Binding of antibiotics to the multi-drug efflux transporter AcrB of *E. coli* investigated by molecular modeling

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The AcrB multidrug efflux transporter of *E. coli* is a large complex homo-trimeric membrane protein able to recognize and expel a wide variety of compounds out of the cell [1]. Obtaining co-crystal structures of AcrB bound to substrates has proven to be difficult. To date, only a few compounds have been successfully co-crystallized with the protein. From these studies, two main recognition sites were identified in different monomers, the so-called Access Pocket (AP) in the Loose monomer and the Distal Pocket (DP) in the Tight monomer. The lack of co-crystal structures for most compounds still hinders a full understanding of molecular recognition and transport mechanisms.

As a part of an extensive computational research activity on bacterial efflux pumps, we performed a systematic molecular modeling campaign to characterize the putative binding sites of antimicrobial compounds from different classes, namely carbapenems, cephalosporins, fluoroquinolones, penicillins, and tetracyclines. In particular, we performed a compendium of a completely blind docking campaign [2] and a Markov-Chain Monte-Carlo (MCMC) analysis of multiple interactions [3]. For the docking study we took into account flexibility by considering ensemble of conformations extracted from molecular-dynamics simulations for both ligand [4] and receptor [5]. For the MCMC analysis we adopted homogeneously the DFT-optimized configuration of each ligand and some of the available X-ray structures of AcrB. Here we compare the patterns of interactions observed for the different compounds in the putative binding sites AP and DP of AcrB, in terms of statistics of the most contacted residues and effective number of binding sites within the framework of a diffusive binding picture.

References

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