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Docking into Symmetric Binding Sites: Problems and Solutions Exemplified on the hERG Potassium Channel

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The hERG potassium channel is highly related to severe cardiac side effects. With the technique of homology modelling it is possible to model the homo tetrameric subunits of the hERG channel in the closed and open state, using KcsA and KirBac1.1 as well as MthK and KvAP as templates. Usually only the S5, P, and S6 segments of one subunit are modelled, while the other three subunits are just copies of the first one. This operation results in an artificial symmetry of the hERG channel, so the binding site in the internal part of the channel is also symmetric. This symmetry renders ligand-docking into hERG channel a quite challenging task. In order to investigate the molecular basis of drug trapping/non trapping in the hERG channel we docked a series of propafenone derivatives in a hERG channel homology model of the closed state. Drug trapping was experimentally determined in voltage clamp experiments on *Xenopus* oocytes.

The fourfold symmetry enables the ligand to adopt four different orientations within the protein, which are in principle unique but are rotated by 90° through the channel axis. As a consequence, a lot of poses, although different in their absolute positioning, are identical with respect to their interaction pattern. In principle all poses within a docking database could be presented in one quarter of the tetrameric hERG channel. Thus, we wrote a SVL-script (ROTALI) in the MOE.2007.09 [1] software package that automatically aligned all poses in one quarter of the protein. This alignment enabled the detection and deletion of duplicates and additionally facilitated the comparison of the remaining poses.

In the case of propafenon derivative GPV0574 docking, 1741 poses were generated by a standard protocol. The application of ROTALI reduced the number of poses by 616, resulting in 1125 poses, which then could be analysed by rmsd clustering and interaction fingerprints.

[1] Molecular Operating Environment, 2007.09 ed.; Chemical Computing Group, Inc.: Montreal, Quebec, Canada.