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Coarse-grained Simulations of Substrate Export through Multidrug Efflux Transporter AcrB[1] YEAD JEWEL, PRASHANTA DUTTA, JIN LIU, Washington State University, Pullman WA — The treatment of bacterial infectious diseases hampered by the overexpression of multidrug resistance (MDR) systems. The MDR system actively pumps the antibiotic drugs as well as other toxic compounds out of the cells. During the pumping, AcrB (one of the key MDR components) undergoes a series of large-scale proton/substrate dependent conformational changes. In this work, we implement a hybrid coarse-grained PACE force field that couples the united-atom protein model with the coarse-grained MARTINI water/lipid, to investigate the conformational changes of AcrB. We first develop the substrate force field which is compatible with PACE, then we implement the force field to explore large scale structural changes of AcrB in microsecond simulations. The effects of the substrate and the protonation states of two key residues: Asp407 and Asp408, are investigated. Our results show that the drug export through AcrB is proton as well as substrate dependent. Our simulations explain molecular mechanisms of substrate transport through AcrB complex, as well as provide valuable insights for designing proper antibiotic drugs.

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