The binding of morphine and nicardipine to the multidrug transporter P-glycoprotein

N. Subramanian,[1] M.L. O'Mara[1,2] and A.E. Mark,[1,3] [1]School of Chemistry and Molecular Biosciences, The University of Queensland, St Lucia, QLD 4072, Australia, [2]School of Mathematics and Physics, The University of Queensland, St Lucia, QLD 4072, Australia and [3]Institute for Molecular Bioscience, The University of Queensland, St Lucia, QLD 4072, Australia.

The ABC transporter P-glycoprotein transports a large number of structurally unrelated drugs and other compounds out of the cell. The expression of P-glycoprotein in cancer cells results in chemotherapy resistance, one of the leading causes of cancer-related deaths. P-glycoprotein and other ABC transporters contain two intracellular nucleotide binding domains (NBDs) that bind and hydrolyse ATP. These are coupled to two transmembrane domains (TMDs) that facilitate the transport of substrate across the membrane and out of the cell. The precise location at which transport substrates bind and the mechanism by which compounds enter P-glycoprotein is currently unknown.

In this study we use molecular dynamics (MD) simulation techniques to identify substrate or inhibitor binding sites. Unbiased MD simulations of membrane-embedded P-glycoprotein in the presence of physiological concentrations of morphine or nicardipine have been used to investigate whether the compounds bind directly to intracellular regions of P-glycoprotein or first partition into the membrane. Using umbrella sampling techniques we have also determined the potential of mean force (PMF) for morphine and nicardipine into the P-glycoprotein translocation pore from the intracellular side. Based on these PMFs, it is possible to identify the specific locations within the translocation pore where a given compound binds and to identify specific residues that stabilize the interactions between the compound and the P-glycoprotein.