A system for automated validation of GPCRs homology models against mutational data

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Homology modeling of G Protein-Coupled Receptors is a very challenging task. Little number of crystal templates and low sequence similarity (especialy for non class A GPCRs) between target and template render the sequence alignment ambiguous in most cases. For the above reasons data acquired from site-directed mutagenesis become a vital aspect of homology modeling, as they can be used to evaluate created models.

In this study we present a tool for automated checking of homology models against the mutational data collected within tinyGRAP database. tinyGRAP [1] database is querried for the investigated sequence and its close homologs (i.e. group members), and substitution mutations are retrieved. Query results are then checked whether apropriate residues face inside of the receptor (with some margin), and if not, the tool produces report in PyMol .pse file pointing amino acids violating mutational „constrains".

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References

1. Beukers MW, Kristiansen K, IJzerman AP, Edvardsen I, **TinyGRAP database: a bioinformatics tool to mine G protein-coupled receptor mutant data.**, Trends Pharmacol Sci. 1999 Dec;**20(12)**:475-7.