Towards in-silica screening of molecule permeation through outer membrane channels in Gram-negative bacteria.

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The demand of new drugs for combating multidrug-resistant bacteria appears more urgent for Gram-negative bacteria: the presence of the outer membrane, which hinders the access of molecules to internal targets, renders the development of anti-infectives more challenging. Today neither a robust screening method for permeation nor defined physical/chemical rules governing permeation through the outer membrane are available [1].

By assuming diffusion as the physical mechanism of the transport of molecules through the channels, we suggest a simple model for the free energy profile of the molecule-pore interaction. The diffusional flux of molecules through channels is then calculated with the analytic solution to the Nernst-Plank equation provided the chemical potential difference at the sides of the membrane is known. Being based on the clear physical conception, the parameters of the model may be obtained from the all-atom MD simulations for a membrane channel and the molecules separately [2,3]. Alternatively, the model may be considered as a scoring function for fast quantification of the pore permeability for molecules with the parameters fit to the available experimental data. This, in particular, opens up the possibility for the computational screening of virtual libraries of possible modifications of an antibiotic in order to improve its permeability through the membrane.

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[2] S. Acosta-Gutierrez, et al. (2015). Filtering with Electric Field: The Case of E. coli Porins. *J. Phys. Chem. Lett.*, *6*, 1807–1812

[3] S. Acosta-Gutierrez, et al. (2016). Macroscopic Electric Field Inside Water-Filled Biological Nanopores *PCCP* 18, 8855–64.