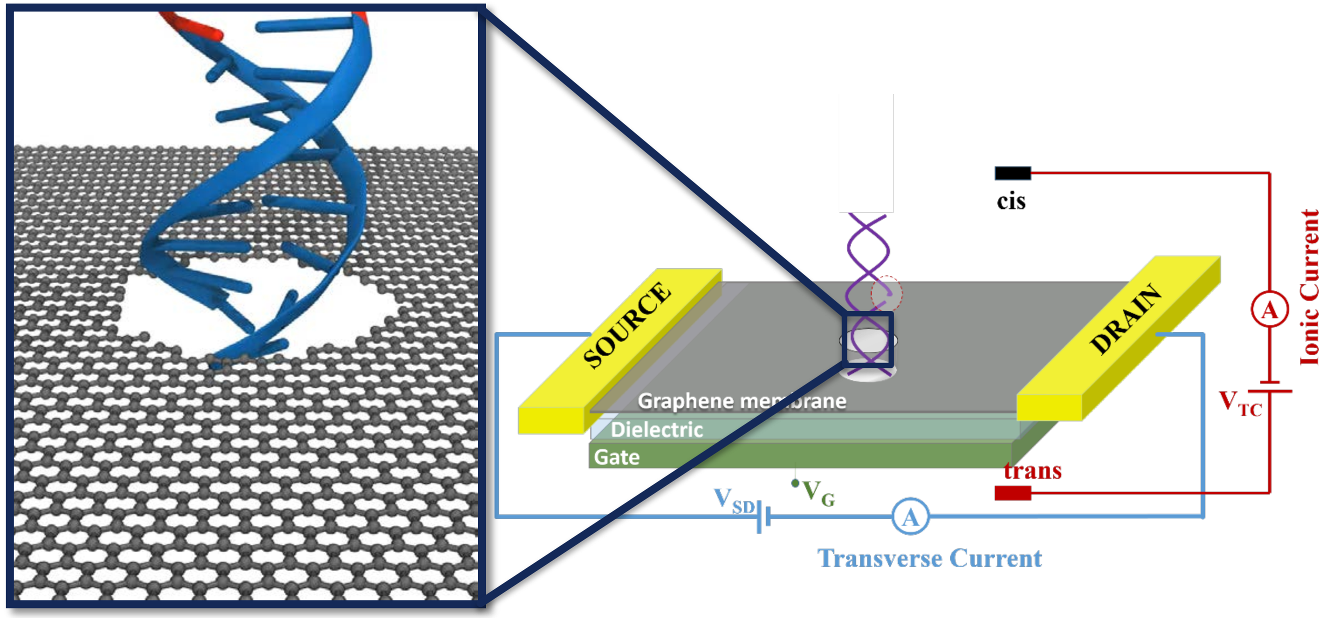


DNA-nick Detection in 2D Nanopore Membranes

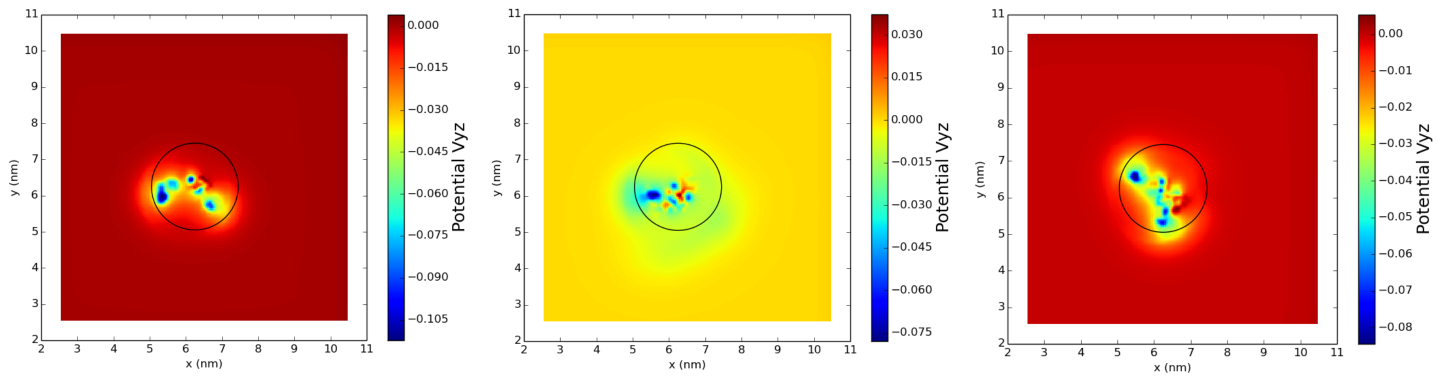
- Human Cell is subjected to ~70,000 lesions/day. Majority of them arise from **DNA backbone breaks**.
- These breaks in critical gene cause the cell to undergo **apoptosis**.
- Contrarily, if repair mechanism fails, the DNA breaks cause chromosomal instability leading to **tumorigenesis**.
- No existing technology can efficiently detect these DNA-nicks.
- Our efforts are directed towards unraveling the potential of **Two-dimensional** solid-state **nanopore membranes** to detect and map these site-specific nicks along the genome with **single-base resolution**.

