P.5-24

GPCRdb homology models - "less model & more crystal"

Pandy-Szekeres G[1,2*], Mordalski S[2], Bojarski AJ[2], Gloriam DE.[1]

[1]*Department of Drug Design and Pharmacology, University of Copenhagen, Jagtvej 162, 2100 Copenhagen, Denmark;* [2]*Department of Medicinal Chemistry, Polish Academy of Sciences, Smetna 12, 31-343 Krakow, Poland*
**Corresponding author: pszgaspar@gmail.com*

Background: Although methods to determine protein 3D structures are improving, from the ~800 GPCRs we still only know the structure of 33 unique receptors. This prompts the need for receptor models that can capture the intricate structural characteristics of GPCRs. GPCRdb now introduces models of human non-olfactory GPCRs built on the principle of "less model & more crystal". This employs a multi-template method that resulted in the best serotonin 5-HT_{1B} receptor model in the latest GPCR Dock assessment.
Materials and methods: The coverage from experimental structures is maximized, while *de novo* modeling is left as a last resort. Specifically, segments that are missing (e.g. loops, helix ends), non-representative (e.g. distorted, deleted or fused segments) or differ (e.g. TM helix bulges and constrictions) are replaced with more optimal local templates. Next, an in-house rotamer library is utilized that has been extracted from all GPCR structures and provides a specific rotamer for each position of the structure (by use of generic residue numbers). Finally, MODELLER is used to model regions where no template was available. The models are automatically updated in new GPCRdb releases, providing increased precision as new templates become available.
Results: Inactive models were built for 278 receptors from class A. All of them are accessible through the gpcrdb.org website along with information about the templates. Models for three recently determined structures were assessed along with corresponding models from other homology modeling services. Root-mean-square deviation calculations were used to compare the performance of the different services.
Conclusions: Our models exhibit a close approximation to the experimentally determined crystal structures mainly excelling in the 7TM RMSD comparison. The modeling of loops needs further improvement.
Acknowledgements: Thank you to Vignir Isberg, Christian Munk, Alexander Hauser and Mohamed Shehata for their contribution. This work was supported by the European Research Council and the Lundbeck Foundation.