Binding of antibiotics to the multidrug efflux pump AcrB of *E. coli* investigated by molecular docking

G. Malloci, G. Serra, A. Bosin, A. V. Vargiu and P. Ruggerone

Department of Physics, University of Cagliari,
Cittadella Universitaria, S.P. 8 km 0.700, 09042 Monserrato (CA), Italy
E-mail: giuliano.malloci@dsf.unica.it

The AcrB multidrug efflux transporter of *E. coli* is a giant homotrimeric membrane protein able to recognize and expel a wide variety of compounds out of the cell [1]. Obtaining the co-crystal structures of AcrB bound to its substrates has proven to be difficult, and to date only a few antibiotics have been successfully co-crystallized with the protein. From these studies, two main recognition sites were identified in two different monomers. The lack of co-crystal structures for most compounds still hinders a full understanding of the molecular recognition mechanism. As a part of an extensive computational research activity on efflux pumps, we performed a systematic docking campaign to find the putative binding sites of antimicrobial compounds from different classes, namely carbapenems, cephalosporins, fluoroquinolones, penicillines, and beta-lactamase inhibitors.
In particular, for each compound we screened for possible binding sites on the whole protein, including thus possible binding pockets other than those already known. Flexibility has been taken into account by considering ensembles of rigid structures for both the ligand and the receptor. Ligand conformations have been extracted from microsecond-long molecular dynamics (MD) simulations in explicit water [2]. For the protein we considered a large set of conformations (128), including structures from both high-resolution X-ray and MD simulations [3].
We present the preliminary results of this systematic investigation by comparing the patterns of interactions observed for the different compounds. The binding properties of the transporter are discussed in terms of statistics of the most contacted residues.

References

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