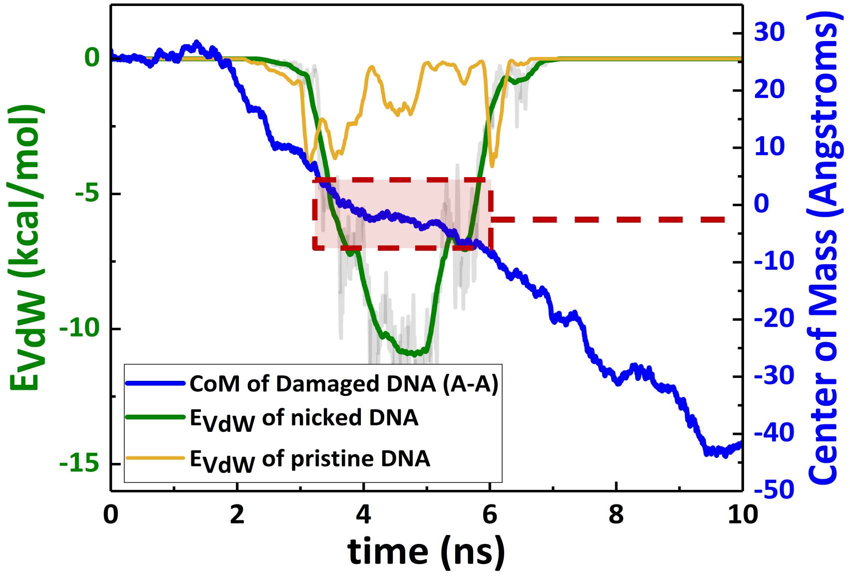


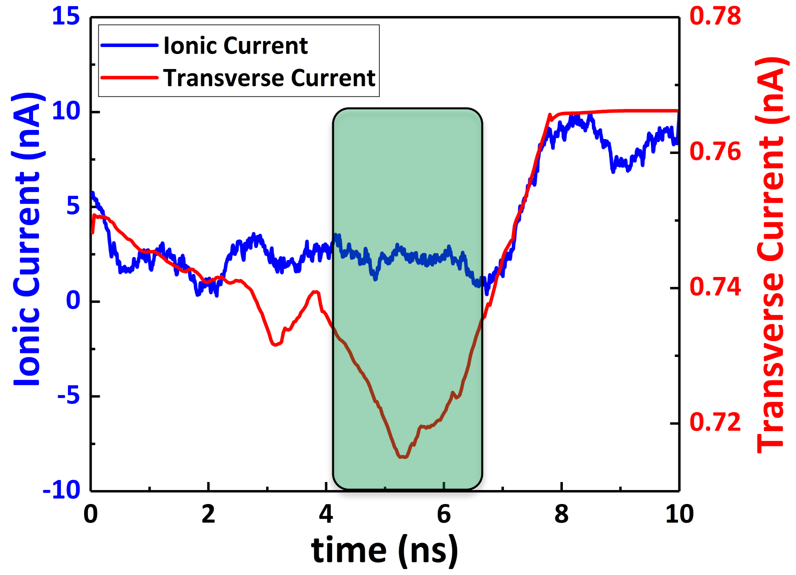
Site of the nick: A-A



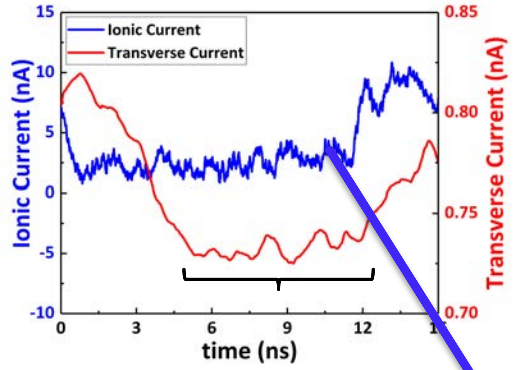
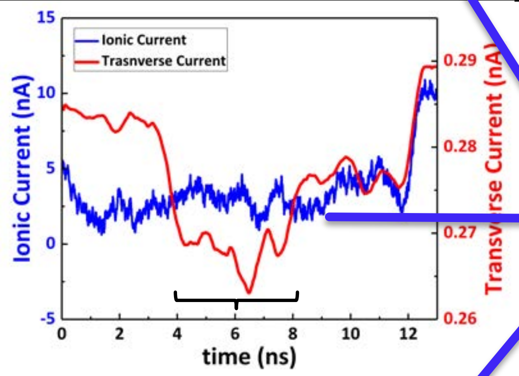
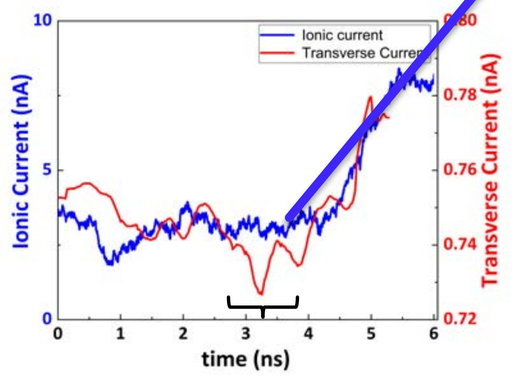
Potential Profile of Damaged dsDNA translocation





