

Pseudoreceptor: Concept and an Overview

Gugan Kothandan¹, Thirumurthy Madhavan¹, Changdev G. Gadhe¹ and Seung Joo Cho^{1,2†}

Abstract

A pseudoreceptor combines structure-based and ligand-based techniques to represent a unifying concept for both receptor mapping and ligand matching. In this molecular modeling approach, there are opportunities to construct the pseudoreceptor models using a set of small molecules. To build a reliable pseudoreceptor model, we need a set of ligand molecules with known affinity (biological activity) to generate 3D bioactive conformation for each of these ligand molecules. Several software packages are available to generate a pseudoreceptor model and this can provide an entry point for structure based drug discovery in cases where receptor structure information is not available. In this review, we presented the concept of pseudoreceptor, as well as discussed about various software packages available to generate a pseudoreceptor model

Key words : Pseudoreceptor, Virtual screening, QSAR

1. Introduction

To design a drug successfully through computational modeling, experimental structure of interested target is necessary. But, in absence of experimental structure of target protein solved by X-ray crystallography or NMR method, people used template derived homology model for study. The two principle techniques: structure based drug design (SBDD) and ligand based drug design (LBDD) supported pharmaceutical research over last three decades for the development of drugs.^[1-3] 3D-QSAR derived implementation of contour maps into new lead generation is not always helpful for synthetic chemists. But, atomistic receptor model allows us to gain detailed insight into the key interactions between ligand-receptor complexes. Concept of pseudoreceptor was introduced in late 1980s. Ligand based and receptor based techniques are used simultaneously in pseudoreceptor modeling, which fills the gap between pure ligand based and structure based design.^[4-8] In pseudoreceptor modeling, the 3D-QSAR techniques such as CoMFA^[9],

CoMSIA^[10] and GOLPE^[11] are used to map molecular feature into a physical property of the spatially aligned ligand conformers. The idea behind pseudoreceptor modeling is to generate a receptor environment for single ligand or group of ligands (superimposed) and mimics the interaction patterns as like real binding site. The successful pseudoreceptor modeling can be achieved when the derived model attempts to capture the shape of binding site and its interaction pattern, which is needed for successful ligand binding. Pseudoreceptor can trace the shape of a receptor replacement that mimics an alternative host system, which is capable to produce non-covalent interactions with known ligands having binding affinity. Manually the pseudoreceptors are modeled by some pioneer to construct virtual host system.^[12,13] At the same time pseudoreceptor modeling software packages are also invented. Concept of minireceptor (an unconnected set of small molecules imitating receptor side chains encircling a ligand) was introduced by the Vedani and co-workers and they believe that it is different from that of the pseudoreceptor^[14] (fully linked peptidic or non-peptidic molecules forming a binding pocket). We will consider both as pseudoreceptor model. The main aim of this review is to understand the general concept and the methodology behind pseudoreceptor modeling. In this study we also discussed about some of the software available for pseudoreceptor generation such as ConCept^[15], FLARM^[16], PrGen^[17],

¹Department of Bio-New Drug Development, College of Medicine, Chosun University, Gwangju 501-759, Korea

²Department of Cellular, Molecular Medicine and Research Center for Resistant Cells, College of Medicine, Chosun University, Gwangju 501-759, Korea

[†]Corresponding author: chosj@chosun.ac.kr

(Received : September 1, 2010, Revised : September 17, 2010, Accepted : September 27, 2010)

Quasar^[18], RECEPTS^[19,20], RECEPTOR^[21-23], SKEL-GEN^[24,25] Yak.^[14,26,27] Literature survey shows that previously many people attempted pseudoreceptor approach for modeling purposes.^[18,28-40]

2. Concept of Pseudoreceptor

Methodology of pseudoreceptor generation involves fundamental four steps and it is shown in Fig. 1. First, superimposition of set of 3D-conformer of ligands; second, identification of key interaction sites of aligned ligand set (anchor points); third, assembling core pseudoreceptor model around anchor points; and fourth, optimization of model coordinates to find out accurate binding free energy. There are wide variety of routes are available to generate pseudoreceptor. The main aim of development of the pseudoreceptor model is the ligand adopts a conformation which is comparable to real macromolecule. The optimized pseudoreceptor model is used for affinity prediction and other modeling study. Reader should note the thing that if there is any systemic error, pseudoreceptor can't mimic 100% real receptor structure.

