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
DNA: The Blue Print of Life

Applications of Decoding the Genome

- Personalized Medicine
- Pharmaceutical Research
- Point-of-care Genomic Testing

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

Sequencing Technologies

Nanopore Sequencing is a potential solution

New target < $100
Principle of Nanopore Sensing

- $\delta I$: Average amplitude
- $t_d$: Dwell time
- $\delta t$: Waiting time between two events


Biological Nanopores

Solid-state Nanopores

Oxford Nanopore Technologies

Electrical & Computer Engineering
Towards Electronic Detection of Bio-molecules

<table>
<thead>
<tr>
<th>Sheet Current</th>
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<tr>
<td>1. Tunable sensitivity of detection.</td>
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<tr>
<td>2. Easily integrated into semiconductor</td>
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<tr>
<td>3. Massively parallel detection.</td>
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</tbody>
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Previous Work

Leburton Group, UIUC, 2013

Radenovic Group, EPFL, 2013
Modeling Ionic Currents using BW Nodes

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

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

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

\[ \nabla \cdot \left[ \varepsilon(\vec{r}) \nabla \phi(\vec{r}) \right] = -e \left[ K^+(\vec{r}, \phi) - C_l^- (\vec{r}, \phi) \right] - \rho_{DNA}(\vec{r}) \]
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**.

**Electrical & Computer Engineering**
Site of the nick: A-A

Potential Profile of Damaged dsDNA translocation
Site Specificity of the nick positions

<table>
<thead>
<tr>
<th>SITE OF THE DNA DAMAGE</th>
<th>CURRENT TRACES</th>
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<tbody>
<tr>
<td>T-T</td>
<td></td>
</tr>
<tr>
<td>C-C</td>
<td></td>
</tr>
<tr>
<td>G-G</td>
<td></td>
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</tbody>
</table>

Not recognizable by ionic currents
Voltage ($V_{\text{cis-Trans}}$) dependence

Normal translocation  Denaturing of the DNA

Electrical & Computer Engineering
Voltage ($V_{\text{cis-Trans}}$) dependence

Breaking point!
Future Work

- Different electrically active 2D materials: Semi-conductor (MoS$_2$)
- Complete voltage dependence analysis
ACKNOWLEDGEMENTS

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Olgica Milenkovic
THANK YOU
Appendix
Multigrid Solution of Semiconductor PBE

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

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

\[ K^+(\mathbf{r}, \varphi) = C_0 e^{e\varphi/k_BT} \quad C_l^-(\mathbf{r}, \varphi) = C_0 e^{e\varphi/k_BT} \]

\[ p(\mathbf{r}) = N_v \frac{2}{\sqrt{\pi}} F_{1/2} \left( \frac{-e\varphi(\mathbf{r}) - E_F}{k_BT} \right) \]

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

Half Order Fermi-Dirac Function

Need to solve 3D Poisson Boltzmann Equation with Newton Multigrid

Multigrid gives \( O(N) \) performance

Graphene Nanopore Sheet Conductance Model

Graphene honeycomb lattice

Tight-binding Hamiltonian

\[ H = \sum_n (\varepsilon - e\varphi(r_n)) + \sum_{\langle i,j \rangle} [t_{ij}c^*_ic_j + h.c] \]

Non-Equilibrium Green’s Function

\[ [E \pm i\eta - \hat{H}(r, r')]\hat{G}(r, r') = \delta(r - r') \]

\[ \hat{G}(E) = [E\hat{1} - \hat{H}]^{-1} \]

\[ \overline{T}(E) = -Tr \left[ \left( \Sigma_S - \Sigma_S^+ \right) G_C (\Sigma_D - \Sigma_D^+) G_C^+ \right] \]

Landauer-Buttiker Formula

Conductance

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

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

\[ H = \sum_i (\epsilon_i - \epsilon_i^\phi_i) a_i^\dagger a_i + \sum_{ij} t_{ij} a_i^\dagger a_j \]

\[ H\psi = E\psi \]

\[ T(E) = \int \frac{\delta(\vec{r} - \vec{r}')}{2\pi}\Gamma(E)\Gamma(E')d\vec{r}' \]

\[ H = \sum_i (\epsilon_i - \epsilon_i^\phi_i) a_i^\dagger a_i + \sum_{ij} t_{ij} a_i^\dagger a_j \]

\[ \Psi = \int \frac{\delta(\vec{r} - \vec{r}')}{2\pi}\Gamma(E)\Gamma(E')d\vec{r}' \]

\[ I = \frac{2e}{h} \int_{0}^{\infty} T(E)[f_1(E) - f_2(E)]dE \]
All-atom MD Simulations

\[ U(\vec{R}) = \sum_{\text{bonds}} k_i^{\text{bond}} (r_i - r_0)^2 + \sum_{\text{angles}} k_i^{\text{angle}} (\theta_i - \theta_0)^2 + \]

\[ \sum_{\text{dihedrals}} k_i^{\text{dihed}} [1 + \cos (n_i \phi_i + \delta_i)] + \]

\[ \sum_{i \neq j} 4 \epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \sum_i \sum_{j \neq i} \epsilon r_{ij} + \]

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

\[ \vec{r}_i(t + \Delta t) = 2\vec{r}_i(t) - \vec{r}_i(t - \Delta t) + \frac{\Delta t^2}{m_i} \vec{F}_i(t) \]
Detection of DNA molecule: Ionic Currents

Current blockade is stronger for lower applied bias!
Detecting Stepwise ssDNA Translocation

\[
\nabla \cdot \left( \epsilon(r) \nabla \phi(r) \right) = -e \left[ C_{K^+}(r) - C_{Cl^-}(r) \right] - \rho_{DNA}(r)
\]

Electrostatics of nanopore system

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