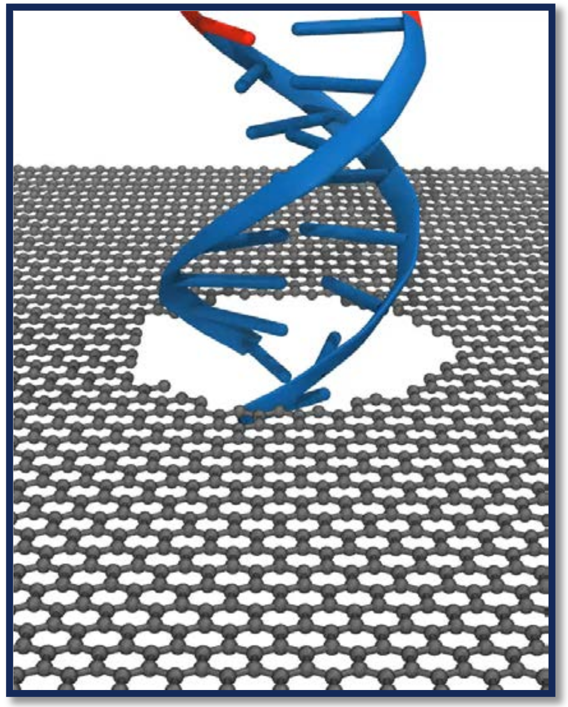


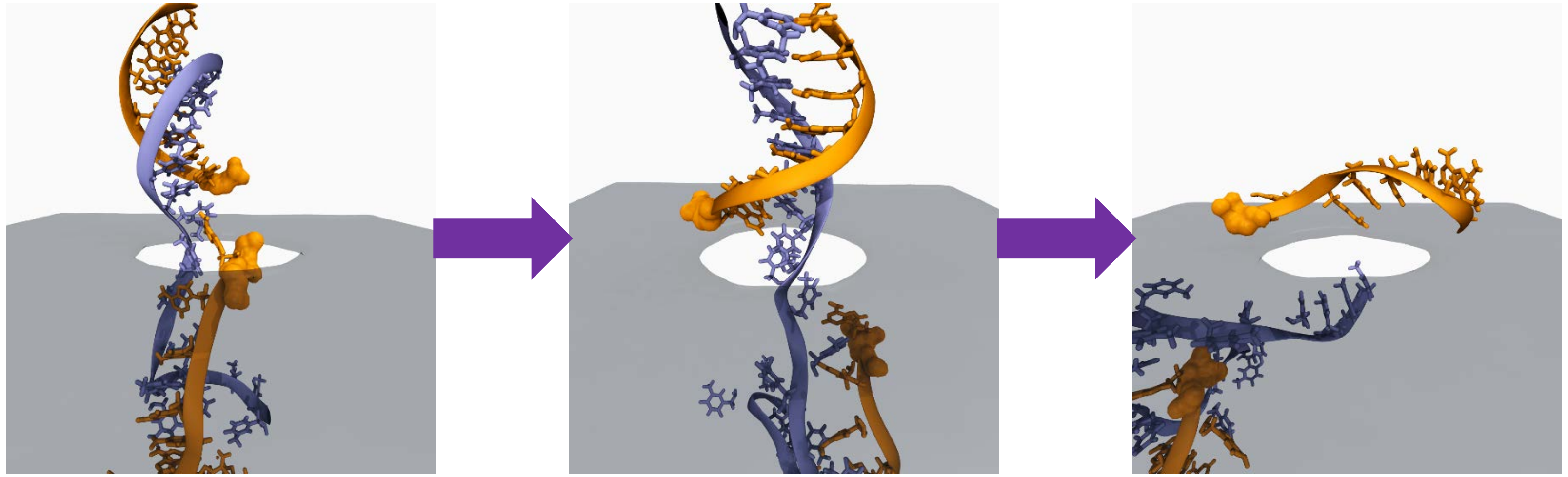
Site Specificity of the nick positions

SITE OF THE DNA DAMAGE	CURRENT TRACES
T-T	
C-C	
G-G	

Not recognizable by ionic currents

Voltage ($V_{cis\text{-}Trans}$) dependence

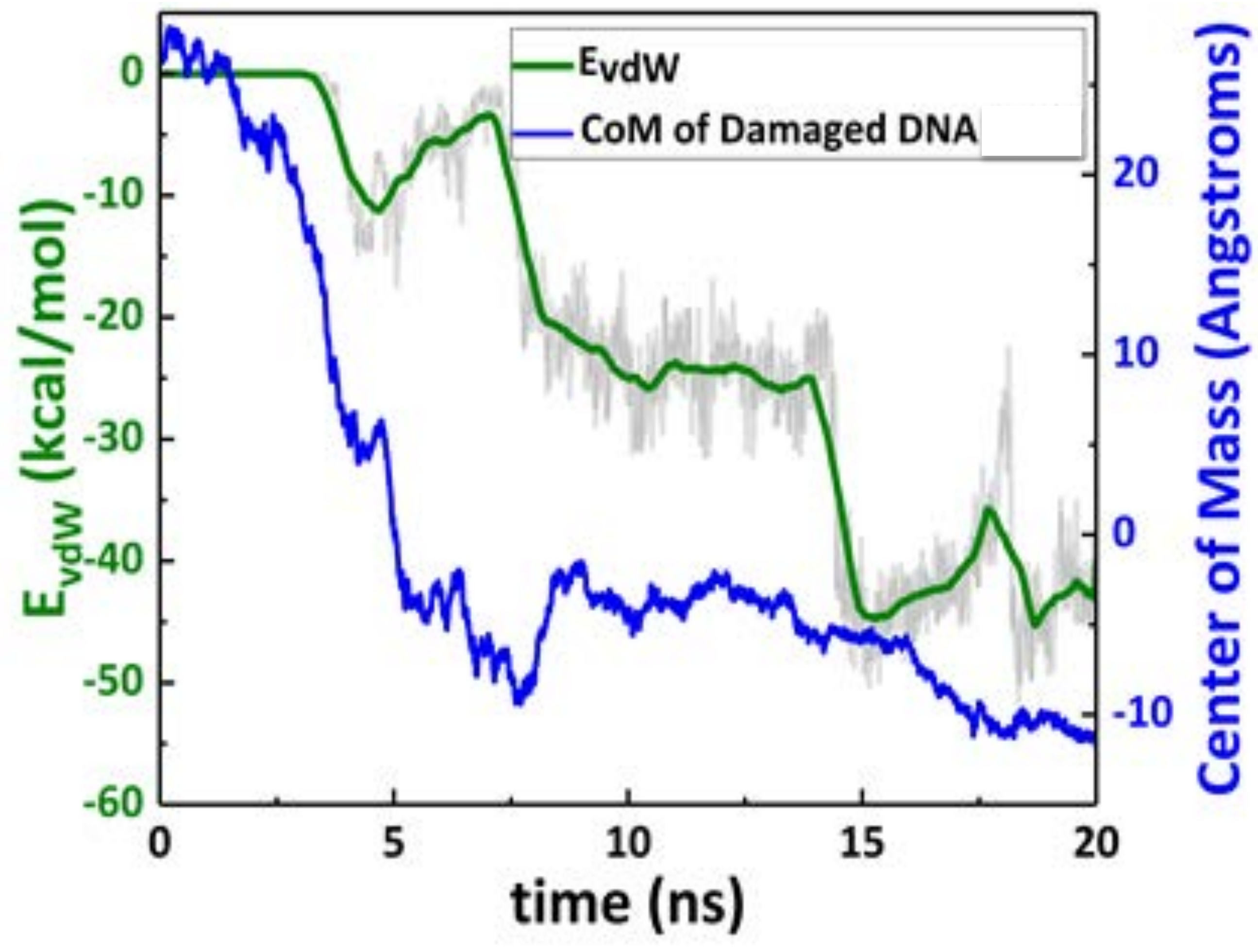


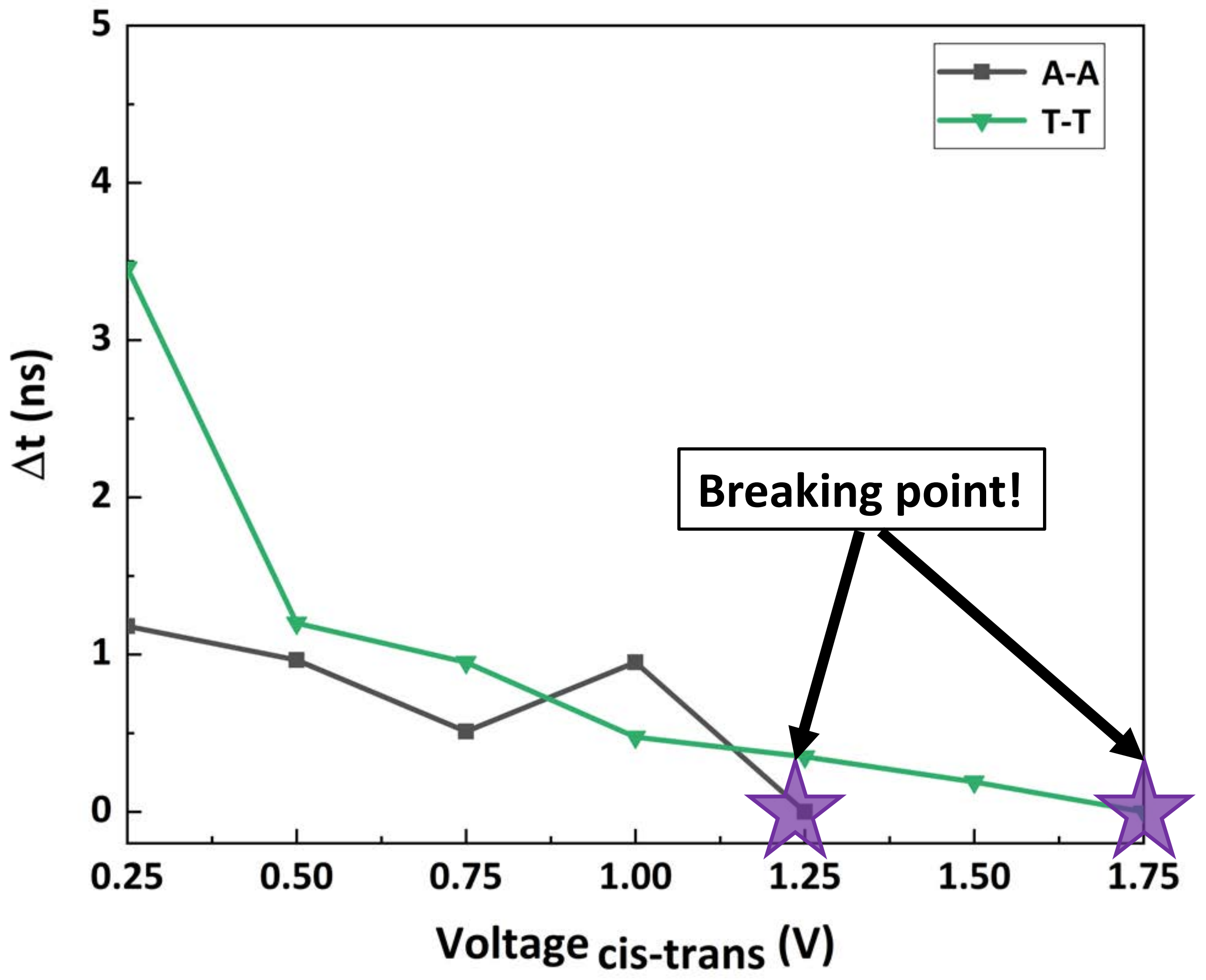


Normal translocation

Denaturing of the DNA

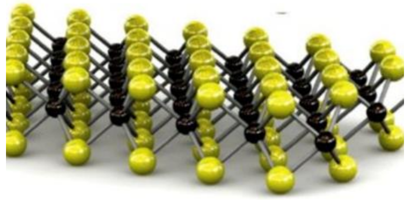
Voltage ($V_{cis\text{-}Trans}$) dependence





Future Work

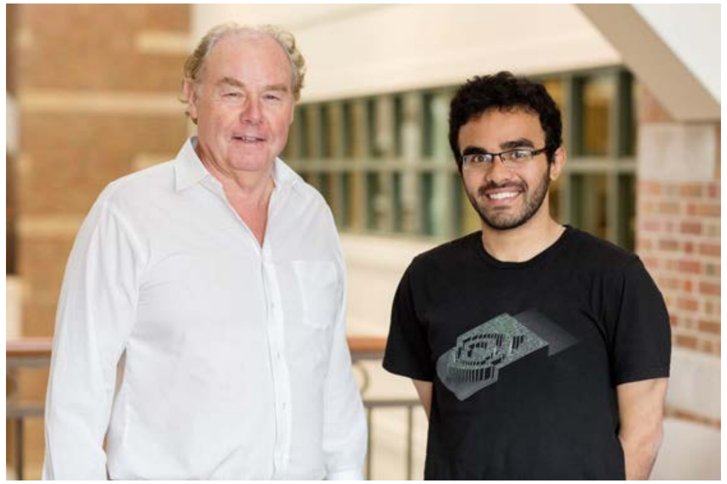
- Cross-base pairs (A-C, A-G, A-T, C-G, C-T, T-G)
- Different electrically active 2D materials:



Semi-conductor (MoS_2)

- Complete voltage dependence analysis

ACKNOWLEDGEMENTS



Jean-Pierre Leburton & Aditya Sarathy

Olgica Milenkovic

NSF

NCSA

BLUE WATERS
SUSTAINED PETASCALE COMPUTING

THANK YOU

Appendix

Multigrid Solution of Semiconductor PBE

$$\nabla \cdot [\varepsilon(\mathbf{r})\nabla\varphi(\mathbf{r})] = -e[K^+(\mathbf{r},\varphi) - Cl^-(\mathbf{r},\varphi)] - \rho_{DNA} - \rho_{SC}$$

$$\rho_{SC}(\mathbf{r}) = e[N_D^+(\mathbf{r}) - N_A^-(\mathbf{r}) + p(\mathbf{r}) - n(\mathbf{r})]$$

$$K^+(\mathbf{r},\varphi) = C_0 e^{\frac{-e\varphi}{k_B T}} \qquad Cl^-(\mathbf{r},\varphi) = C_0 e^{\frac{e\varphi}{k_B T}}$$

$$n(\mathbf{r}) = N_C \frac{2}{\sqrt{\pi}} F_{1/2}\left(\frac{E_F + e\varphi(\mathbf{r}) + E_{Gap}}{k_B t}\right)$$

