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Coarse-grained Simulations of Conformational Changes in Multidrug Resistance Transporters[1] S M YEAD JEWEL, PRASHANTA DUTTA, JIN LIU, Washington State University — The overexpression of multidrug resistance (MDR) systems on the gram negative bacteria causes serious problems for treatment of bacterial infectious diseases. The system effectively pumps the antibiotic drugs out of the bacterial cells. During the pumping process one of the MDR components, AcrB undergoes a series of large-scale conformational changes which are responsible for drug recognition, binding and expelling. All-atom simulations are unable to capture those conformational changes because of computational cost. Here, we implement a hybrid coarse-grained force field that couples the united-atom protein models with the coarse-grained MARTINI water/lipid, to investigate the proton-dependent conformational changes of AcrB. The simulation results in early stage (˜100 ns) of proton-dependent conformational changes agree with all-atom simulations, validating the coarse-grained model. The coarse-grained force field allows us to explore the process in microsecond simulations. Starting from the crystal structures of Access(A)/Binding(B)/Extrusion(E) monomers in AcrB, we find that deprotonation of Asp407 and Asp408 in monomer E causes a series of large-scale conformational changes from ABE to AAA in absence of drug molecules, which is consistent with experimental findings.

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