Metadynamics Simulations of β-Lactamase Inhibitors Translocation through OmpF

Alessandro Pira [1], Mariano Andrea Scorciapino [3], Matteo Ceccarelli [2]

[1]Department of Chemical and Geological Sciences, University of Cagliari, Monserrato (CA), Italy; [2]Department of Physics, University of Cagliari, Monserrato (CA), Italy; [3]Department of Biomedical Sciences, Biochemistry Unit, University of Cagliari, Monserrato (CA), Italy.

alessandro.pira@dsf.unica.it

In recent decades there was a drastic drop in the development of new antibiotics. This has increased the difficulty to counter the growing resistance to currently available antibiotics of many pathogens, such as Gram-negative bacteria. Such a situation highlights the importance of developing alternative strategies aimed at looking for new scaffolds characterized by desired properties.
Gram-negative bacteria are characterized by the presence of an outer membrane (OM) representing an additional defense for polar antibiotics, making them challenging system for drug discovery.
Water-filled porins have been identified as the main access route to internal targets for β-lactam antibiotics and β-lactamase inhibitors; therefore a better understanding of the permeability mechanism is needed. The development of β-lactamase inhibitors may play a key role in giving β-lactam antibiotics a chance to fight bacteria due to the presence, in the periplasmic space, of the β-lactamase enzymes that recognize this type of antibiotics rendering them inactive.
Molecular Dynamics Simulations (MD) of porins and small molecules at an all-atom level allow investigating the physical-chemical parameters involved in their mutual interactions. However, the permeation occurs on the millisecond time scale, not reachable with standard MD techniques. The complexity of the hypersurface describing the potential of the process limits the ergodicity of the sampling. The well-tempered metadynamics through Plumed 2.2 plug-in allows overcoming these limitations.
In this work we did an in silico study of the permeability of three β-lactamase inhibitors through OmpF, the most studied porin from *E. Coli*. The free energy surface of the permeation process was reconstructed in order to identify the main path and the main interaction between the porin and substrates through the analysis of energy minima.

References:

[1] Silvia Acosta-Gutierrez, Mariano Andrea Scorciapino, Igor Bodrenco, and Matteo Ceccarelli "Filtering with electric field: The case of E.coli porins" J. Phys. Chem. Lett. 2015, 6, 1807-1812.
[2] Matteo Ceccarelli and Paolo Ruggerone "Physical Insights into Permeation of and Resistance to Antibiotics in Bacteria" Current Drug Targets, 2008, 9, 779-788.
[3] Vincent P. Sandanayaka and Amar S. Prashad "Resistance to β-Lactam Antibiotics: Structure and Mechanism Based Design of β-Lactamase Inhibitors" Current Medicinal Chemistry, 2002, 9, 1145-1165.
[4] Mariano Andrea Scorciapino, Tommaso D'Agostino, Silvia Acosta-Gutierrez, Giuliano Malloci, Igor Bodrenko, and Matteo Ceccarelli "Exploiting the porin pathway for polar compound delivery into Gram-negative bacteria" Future Medicinal Chemistry 2016, 8, 1047-1062.
[5] World Health Organization "ANTIMICROBIAL RESISTANCE" Global Report on Surveillance 2014.