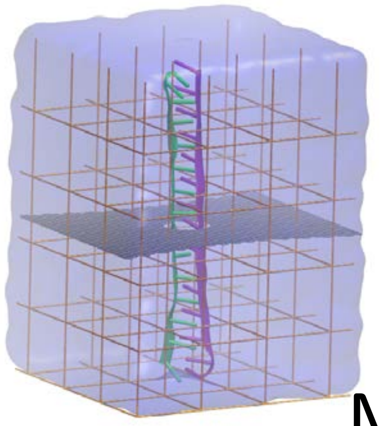
$$p(\mathbf{r}) = N_V \frac{2}{\sqrt{\pi}} F_{1/2}\left(\frac{-e\varphi(\mathbf{r}) - E_F}{k_B T}\right)$$

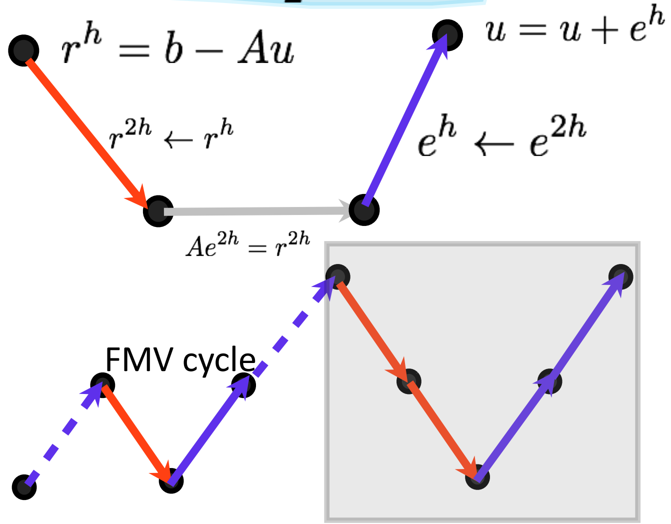
Half Order Fermi-Dirac Function

Need to solve 3D Poisson Boltzmann Equation with Newton Multigrid

$$\nabla^2 u = -f$$

$$u_j = \frac{-u_{j+1} - u_{j-1} + h^2 f}{2} \Rightarrow Au = b$$



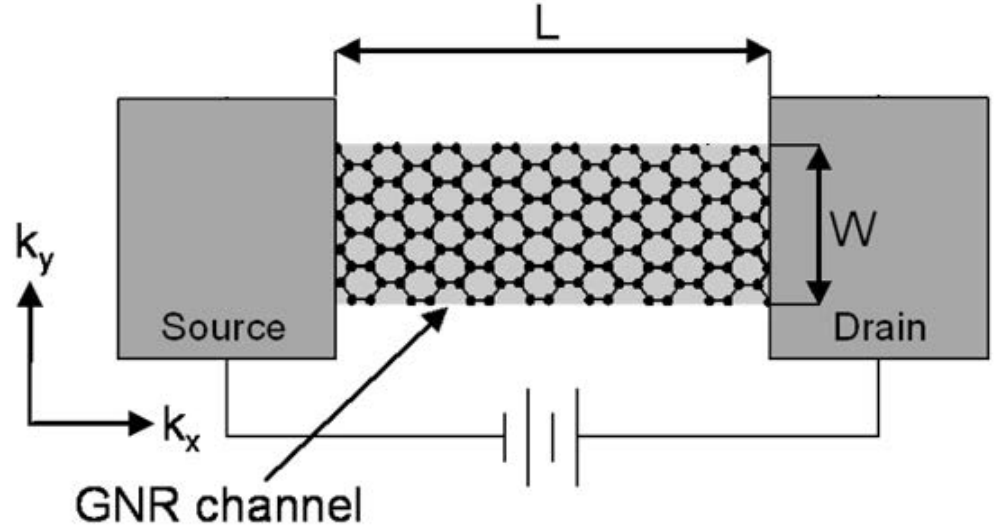


Multigrid gives O(N) performance

Gracheva, Maria E., et al. "Simulation of the electric response of DNA translocation through a semiconductor nanopore–capacitor." *Nanotechnology* 17.3 (2006): 622.

Graphene Nanopore Sheet Conductance Model

Graphene honeycomb lattice



A. Girdhar, C. Sathe, K. Schulten, and J. P. Leburton *PNAS* (2013)

Tight-binding Hamiltonian

$$H = \sum_n (\epsilon - e\varphi(\mathbf{r}_n)) + \sum_{\langle i,j \rangle} [t_{ij} c_i^\dagger c_j + h.c]$$

Non-Equilibrium Green's Function

$$[E \pm i\eta - \bar{\boldsymbol{H}}(\mathbf{r},\mathbf{r}')]\bar{\mathbf{G}}(\mathbf{r},\mathbf{r}') = \delta(\mathbf{r} - \mathbf{r}')$$

$$\bar{\mathbf{G}}(E) = [E\bar{\mathbf{I}} - \bar{\mathbf{H}}]^{-1}$$

$$\bar{T}(E) = -Tr\left[\left(\Sigma_S - \Sigma_S^\dagger\right)G_C(\Sigma_D - \Sigma_D^\dagger)G_C^\dagger\right]$$

Landauer-Buttiker Formula

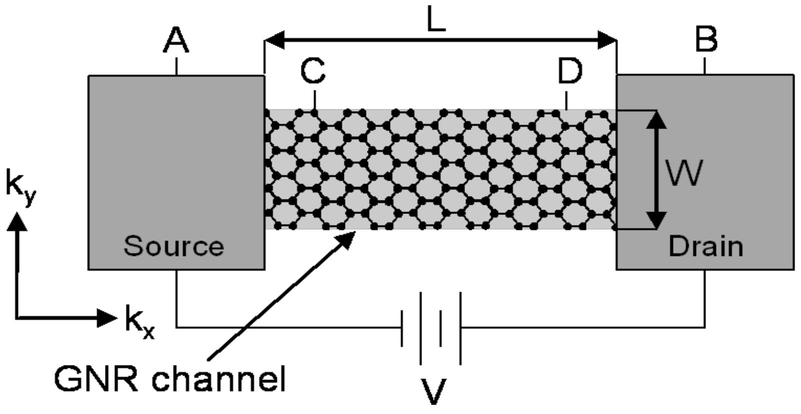
Conductance $$G = \frac{2e}{hV_{DS}} \int_{\infty}^{\infty} \bar{T}(E)[f_S(E) - f_D(E)]dE$$

Graphene Nanoribbon Transverse Conductance

Fisher-Lee Relation

$$T(E) = -Tr[(\Sigma_A - \Sigma_A^\dagger)G_f(\Sigma_B - \Sigma_B^\dagger)G_f^\dagger]$$