3. Methodology

The first and foremost thing in pseudoreceptor generation is a set of superimposed 3D-conformer of interested ligands. As in any QSAR approach for successful model generation it requires four orders of magnitude of binding affinities. In 3D-QSAR every ligand shows common binding mode, by assuming this rule all ligands are superimposed so that all chemical functional

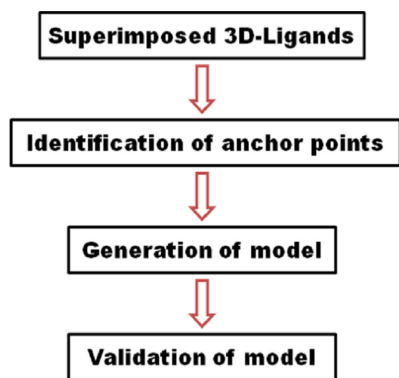


Fig. 1. Flowchart to develop pseudoreceptor model.

groups are arranged in a similar direction. Therefore, it is advised to select the reference (Bioactive) molecules for which the binding mode is experimentally supported to avoid the conformation selection problem. The initial alignment of pharmacophoric points is a crucial step, as it provides the starting point for pseudoreceptor generation, and it sets the course for optimization of final model in terms of quality and applicability. Small changes in the pharmacophoric point alignment may result in completely different models. First step followed by selection, placement, transformation and rotation of amino acid residues ahead of anchor points for generating assembly of pseudoreceptor. In validation step the energy of developed pseudoreceptor model could be minimized. Alternate minimization of receptor and ligand is carried out by keeping one constant with suitable method like molecular mechanics, monte-carlo simulation or molecular dynamics. The ultimate aim of last step is to minimize geometry in XYZ coordinates to calculate more accurately binding free energy and mimic accurately host-guest system as like real.

4. Popular pseudoreceptor programs

There are popular software's available for pseudoreceptor generation and they works on different basis such as fragment based, atom based, peptide based, grid based, isosurface based and partition based method as follows.

4.1. ConCept - Fragment Based Model

This methodology was proposed by Wei chen and Michael Glison.^[15] This is a novel evolutionary method for automated de novo design of small targeted receptors, which uses the M2 algorithm^[41-44] as a final step in evaluating the leading candidate designs. The ConCept design methodology comprises two main steps. First, a simple energy model is used to guide an evolutionary process in which a large number of candidate receptors are automatically constructed around a stable conformation of the targeted ligand. Second, the M2 method of computing affinities is used to evaluate the more promising designed receptors.

4.2. FLARM - Atom Based Model

GERM is Genetic Evolved Receptor Model proposed by Walters and his group.^[45] PARM (Pseudo atomic Receptor Model) is an algorithm which is an advance

version of GERM. It was proposed by Jiaju et al.^[46] FLARM (Flexible Atom Receptor Model) is a new method to do 3D-QSAR and receptor modeling.^[16] The basis is similar to that of GERM and PARM and it is an improved version of PARM. Its purpose is to perform 3D QSAR and receptor modeling under the condition that the 3D structure of the target receptor is unavailable. This approach can predict the activity of new drugs. And the explicit atom models can help to understand the mechanism of the interaction between ligands and receptors and even to preliminarily predict the active sites of the real receptors. The open receptor model can provide a better simulation of the real receptor and may rationally correspond to the pharmacophore model. And 3D database searching can then be done with some 3D databases such as NCI-3D or ACD-3D to find new lead compounds.

4.3. PrGen and Yak - Peptide Based Model

Yak and its successor PrGen is a commercially available pseudoreceptor modeling package^[14,17,26,27] proposed by A. Vedani and his group. This concept allowed the construction of a three-dimensional peptidic pseudoreceptor model around a single molecule or a set of superimposed ligand molecules. The goal of this concept is to engage the superimposed molecules in specific non-covalent ligand-target interactions so as to mimic the receptor-bound state for each ligand. This program is one of the most successful pseudoreceptor modeling technique and a lot of positive outcomes were achieved with this technique.

4.4. Quasar - Atom Based

Quasar is a “quasi atomistic receptor model” refers to a three dimensional receptor surface, populated with atomistic properties such as hydrogen bonds, salt bridges, hydrophobic particles mapped on to the model.^[18] In contrast to other 3-D QSAR techniques, this approach includes receptor envelopes, individually adapted to the topology of the various ligand molecules as well as H-bond flip-flop particles (mimicking Ser, Thr, Tyr, Cys, His, Asn, and Gln residues at the true biological receptor) engaging in differently directed hydrogen bonds with different ligand molecules, simultaneously binding to the receptor. In Quasar, a family of receptor-surface models is generated by means of a genetic algorithm combined with cross-validation.

