Computer simulation of the assembled AcrAB-TolC multidrug efflux pump

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With known antibiotics losing their efficiency faster than new ones can be developed, a better understanding of the underlying molecular mechanisms is paramount. Multidrug resistance is often caused by an over-production of efflux transporters that expel drug molecules before they can affect their targets inside the bacterial cell.

In *Escherichia coli*, AcrAB-TolC serves as the major multidrug efflux pump using proton-motive force over the inner membrane to extrude drugs out of the cell. While x-ray structures have been solved separately for the individual components, the best structural information on the assembled efflux pump is a docking structure based on biochemical cross-linking data [1]. To gain insight into the conformational dynamics of AcrB, AcrA & TolC in complex, we have embedded the docking structure in two phospholipid bilayers solvated in a 150 mM NaCl solution, and carried out multiple unbiased 50 ns molecular dynamics (MD) simulations. Each AcrB monomer was considered in a different protonation state as suggested in [2].

Performed using GroMACS 4.0.3 and the GROMOS96 53a6 force field, the simulations provide in atomistic detail a glance on the AcrAB-TolC subunit interplay, complex stability and structure flexibility, protein-membrane interactions, and the dynamics of transport pathways. To further assess the influence of the AcrA adaptor protein, MD runs were performed with and without AcrA.

References

[1] Symmons et al. (2008). PNAS 106(17):7173-8

[2] Pos (2009). BBA 1794(5):782-93