G: Transverse conductance of the sheet; T(E): Transmission coefficient
f(E): Fermi-Dirac distribution



Non-equilibrium Green's function (NEGF)

$$H = \sum_i [\epsilon_i - e\phi_i \quad] a_i^\dagger a_i + \sum_{ij} t_{ij} a_i^\dagger a_j$$

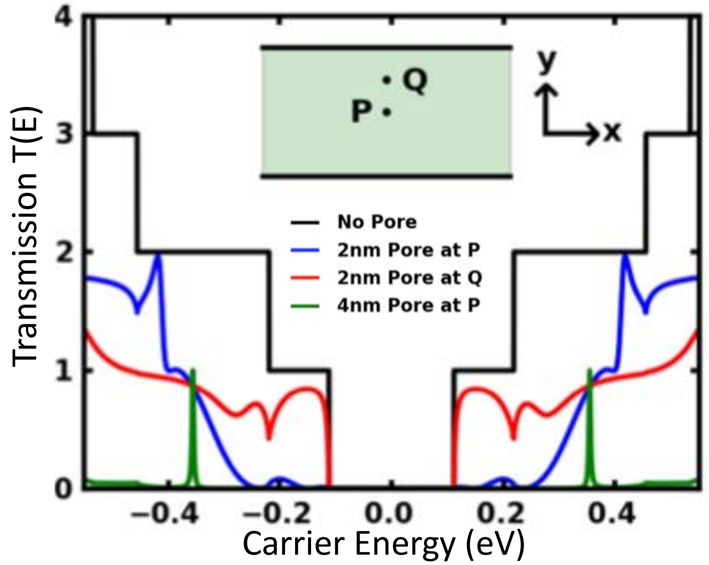
$$H\Psi = E\Psi$$

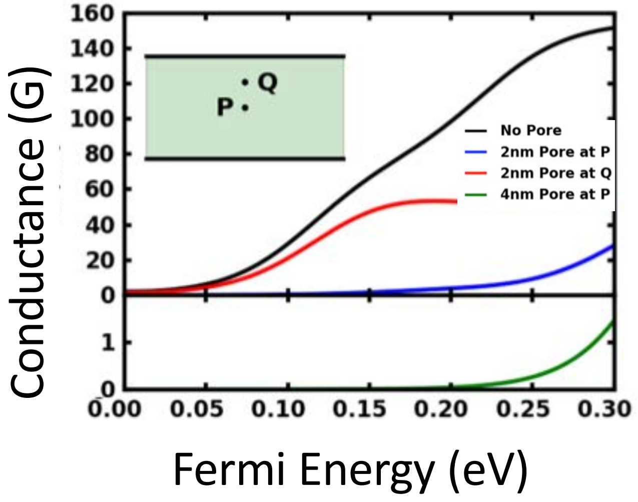
$$[E \pm i\eta - H(\vec{r}, \vec{r'})]G_f(\vec{r}, \vec{r'}) = \delta(\vec{r} - \vec{r'})$$

$$\begin{bmatrix} G_1 & G_{1C} \\ G_{C1} & G_C \end{bmatrix} = \begin{bmatrix} (E + i\eta)\bar{\boldsymbol{I}} - H_1 & V_{1C} \\ V_{C1} & (E + i\eta)\bar{\boldsymbol{I}} - HC \end{bmatrix}^{-1}$$

$$\Sigma = V_{1C}^\dagger[(E + i\eta)\bar{\boldsymbol{I}} - H_1]^{-1} V_{C1}$$

$$I = \frac{2e}{h}\int_{\infty}^{\infty} \bar{T}(E)[f_1(E) - f_2(E)]dE$$





All-atom MD Simulations

$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} +$$

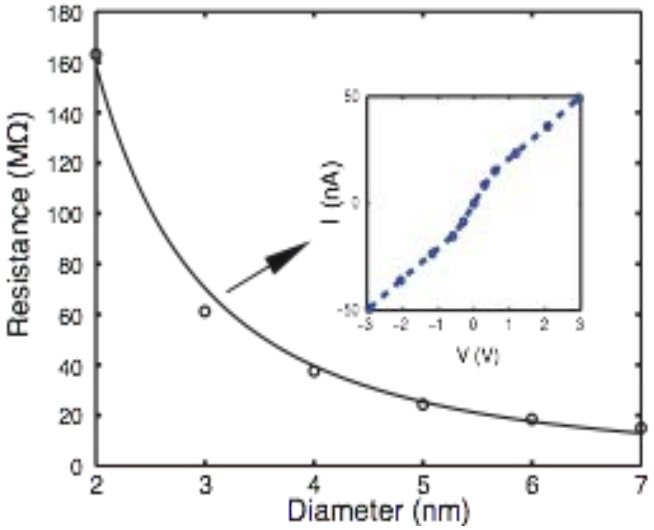
$$\underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} +$$

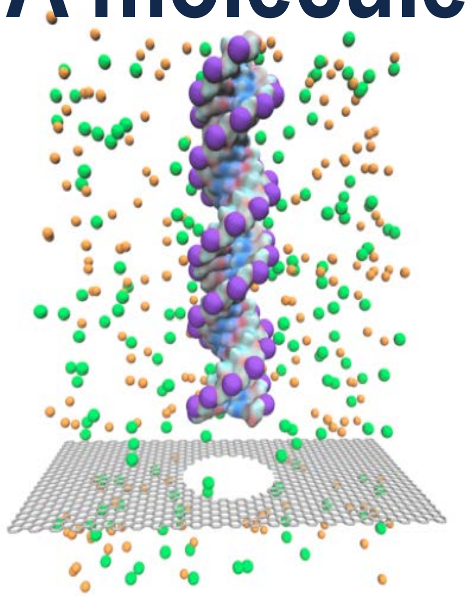
$$\underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

