Simulation of DNA sequencing using GROMACS*

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Raphaël LANÇON-VILLE[1] Marc ANTONINI[1] Frédéric PAYAN[1]

[1] Université Côte d'Azur, CNRS, I3S, France
{lanconville, am, fpayan }@i3s.unice.fr

I. Background

Nanopore sequencing, popularized by Oxford Nanopore devices [1], relies on a simple principle: a DNA strand passes through a nanometer-scale pore, and modulation of the measured current enables inference of the sequence. Understanding how the pore structure, membrane, ions, and DNA interact at the molecular scale remains challenging, as the signal arises from a complex coupling between geometry, electrostatics, and dynamics.

II. Approach and simulated system

In this work, we aim to reproduce *in silico* nanopore sequencing using molecular dynamics (MD) simulations performed with GROMACS [2], with the primary objective of generating a realistic electrical signal (see Figure 1). To this end, we built a realistic atomistic system largely generated via CHARMM-GUI [3], comprising: an α-hemolysin nanopore [4] inserted into a POPC bilayer [5], a single-stranded DNA, water, and ions (this is currently a very large system, with about 700,000 atoms, and is therefore computationally expensive). We run translocation test simulations, in particular using "pulling" approaches to trigger an otherwise naturally rare DNA insertion event.

III. Challenges

Our initial results highlight the main bottlenecks in the state of the art: (i) timescale — real translocation typically occurs well beyond the time window accessible to atomistic MD (our tests reach 40 ns/day on a GPU, which calls for acceleration strategies); (ii) the trade-off between realism and artificiality — force-based initiation facilitates observation but may bias certain steps; (iii) mechanical stability and DNA–pore–membrane interactions, which can perturb nanopore anchoring and membrane dynamics.

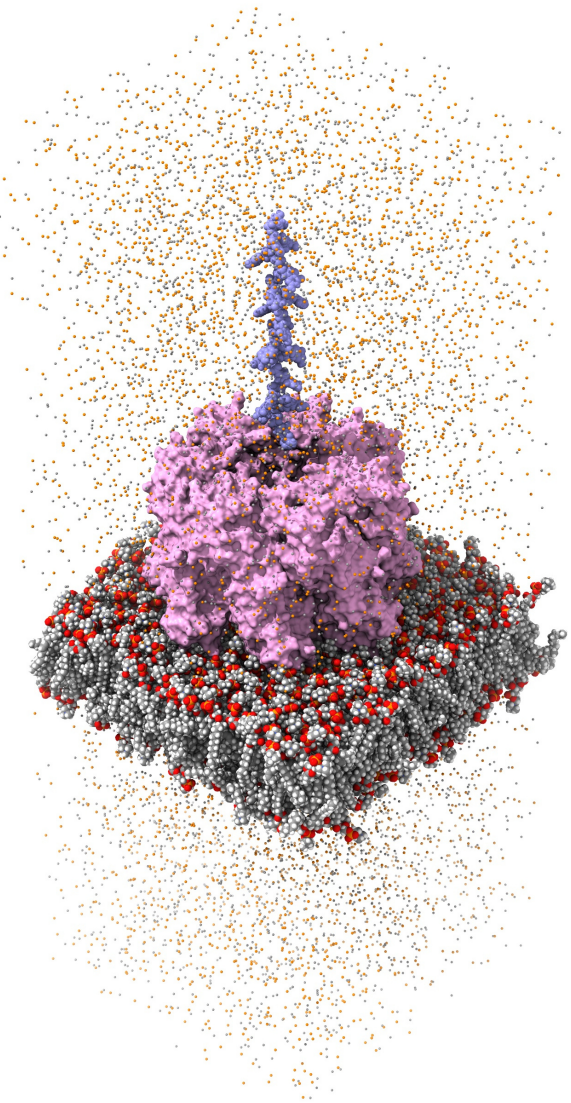

Fig. 1. Rendering of our GROMACS simulation system: an alpha-hemolysin nanopore inserted into a POPC lipid bilayer, a single-stranded DNA positioned near the pore entrance, and an ionic environment. Water molecules are hidden to improve the readability of the scene.

IV. Outlook

In the short term, our goal is to extract observables comparable to experiments (ionic current, forces, and interaction energies) and to define a robust protocol enabling larger-scale simulation campaigns. In the longer term, we aim to develop simplified versions of these simulations, notably using *coarse-grained* approaches [6], enabling systems with far fewer atoms. In the longer term, these simulations could be used to identify nucleotide sequences that are more robust to sequencing noise, or more generally to better understand the physico-chemical determinants of the generated signal in order to improve sequencing interpretation and performance [7].

V. Acknowledgements

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