Electrokinetic Brownian dynamics of current blockade of a dsDNA through a nanopore(*)

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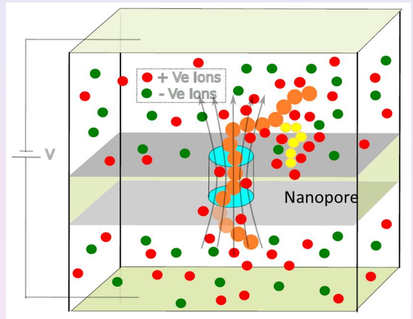
Abstract

- Accurate genome mapping has direct applications in identifying and characterizing unknown species, **restoring biodiversity**, unambiguously **labeling food specimens**, **authenticating herbal products**, protecting endangered species, and in **taxonomical research**.
- Detection the genomic motifs relies on the accuracy **current blockade traces** measured at the nanopores which is often very noisy.
- We implement full fledge **electrokinetic transport of dsDNA** with sidechains in presence of explicit co and counter ions.
- We also propose a novel protocol to reconstruct current blockade from the Brownian dynamics (BD) simulation. When compared with the ionic current, we get an excellent correlation that can be exploited to get current data for a longer DNA.

Model & the Method

Single Nanopore setup with explicit Co & Counter ions



Motion of the dsDNA

We coarse-grain 128 nm long λphage DNA into 64 beads. This implies $\sigma \sim 1bp$ (2 nm resolution).

Positive Ions = 500
Negative ions = 500

Nanopore diameter = 4σ

Simulation Details

Bead Spring Model of DNA

$$U_{LJ}(r) = 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] + \epsilon \quad \text{for } r \le 2^{1/6}\sigma$$
$$= 0 \quad \text{for } r > 2^{1/6}\sigma.$$

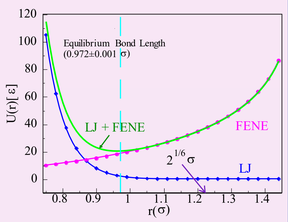
LJ Potential

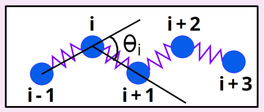
$$U_{\text{FENE}}(r) = -\frac{1}{2}kR_0^2 \ln\left(1 - r^2/R_0^2\right)$$

Spring Potential

$$U_{\text{bend}}(\theta_i) = \kappa(1 - \cos\theta_i)$$

Bending Potential





Electrostatic Interaction

Coulombic interactions between any two charged particles q_i and q_j, and separated by a distance r_{ij}

$$U_{electrostatic}(r_{ij}) = k_B T l_B \frac{q_i q_j}{r_{ij}}, \qquad l_B = \frac{e^2}{4\pi\varepsilon_0 \varepsilon k_B T}$$

The monomers are charged with $q_{bead} = -1.0$ & $q_{tag} = 0.5$.

Due to the extended electric field, each monomer experience an additional force $\vec{F}_{elec}(m) = q(m)\vec{E}$.

Equation of Motion:

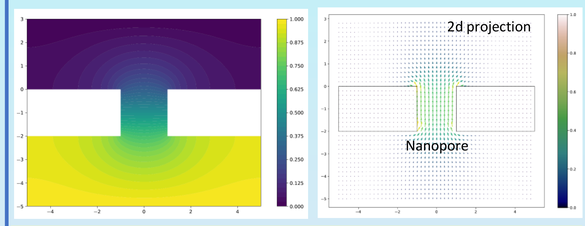
$$m_i \frac{d^2\vec{r}_i}{dt^2} = -\vec{\nabla}\left(U_{LJ} + U_{FENE} + U_{Bend}\right) - \gamma_i \frac{d\vec{r}_i}{dt} + \vec{R}_i(t)$$

With $< \vec{R}_i\ (t)\ \vec{R}_j(t') > = 2dk_BT\gamma\delta_{ij}\delta(t - t')$

d = dimension of the system, γ = Frictional Coefficient

Extended Electric Field

Potential Φ **Electric Field**



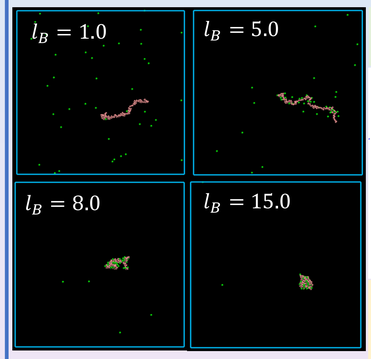
We solve the Poisson equation to get the electric field inside the nanopore using the Finite Element method.