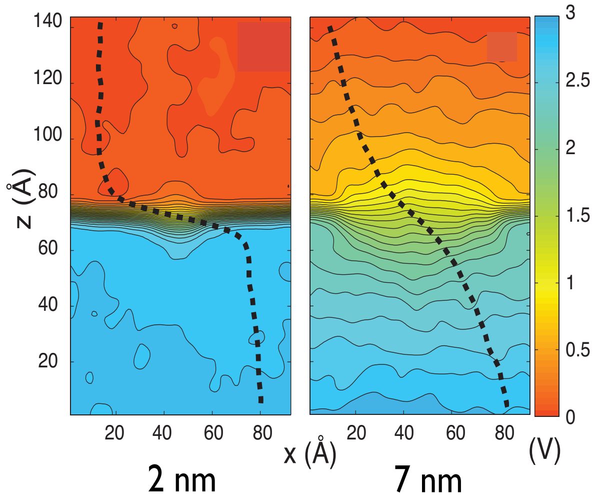
$$m_i \frac{d^2 \vec{r}_i}{dt^2} = \vec{F}_i = -\vec{\nabla} U(\vec{R})$$

$$\vec{r}_i(t + \Delta t) = 2\vec{r}_i(t) - \vec{r}_i(t - \Delta t) + \frac{\Delta t^2}{m_i} \vec{F}_i(t)$$

Detection of DNA molecule: Ionic Currents

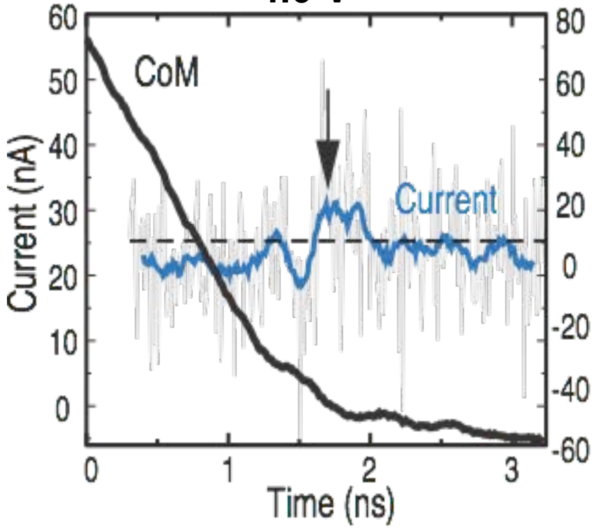




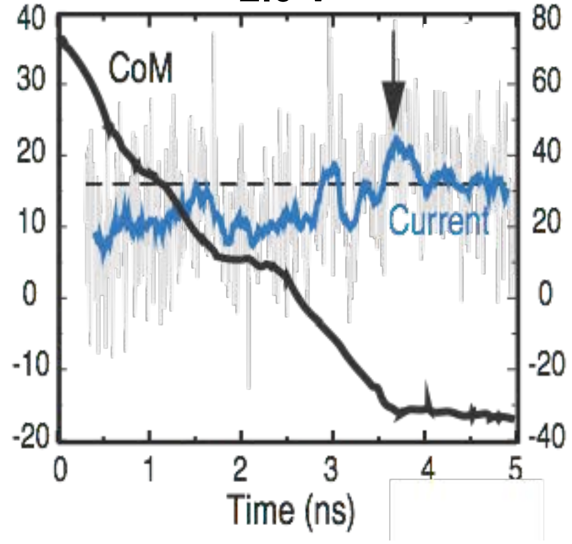


Potential profile

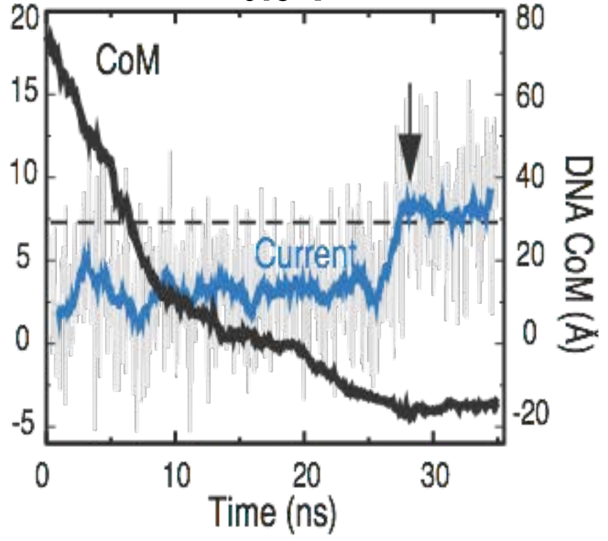
4.3 V



2.5 V



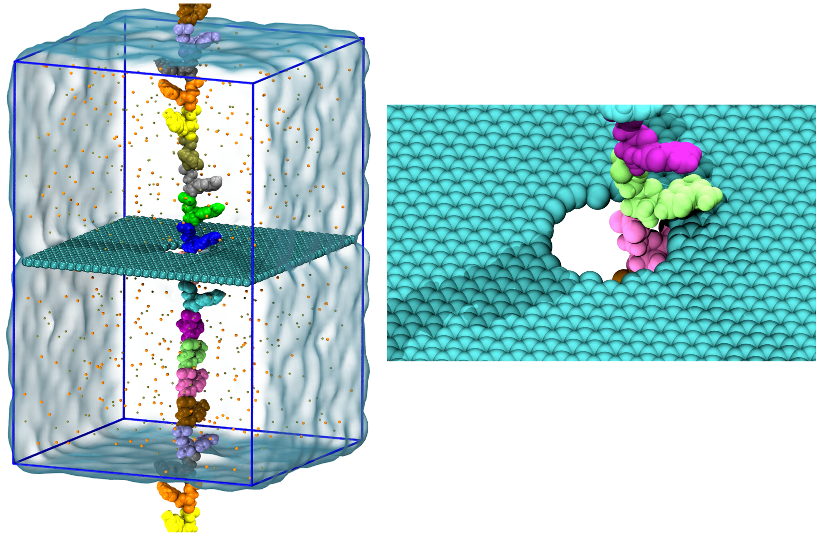
0.8 V



C. Sathe, X. Zou, J. P. Leburton, and K. Schulten. *ACS Nano* 2011.

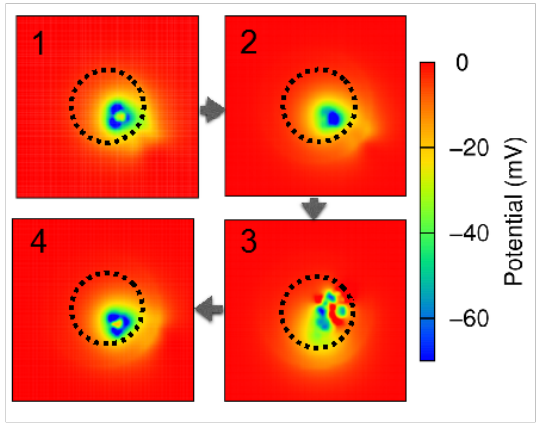
Current blockade is stronger for lower applied bias!