4.5. RECEPTS - Grid-Based Model

Kato and his group proposed a rational method of molecular superposition. This method was implemented in a computer program called RECEPTS in the year 1987.^[19,20] With this program, one can superpose molecules manually by making use of 3D grid points for evaluating the similarity of spatial arrangements of sub-molecular physical and chemical properties of molecules. Based on the superposed structures of multiple active molecules, a 3D receptor model will be constructed.

4.6. RECEPTOR - Isosurface Based

A receptor surface model is a hypothetical model which characterizes the putative active site of a receptor. This method was proposed by Mathew Hahn.^[21-23] In brief it is a non-atomistic model that uses explicit surfaces to characterize the shape of the binding site. A receptor surface model is visually intuitive and is modifiable as the hypothesis is refined. This approach was applied in QSAR and it was proved successful.

4.7. SKELGEN - Partition-Based Model

SKELGEN is an algorithm for the automated generation of molecular structures subject to geometric and connectivity constraints and it was proposed by Todorov and his group.^[24,25] This is a structure generation algorithm that uses an optimization method (simulated annealing) to minimize a penalty function reflecting the suitability of a chemical structure as a solution to a particular problem. Structures are built by joining together predefined 3D molecular templates. The algorithm navigates through the space of connectivity classes, conformations and rigid body transformations of various structures, guided by the function, until a skeleton is encountered that satisfies all set criteria.

5. Application of Pseudoreceptor

1. To study ligand-receptor interaction sites.
2. Reconstruction of receptor sites.
3. Prediction of binding affinity of new molecules comparing the results obtained from 3D-QSAR technique.
4. To find out bioactive conformation of any ligand by minimizing in pseudoreceptor model.
5. To evaluate interactions energy.

6. Conclusions

Pseudoreceptors can be used for early stage of hit and lead identification process, thus complementing conventional ligand-based and receptor-based virtual screening procedure. The pseudoreceptor model could give valuable information such as essential interacting amino acid side chains, the volume and shape of the ligand binding cavity, and hotspots for receptor-ligand interaction. It is important to understand that the optimized model do not precisely mimic the real receptor binding site, but it is possible and justified to use virtual screening of unsolved receptors sites. However, finding a novel ligand structures with alternative potential binding mode for same receptor pocket is unachievable goal, so the generated model should be treated with more caution because it is known that different ligand modes and multiple binding sites may exist for single target. Keeping these limitations in mind, more validation study has to be done to check the performance of pseudoreceptor modeling programs. Especially, it can be used for remarkable drug design methodology for membrane protein targets and Ion channels.