The DNA beads are negatively charged with $q_{monomer}$ = -1.0

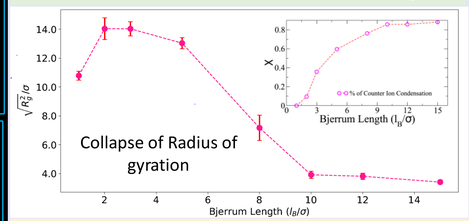
$$q_{tag} = \frac{1}{2} q_{monomer}$$
$$l_{tag} = 12$$

The co & the counter ions contain $q_{ion}^{-ve} = -1.0$ and $q_{ion}^{-ve} = 1.0$

Collapse of polymer with Bjerrum Length



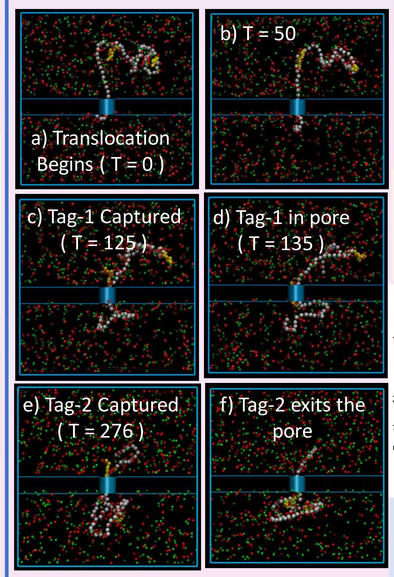
DNA Length = 124 & Fraction of charge = 1/3
Counter Ions = 42 ➔ volume fraction = $10^{-4}/\sigma^3$



- With larger Bjerrum length, a greater number of counter ions are condensing.
- Leads to a collapse of the polymer configuration.

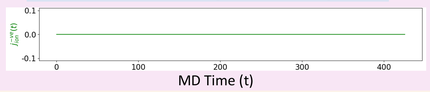
Ion Flow through nanopore

Simulation snapshots of translocation events

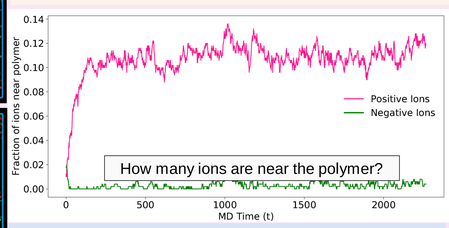


Counter Ion Flow through the nanopore:

Co Ion Flow through the nanopore:

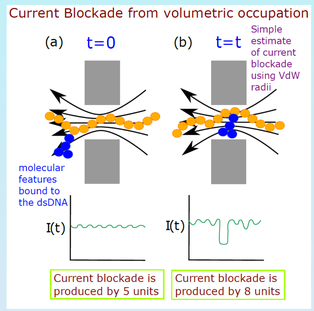


- ❖ Counter ions (+ve) are flowing in the opposite direction of the polymer motion.
- ❖ However, co-ion (-ve) flow is completely hindered.



- ➢ The +ve counter ions are significantly larger in number in the near vicinity of the dsDNA.
- ➢ The –ve co-ions are repelled by the electrostatic interactions.

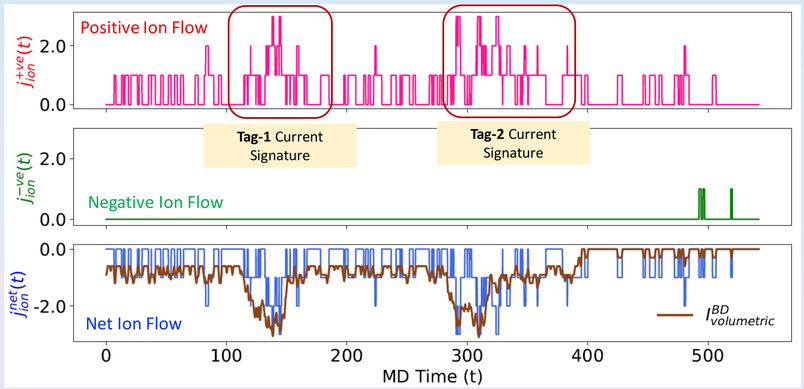
Volumetric Occupation Model



Is there other way to get current blockade from simulation?

Volumetric occupation inside the pore are translated to current blockade magnitude as monomers and side chains pass through the pore as time progresses.

We observe an upsurge in the counter ion flow while sidechain ssDNA tags are in the nanopore.



Conclusions

- ❖ Implementation of the **explicit (co & counter)** ions along with the charged dsDNA with tags provide **accurate current traces**.
- ❖ By measuring the **volumetric occupation** of the species inside the nanopore from BD simulation, current blockade traces can be generated.
- ❖ Our BD simulation confirms that there is a **high correlation** between the actual ion flow and the volumetric occupation current traces.

References

1. **Seth S.**, Rand A., Reisner W., Dunbar W. B., Sladek R. and Bhattacharya A. "Discriminating protein tags on a dsDNA construct using a Dual Nanopore Device." *Sci Rep*, 2022, 12 (1), 11305.
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4. **Seth S.** and Bhattacharya A. "DNA barcode by flossing through a cylindrical nanopore." *RSC Advances*, 2021, 11 (34), 20781-20787.

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