Detecting Stepwise ssDNA Translocation

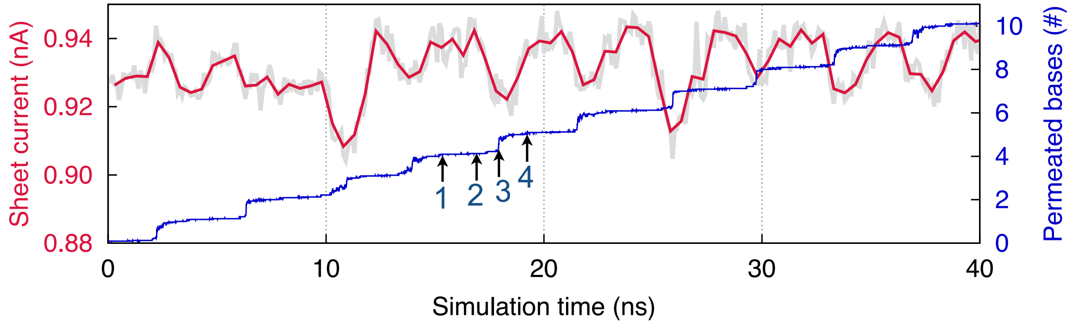


Electrostatics of nanopore system

$$\nabla \cdot [\epsilon(\mathbf{r})\nabla\varphi(\mathbf{r})] = -e[C_{K^+}(\mathbf{r}) - C_{Cl^-}(\mathbf{r})] - \rho_{DNA}(\mathbf{r})$$

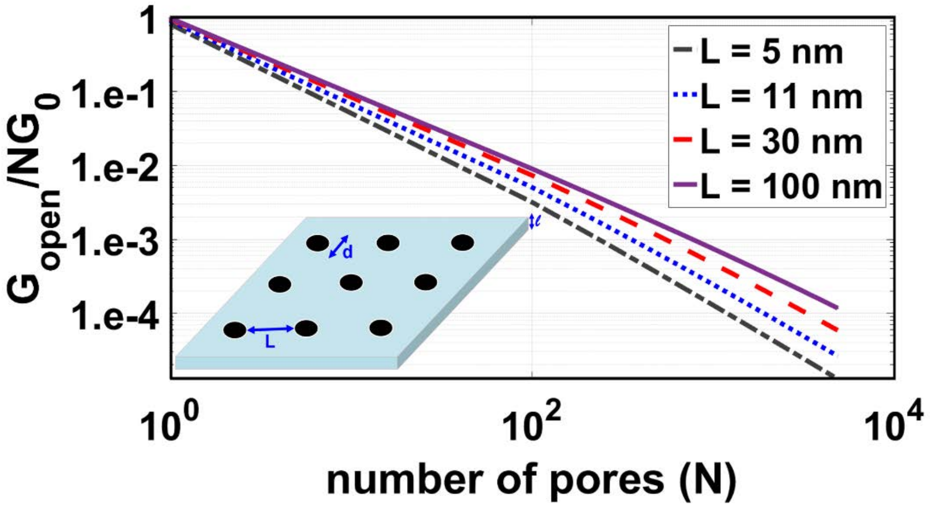


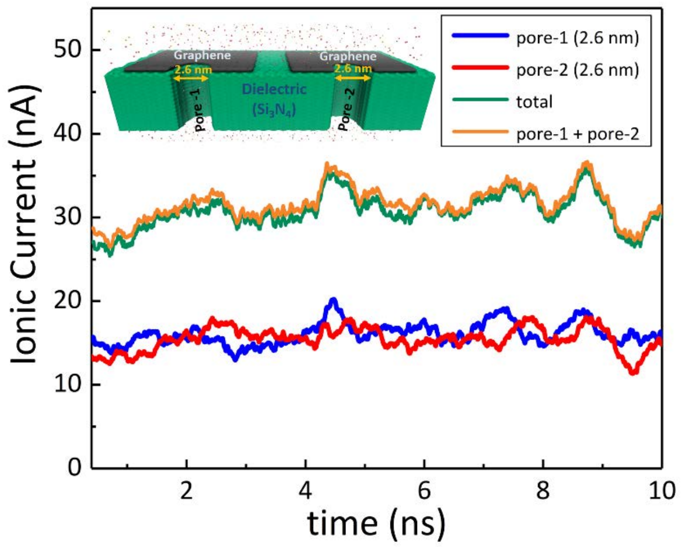
Conductance in the 2D Membranes due to change in electrostatic potential

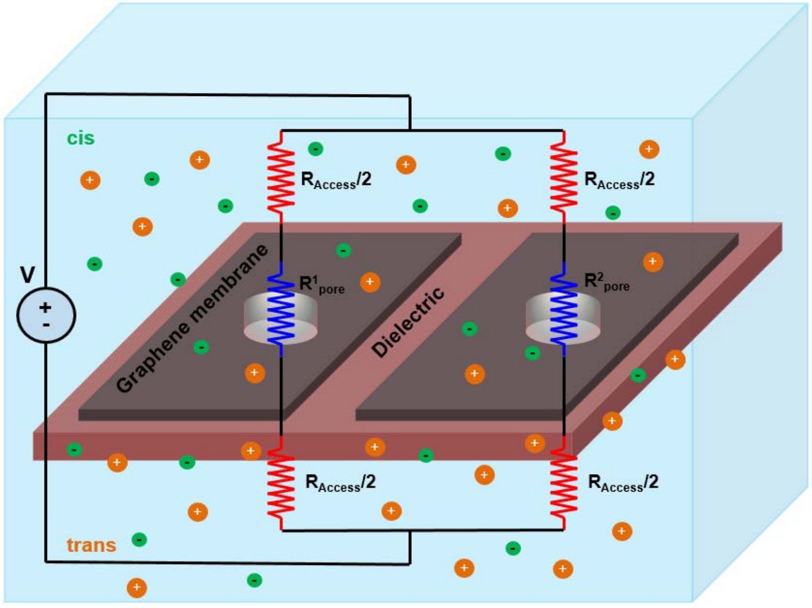


H. Qiu A. Sarathy, J-P Leburton and K. Schulten Nanoletters (2015)

Large Scale Parallel DNA Detection in Multi-pore Systems







Large Scale Parallel DNA Detection in Multi-pore Systems