Numerical modelling of single-protein trapping inside a biological nanopore

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The trapping of single proteins and peptides inside a nanopore holds great promise for single-molecule enzymology, bio-marker quantification and analyte recognition. The biological nanopore cytolysin A (ClyA) has been used to trap various proteins, enabling the investigation of enzyme behaviour at the single-molecule level. Interestingly, specific proteins exhibit multiple distinct, transient current levels while trapped inside ClyA [1]. In this work, we used a 2D-axisymmetric computational model of ClyA to gain a deeper insight into the origin of these different states. Numerically solving the coupled Poisson, Nernst-Planck and Navier-Stokes equations yielded estimates of the electrical field, the ionic transport and the water flow inside ClyA. The use of smooth, Gaussian charge and permittivity distributions derived from the ClyA crystal structure, [2] resulted in electrostatic fields that were in good agreement with those obtained from full-atom 3D simulations [3]. Nanoscale confinement effects on ion and water transport were taken into account by implementation of spatially dependent diffusion constants, electrophoretic mobilities and viscosities [4, 5]. By placing a static, charged spherical particle along the central axis of the pore, we were able to estimate the electrophoretic (F_{ep}) and electro-osmotic (F_{eo}) forces at different positions inside the pore. Integration of the resulting force balance along the length of the pore revealed the presence of a single minimum for positively and slightly negatively charged particles. For spheres with a higher negative charge, however, the increased competition between F_{ep} and F_{eo} resulted in multiple stable positions. These findings suggest that, for positively charged proteins, the various current levels observed experimentally might be caused primarily by a reorientation of the protein. For highly negatively charged proteins, we used the force balance to perform 1D Brownian dynamics simulations with confinement-corrected damping coefficients to mimic their positional switching behaviour. We found that the simulated transition rates and dwell times were in good agreement with experimental data of the negatively charged protein DHFR [1].

References

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