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Receptor Surface Model: A Milestone In Drug Discovery

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ABSTRACT

When the drug design target is a receptor for which there is no experimentally determined three dimensional structures, it is often useful to construct models of the receptor site. These models may take the form of graphical surfaces, grid points surrounding the legends, or model atoms and functional groups. A receptor surface model is a hypothetical model that characterizes the putative active site of a receptor. It is based on the construction of surfaces to represent spatial & electrostatic properties of receptor active site. A receptor surface model is visually intuitive and modifiable as the hypothesis is refind. It allows computations comparable to those that can be performed with traditional atomistic models.

KEYWORDS

Receptor;
Receptor model;
Quantitative structure activity relationship(QSAR);
Comparative molecular field(CoMFA);
Genetically evolved receptor;
Models(GERM).

INTRODUCTION

In drug discovery, it is common to have measured activity data for a set of compounds acting upon a particular protein active site. In the absence of such three-dimensional structure, one can attempt to build a hypothetical model of receptor site that can provide insight about receptor site characteristics. Receptor structures can be used to understand structure activity relationships, to make predictions about likely activities of analogs before their synthesis, and even to design completely novel ligands.

In the absence of direct knowledge of the receptor site, the creation of receptor site models relies on the assumption of an underlying complete entirety between the shape and properties of receptor & the compounds that bind.

An important issue in constructing receptor models is whether to use a very few active structures as templates hoping to capture the most important structural requirements for bioactivity, or whether to use ligand with a range of bioactivities, hoping to identify features which discriminate between active and inactive compounds.

Types of receptor model

(1) Surface models.
(2) Grid-based models.
(3) Atom-based and amino-acid-based models.

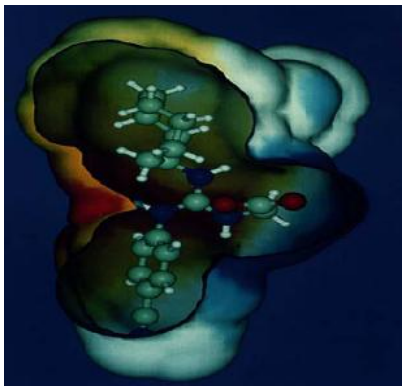
1. Surface models

One of the simplest approaches to receptor model constructions is to superimpose a series of active compounds and then to construct a vander walls surface over the set. Such a surface can visually convey stearic requirements of receptor binding

site. With computer graphics, it is possible to map properties such as electrostatic potential on to this surface, to provide some information about the electronic properties of active analogs.

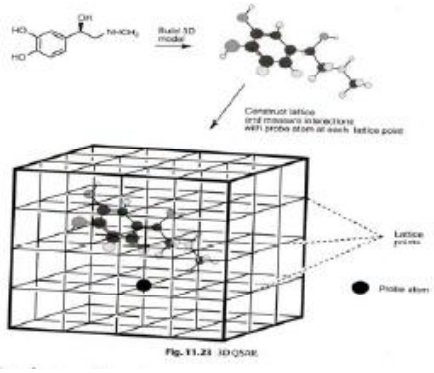
This approach was used in building a receptor model for high potency sweaters. The starting point was a set of five structurally diverse sweet-tasting com pounds which are believed to act at a common receptor site because they share a number of common structural features. Low energy conformers of these compounds are superimposed in a such a way as to get optimal overlap of the carboxylate group, one or two polar N-H groups and a hydrophobic group. A van der walls surface was constructed over the superimposed structures and a composite electrostatic potential from the five compounds was mapped on to the surface.

Recently Hahn has reported a program which interactively constructs receptor surface models. Both closed surfaces and partially open surfaces can be generated. Properties such as electrostatic potential, hydrogen bonding potential and hydrophobosity are readily mapped on the surface models using colour coding. This feature should be most useful in designing and evaluating new analogs.



2. Grid-based models

Another way to construct a model around a series of superimposed analogs is to place the structures in three-dimensional grid and to look at those grid points near the surface of the ligand set. This is the starting point for Comparative Molecular Field Analysis (CoMFA) approach developed by cramer. Field properties are calculated with respect to the ligands at each of the grid points. Quantitative Structure Activity



Relationship (QSAR) methods such as principal component analysis and partial least squares are used to carry out a statistical analysis of the relationship between field interaction energies & bioactivity.

