Computational study of the interaction between antimicrobial compounds and efflux systems of Gram-negative bacteria

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Nowadays, multidrug resistance in Gram-negative bacteria is a major issue for public health. The efflux pump systems of the resistance nodulation division (RND) family play an important role in this phenomenon. A well-known example is represented by the AcrAB-TolC efflux system of *E. coli* in which the inner membrane translocase AcrB is the main responsible for the uptake and extrusion of different compounds. Due to the limited availability of crystallographic structures of AcrB-substrate complexes, computational methods represent an alternative approach to elucidate the nature of interactions between diverse antimicrobial compounds and the efflux protein. Hence, two antbiotics known for their different affinity for the efflux pump in *P. aeruginosa*, namely Meropenem and Imipenem (respectively, strongly and a poorly affected by MexB, the homologous of AcrB in *P. aeruginosa*), were selected for this study. A similar behaviour has not been yet reported in the literature for *E. coli*.

Firstly, a molecular docking approach using an ensemble of both ligands and receptor structures was performed. The lowest scoring docking poses were selected as initial conformations for μs-long molecular dynamics simulations, where the asymmetric AcrB protein was embedded in a phospholipid bilayer and explicitly solvated. The force field parameters for each ligand are derived from both quantum-mechanics and μs-long MD simulations [1].

The aim of this study is to analyse the molecular interactions characteristic for both ligands in order to estimate their binding energy and identify the key residues involved in the possible extrusion/retention process. Additionally, the results will be compared with those obtained with the same compounds interacting with MexB. The ability to understand these different features could help designing new antibiotics less likely to be extruded or inhibitors more effective in blocking the whole efflux process.

References:

[1] Malloci, G.; Vargiu, A.V.; Serra, G.; Bosin, A.; Ruggerone, P.; Ceccarelli, M. *Molecules* **20**, 13997-14021 (2015)