Permeability in gram-negative bacteria: A microscopic journey

S. Acosta Gutiérrez[1], I. Bodrenko[1], Tommaso D'Agostino[1], Alessandro Pira[2], G. Malloci[1], M.A. Scorciapino[3], M. Ceccarelli[1]

[1]Department of Physics, University of Cagliari, Monserrato (CA), Italy.
[2]Department of Chemical and Geological Sciences, University of Cagliari, Monserrato (CA), Italy.
[3]Department of Biomedical Sciences, Biochemistry Unit, University of Cagliari, Monserrato (CA), Italy.
Email: silvia.acosta@dsf.unica.it

New drugs for combating multidrug-resistant bacteria are needed, especially for Gram-negative bacteria. The presence of the outer membrane in this type of bacteria hinders the access of molecules to their internal targets, rendering the development of new drugs even more challenging. To date neither a robust screening method for permeation nor well-established physiochemical rules governing permeation through the outer membrane are available.

Starting from high-resolution crystal structures of different porins, we combine all-atom molecular modeling with molecular dynamics to characterize its electrostatic properties. This together with the aid of enhanced sampling techniques for simulating the permeation of antibiotics through them; provide us a microscopic description of the problem that allows us to identify the key molecular parameters involved in successful permeation of known drugs and model it.

Without a strong and accurate experimental method to assess the flux of antibiotics through porins, our model, based on the fluctuations of simple physical properties of porins and trained in the successful analyzed cases, represents a useful tool to explore the chemical space for searching new scaffolds and/or optimize at the molecular level existing molecules for an enhanced permeation through bacterial porins.

References:

[1] Mariano Andrea Scorciapino, Tommaso D'Agostino, Silvia Acosta-Gutiérrez, Giuliano Malloci, Igor Bodrenko, and Matteo Ceccarelli. Exploiting the porin pathway for polar compound delivery into Gram-negative bacteria (2016) DOI: 10.4155/fmc-2016-0038
[2] Acosta-Gutiérrez, S. et al. (2016). Macroscopic electric field inside water-filled biological nanopores. *Phys. Chem. Chem. Phys.*,**18**, 8855-8864.
[3] Acosta-Gutiérrez, S. et al. (2015). Filtering with Electric Field: The Case of E. coli Porins. *Journal of Physical Chemistry Letters*, **6**, 1807–1812. http://doi.org/10.1021/acs.jpclett.5b00612
[4] Winterhalter & Ceccarelli (2015), Physical methods to quantify small antibiotic molecules uptake into Gram-negative bacteria. *Eur. J. Parm. Biopharm.* **95**:63-7.