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Molecular Dynamics Simulations of Colloids in Single Solid-State Nanopores
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The transport of biomolecules and small particles such as viruses through constrained geometries is critical to understand for efficient molecular separations, detection and selective binding for biomedical and biodefense applications. To develop improved capabilities for isolating and controlling both particles and molecules, there is a need for models developed by computational techniques and matched by well-integrated experiments. Here, we use molecular dynamics simulations to study the flow of colloidal silica particles (diameter ~50-100 nm) through cylindrical nanopores with diameter 200nm, and lengths 50-100 nm. Particle translocation is investigated in the presence of an applied electric field. We demonstrate the molecular origin of the pore resistance change that occurs once the colloid is inside the pore. The rate at which particles transit the nanopore is highly dependent on the dispersion forces and the electric field, which is in turn a function of both the applied voltage and the pore geometry. Models are supported by experimental findings obtained with resistive pulse sensing.
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Exploring Dynamic Events of Bacterial Microcompartment Shell Pores
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Bacterial Microcompartments (BMCs) are proteinaceous organelles that sequester key metabolic reactions to increase enzymatic efficiency and prevent the loss of volatile or cytotoxic intermediates. 7 distinct BMC-type operons have been identified in 20-25% of bacteria, including BMCs involved in carbon fixation, propanediol catabolism, and ethanolamine catabolism. Ranging from 100 to 150 nm in width, BMCs are encapsulated in a protein shell consisting of hexagonal tiles of the conserved BMC-fold proteins. The BMC-fold proteins homo-oligomerize into hexameric or pseudo-hexameric assemblies with unique functionalities. High resolution X-ray determined structures have previously elucidated the organization and tiling interactions of several shell proteins from BMCs. However, it remains unknown how small molecule metabolites may enter or exit the BMC, passing through the protein shell; nor how intermediates may be trapped inside. Here, we present initial findings using current methods in Molecular Dynamics to investigate BMC shell pores, including: (1) Metadynamics and Umbrella Sampling to probe the free energy profile of small molecule metabolites at predicted routes through BMC shell protein hexamer pores; (2) Accelerated MD and Targeted MD to observe the conformational change between BMC shell protein pseudo-hexamers that have been solved in open and closed pore conformations. These experiments shed insight on BMC shell pore dynamics and function, furthering our understanding of BMC systems.

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All-Atoms Md Simulation of Protein Translocation through α-Hemolysin Nanopore: Implications for Protein Sequence/Structural Analyses
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The cell isolation from the external environment and the cellular compartmentalization is due to the presence of membranes composed by phospholipidic bilayers. Different proteins that play numerous biological functions are present in the membrane. These proteins are mainly involved in the communication between the cell and the external environment and between the different cellular compartments. Some of them form pores into the lipid bilayer that allow the translocation of molecules of different size and with different chemical-physical properties. The transport of these molecules across the membrane is crucial for the cellular survival. This feature of the membrane proteins has been extensively studied in order to use them as nanopores in biochemical and industrial fields.
During the last decades nanopores have been exploited in the development of new techniques for nucleic acids sequencing. Much less effort has been dedicated to protein and polypeptide analysis using nanopores. Only in the last years pioneering studies appeared in the literature suggesting potentially revolutionary applications in the study of protein sequence and structure. Recent experimental data have demonstrated that, in order to be translocated across nanopores, proteins must be unfolded, with the unfolding process occurring through a multi-step mechanism. It has been observed, for instance, that the transport of the thioredoxin through the α-hemolysin nanopore occurs via a four steps process.
In this work, all atom molecular dynamics simulations of the thioredoxin translocation across the α-hemolysin nanopore have been performed. The data obtained allowed the description of the molecular mechanisms at the basis of the protein transport at the atomic level. Our results allowed us to gain a deeper knowledge regarding the translocation of protein through nanopores, useful for the development of nanopore based applications for several crucial biochemical analyses.

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Coarse-Grained Modeling of DNA-Vesicle Systems with the Martini Force Field
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Computational modeling of DNA is a prime example of both recent advances in force field development as well as lingering difficulties in MD simulations. Coarse-grained models reduce the number of particles in the system and increase the available time and length scales of MD simulations [1]. However, most of the coarse-grained DNA models handle just DNA or, at most, only a few other classes of biomolecules which limits the range of applications for which they can be used. We are developing a coarse-grained model for DNA that is compatible with the Martini force field [2] and, thus, allows simulation studies of various DNA/biomolecular systems. We present the implementation of the current Martini DNA model and compare it to atomistic simulations and experimental results. We applied our model to study the behavior of DNA-copolymers in lipid membranes and vesicles. This work complements the work of our experimental collaborators working on selective fusion of vesicles, based on block copolymers containing single-stranded DNA that are placed on the surfaces of the vesicles. The selectivity in fusion is based on the hybridization of complementary DNA strands. Our Martini simulations provide near-atomic detail on the DNA-polymer-membrane interactions that is used to guide the experimental work.
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Refinement of Multisite Ion Model through Simulation of Osmotic Pressure: Applications on Ion-Mediated Calculations of SsRNA
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Accurate force field parameters for ions are essential for meaningful simulation studies of proteins and nucleic acids. Currently accepted models of ions, especially for divalent ions, do not necessarily reproduce the right physiological behavior. In our previous work, we found a model, called the multisite-ion model, where instead of treating the ions as an isolated sphere, we split the charge into multiple sites (Saxena et al, 2013). With this new model, we were not only able to achieve accurate coordination geometries around the ion, but were also able to predict better free energies for proteins and nucleic acids. Here, we further refine the model by focusing on the behavior of divalent ions in concentrated electrolyte solutions. With several ions present in water, it is important that there are no artifacts such as unusual ion-ion pairing or crystallization. Recently, Luo and Roux showed that osmotic pressure could be successfully used for refinement of ion parameters in NaCl and KCl solutions. We use the same method to test and calibrate the multisite-model of Mg^{2+} and Ca^{2+} in concentrated solution with Cl-. We find that after refinement the solution gets rid of direct ion-pairs, matching the experimentally observed behavior. Subsequently, we use the refined parameters to observe the dependence of counterions on the flexibility of ssRNA. We compare our results to smFRET experiments by Chen et al, which show that Mg^{2+} has more charge screening efficiency than Na^{+} on a 40-mer uridylate (rU40).
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