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Impact of template choice on quality of 5-HT_6 receptor homology models

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Homology modelling is extremely helpful in determining structures of transmembrane proteins, since solving their three-dimensional structures by means of common physical methods is extremely difficult.

G-protein coupled receptors (GPCRs) comprise a vast superfamily of transmembrane receptors. In present study we have focused on serotonin (5-hydroksytryptamine) receptor type 6 (5-HT_6R). They are expressed in neural tissue, and their dysfunctions contribute to CNS diseases, such as depression and anxiety.

In the present study a number of 5-HT_6R homology models was generated on different GPCR templates available: adenosine 2 receptor (PDB ID: 3QAK), beta1 (PDB ID: 2Y00) and beta2 (PDB ID: 3P0G) adrenergic receptors, C-X-C chemokine receptor type 4 (PDB ID: 3OE0), dopamine 3 receptor (PDB ID: 3PBL) and histamine H1 receptor (PDB ID: 3RZE). Next, a set of representative ligands, from chemically diversified clusters, was used for selecting the best models. They were used for docking of a complete set of 5-HT_6R ligands (obtained from ChEMBL database) to determine the best models for further research.

The scope of this study is to determine whether there is a correlation between evolutionary distance in modeled protein and template, and the quality of produced models.

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