References

- [1] G. Schneider and K. H. Baringhaus, "Molecular Design: Concepts and Applications", Wiley-VCH, Weinheim., pp. 1-277, 2008.
- [2] G. Klebe, "Virtual ligand screening: strategies, perspectives and limitations", *Drug Discov. Today.*, Vol. 11, pp. 580-594, 2006.
- [3] M. Congreve, C. W. Murray and T. L. Blundell, "Structural biology and drug discovery", *Drug Discov. Today.*, Vol. 10, pp. 895-907, 2005.
- [4] H. Fruhbeis, R. Klein and H. Wallmeier, "Computer-Assisted Molecular Design - An Overview", *Angew. Chem. Int. Ed. Engl.*, Vol. 26, pp. 403-418, 1987.
- [5] J. P. Snyder and S. N. Rao, "Pseudoreceptors: A bridge between receptor fitting and receptor mapping in drug design", *Chem. Des. Autom. News.*, Vol. 4, pp. 13-15, 1989.
- [6] H. D. Holtje and S. Anzali, "Molecular modeling studies on the digitalis binding site of the Na⁺/K⁺-ATPase", *Pharmazie.*, Vol. 47, pp. 691-698, 1992.
- [7] J. P. Snyder, S. N. Rao, K. F. Koehler and R. Pellicciari, "Trends in Receptor Research", Elsevier., pp. 367-403, 1992.
- [8] J. P. Snyder, S. N. Rao, K. F. Koehler and A. Vedani, "3D QSAR in Drug Design", ESCOM Science Publishers., pp. 336-354, 1993.
- [9] R. D. Cramer, D. E. Patterson and J. D. Bunce, "Comparative molecular field analysis (CoMFA). I. Effect of shape on binding of steroids to carrier proteins", *J. Am. Chem. Soc.*, Vol. 110, pp. 5959-5967, 1988.
- [10] G. Klebe, U. Abraham and T. Mietzner, "Molecular similarity indices in a comparative analysis (CoM-SIA) of drug molecules to correlate and predict their biological potency", *J. Med. Chem.*, Vol. 37, pp. 4130-4146, 1994.
- [11] M. Baroni, G. Costantino, G. Cruciani, D. Riganelli, R. Valigi and S. Clementi, "Generating Optimal Linear PLS Estimations (GOLPE): an advanced chemometric tool for handling 3D-QSAR problems", *Quant. Struct. Act. Relat.*, Vol. 12, pp. 9-20, 1993.
- [12] F. Momany, R. Pitha, V. J. Klimkovsky and C. M. Venkatachalam, "Expert Systems and Applications in Chemistry eds B. A. Hohne, T. H. Pierce", American Chemical Society., Washington DC, pp. 82-91 1989.
- [13] H. D. Holtje and S. Anzali, "Molecular modeling studies on the digitalis binding site of the Na⁺/K⁺-ATPase", *Pharmazie.*, Vol. 47, pp. 691-698, 1992.
- [14] J. P. Snyder, S. N. Rao, K. F. Koehler and A. Vedani, "3D QSAR in Drug Design: Theory, Methods and Applications (ed. Kubinyi, H.)", pp. 336-354, Leiden/Escom, Dordrecht, 1993.
- [15] W. Chen and M. K. Gilson, "Concept: de novo design of synthetic receptors for targeted ligands", *J. Chem. Inf. Model.*, Vol. 47, pp. 425-434, 2007.
- [16] J. Pei and J. Zhou, "Flexible atom receptor model", *Acta Chim. Sin.*, Vol. 60, pp. 973-979, 2002.
- [17] Z. Peter, D. Max, F. Gerd and V. Angelo, "pseudoreceptor modeling using receptor mediated ligand alignment and pharmacophore equilibration", *Quant. Struct. Act. Relat.*, Vol. 17, pp. 122-130, 1998.
- [18] V. Angelo and Z. Peter, "A bridge between 3D QSAR and receptor fitting", *Pharm. Acta Helv.*, Vol. 73, pp. 11-18, 1998.
- [19] K. Yuichi, I. Akiko and I. Yoichi, "A novel method for superimposing molecules and receptor mapping", *Tetrahedron*, Vol. 43, pp. 5229-5236, 1987.
- [20] K. Yuichi, I. Atsushi, Y. Miho, T. Nobuo and I. Akiko, "Automatic superposition of drug molecules based on their common receptor site", *J. Comput. Aided Mol. Des.*, Vol. 6, pp. 475-486, 1992.
- [21] H. Mathew, "Receptor surface models. 1. Definition

- and construction", *J. Med. Chem.*, Vol. 38, pp. 2080-2090, 1995.
- [22] H. Mathew and R. David, "Receptor surface models. 2. Application to quantitative structure-activity relationship studies", *J. Med. Chem.*, Vol. 38, pp. 2091-2102, 1995.
- [23] H. Mathew and R. David, "3D QSAR in Drug Design: Recent Advances", pp.117- 133,1998.
- [24] N. P. Todorov and P. M. Dean, "Evaluation of a method for controlling molecular scaffolds diversity in de novo ligand design", *J. Comput. Aided Mol. Des.*, Vol. 11, pp. 175-192, 1997.
- [25] N. P. Todorov and P. M. Dean, "A branch and bound method for optimal atom-type assignment in de novo ligand design", *J. Comput. Aided Mol. Des.*, Vol. 12, pp. 335-350, 1998.
- [26] A. Vedani, P. Zbinden, J. P. Snyder and P. A. Greenidge, "Pseudo-receptor modeling: a new concept for the three-dimensional construction of receptor binding sites", *J. Recept. Res.*, Vol. 13, pp. 163-177, 1993.
- [27] A. Vedani, P. Zbinden, J. P. Snyder and P. A. Greenidge, "Pseudoreceptor modeling: the construction of three dimensional receptor surrogates", *J. Am. Chem. Soc.*, Vol. 117, pp. 4987-4994, 1995.
- [28] T. Yusuf, P. Ewgenij, W. Tim, G. Tim, T. Nickolay, K. Alexander, K. Tim, S. Kerstin, S. Erich, S. Roland, S. Holger, C. Timothy and S. Gisbert, "Homology Model Adjustment and Ligand Screening with a Pseudoreceptor of the Human Histamine H4 Receptor", *Chem. Med. Chem.*, Vol. 4, pp. 820-827, 2009.
- [29] P. H. Bauer, C. Cui, W. R. Liu, T. Stehle, S.C. Harrison, J. A. DeCaprio and T. L. Benjamin, "Discrimination between Sialic Acid-Containing Receptors and Pseudoreceptors Regulates Polyomavirus Spread in the Mouse", *J. Virol.*, Vol. 73, pp. 5826-5832, 1999.
- [30] M. Laura, M. Fabrizio, C. Federico and B. Maurizio, "3D QSAR studies for the β -tubulin binding site of microtubulestabilizing anticancer agents (MSAAs) A pseudoreceptor model for taxanes based on the experimental structure of tubulin", *IL Farmaco.*, Vol. 58, pp. 659-668, 2003.
- [31] C. M. R. de Sant'Anna, R. Bicca de Alencastro and E. J. Barreiro, "Toward a platelet-activating factor pseudoreceptor 2. Three-dimensional semiempirical models for agonist and antagonist binding", *J. Mol. Struct.: THEOCHEM*, Vol. 490, pp. 167-180, 1999.
- [32] C. H. Chae, S. E. Yoo and W. Shin, "Novel receptor surface approach for 3D-QSAR: The weighted probe interaction energy method", *J. Chem. Inf. Comput. Sci.*, Vol. 44, pp. 1774-1787, 2004.
- [33] A. J. Lu and J. J. Zhou, "Pseudoreceptor models and 3D-QSAR for imidazobenzodiazepines at GABA A/BzR subtypes R x 3 2 [x] 1-3, 5, and 6] via flexible atom receptor model", *J. Chem. Inf. Comput. Sci.*, Vol. 44, pp. 1130-1136, 2004.
- [34] T. Peng, J. Pei and J. Zhou, "3D-QSAR and receptor modeling of tyrosine kinase inhibitors with flexible atom receptor model (FLARM)", *J. Chem. Inf. Comput. Sci.*, Vol. 43, pp. 298-303, 2003.
- [35] S. Forli, F. Manetti, K. H. Altmann and M. Botta, "Evaluation of Novel Epothilone Analogues by means of a Common Pharmacophore and a QSAR Pseudoreceptor Model for Taxanes and Epothilones", *Chem. Med. Chem.*, Vol. 5, pp. 35-40, 2010.
- [36] Y. Zeng, M. Pinard, J. Jaime, L. Bourget, P. U. Le, M. D. O'Connor-McCourt, R. Gilbert and B. Massie, "A ligand-pseudoreceptor system based on de novo designed peptides for the generation of adenoviral vectors with altered tropism", *J. Gene. Med.*, Vol. 10, pp. 355-367, 2008.
- [37] D. G. Lloyd, C. L. Buenemann, N. P. Todorov, D. T. Manallack and P. M. Dean, "Scaffold hopping in de novo design. Ligand generation in the absence of receptor information", *J. Med. Chem.*, Vol. 47, pp. 493-496, 2004.
- [38] A. Bassoli, M. G. B. Drew, L. Merlini and G. Morini, "General pseudoreceptor model for sweet compounds: A semiquantitative prediction of binding affinity for sweet-tasting molecules", *J. Med. Chem.*, Vol. 45, pp. 4402-4409, 2002.
- [39] K. J. Schleifer, "Pseudoreceptor model for ryanodine derivatives at calcium release channels", *J. Comput-Aided Mol. Des.*, Vol. 14, pp. 467-475, 2000.
- [40] S. Schmetzer, P. Greenidge, K. A. Kovar, M. Schulze-Alexandru and G. Folkers, "Structure-activity relationships of cannabinoids: A joint CoMFA and pseudoreceptor modelling study", *J. Comput-Aided Mol. Des.*, Vol. 11, pp. 278-292, 1997.
- [41] M. K. Gilson, J. A. Given, B. L. Bush and J. A. McCammon, "The statistical-thermodynamic basis for computation of binding affinities: a critical review", *Biophys. J.*, Vol. 72, pp. 1047-1069, 1997.
- [42] C. E. Chang and M. K. Gilson, "Tork: conformational analysis method for molecules and complexes", *J. Comput. Chem.*, Vol. 24, pp. 1987-1998, 2003.
- [43] W. Chen, J. Huang and M. K. Gilson, "Identification of symmetries in molecules and complexes", *J. Chem. Inf. Comput. Sci.*, Vol. 44, pp. 1301-1313, 2004.

- [44] C. E. Chang, M. J. Potter and M. K. Gilson, "Calculation of molecular configuration integrals", *J. Phys. Chem. B*, Vol. 107, pp. 1048-1055, 2003.
- [45] D. E. Walters and R. M. Hinds, "Genetically evolved receptor models: A computational approach to construction of receptor models", *J. Med. Chem.*, Vol. 37, pp. 2527-2536, 1994.
- [46] H. Chen, J. Zhou and G. Xie, "PARM: a genetic evolved algorithm to predict bioactivity", *J. Chem. Inf. Comput. Sci.*, Vol. 38, pp. 243-250, 1998.