3. Atom-based and amino acid-based models

In addition to surfaces and grid, receptor models can be made by placing atoms or groups of atoms (such as amino acid side chains) around a set of active ligands. Holtje and Anzali constructed a tripeptide model of the receptor for cardiac glycosides such as digitalis

An interactive program called Yak has been developed for the construction of receptor models.

Generation of receptor surface models

Receptor surface models are different from pharmacophore models, which postulates a 3-D arrangement of atoms recognizable by the active site in terms of similarity of functional groups common to the set of binding molecules. In contrast receptor models do not contain atoms but try to directly represent the essential features of an active site by assuming complementarily between the shape and properties of the receptor site and the set of binding compounds.

The surface is generated from shape field .The atomic co-ordinates of the contributing models are used to compute field values on each point of 3-D grid. The two functions used to calculate the field values are a van der walls function and Wyvill soft function.

Van der walls function calculated by following equation.

V(r)=r-VDWr

Where r=distance from atomic coordinate to the grid point VDWr=Van der walls radius of the atoms

The Wyvill soft function calculated by following equation.

$$V(r)=4r^2/9R^6+17r^4/9R^4-22r^2/9r^2+1$$

The Wyvill soft function is also a function of r but it is bounded and decays completely within the distance R, that is V(r)=0,R is set to be twice the van der walls radious of each atom type.

The Wyvill shape function gives smoother surfaces, whereas the van der walls function produces a molecule shaped surface.

4. Methods for generation of receptor surface models

(1) You must have one or more aligned structures displayed in the model window.If you have a large set of active compounds,it is probably best to use a subset of active compounds,to build your receptor surface model.

(2) Now you can display the properties stored at each vertex,

(3) You can generate the structures to align and use in creating receptor surface model through one of several methods.

- Build one or more structures using 3D sketure or a Builder.
- Use the Analog Builder to generate a series of analogous structures.
- Import previously built structures using the Load Model control panel.

(4) when you generate a receptor model ,the receptor model that you see in the model window is a semi-tranceparent surface that surrounds the template structures. The molecules within the receptors are visible and can be edited ,tranceformed or otherwise manipulated using standard tools.

5. Saving and restoring receptor models

Receptor models can be saved and reloaded at a later time for future work with same or different structures.

6. Listing of receptor model

Listed data forms column such as

Surface point	Coordinates X Y Z	Mol charge atom	esp	h-bond	hydrophobicity

7. Mapping property values

This section describe the properties of the receptor surface that can be mapped .One property can be mapped at a time .Property maps are displayed as colour regions of the receptor surface .These properties reflect the anticipated characteristics of the receptor that is being modeled. Properties that can be mapped include electrostatic potential, hydrogen bonding, hydrophobicity.

Future prospects

We now have various methods, newly developed or being developed, which may allows us to realize the goal behind the construction of receptor surface model. The increasing volume of the innovation. Basic research to solve various difficult problems that still remain, such as handling protein structures or predicting binding constants for putative ligands, will become more and more important.

A number of methods for constructing receptor site model have been described.

(1) HASL[Hypothetical active site lattice]

This approach represents the molecules inside an active site as a collection of grid points.

(2) Receps

This program was developed for the purpose of superposing molecules with dissimilar structures which can bind to the same target receptor competitively and constructing a 3-D receptor cavity model.

(3) CoMFA[Comparative molecular field analysis]

These models are effectively receptor surface models that represents the 3-D field properties around a set of superimposed molecules as a set of grid-based probe interaction energies.

(4) GERM[Genetically evolved receptor models]

The objective of this method is to produce atomic level models of receptor sites based on trial set of ligands. Receptor models are made by placing atoms at points in space in which they can stimulate receptor surface and interact with ligands.

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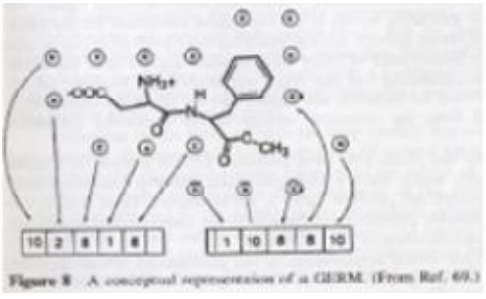
Softwares

SYBL, MOPAC, SILICON GRAPHICS, MM2, CORDANO, DRAGON, CACHEE, Cerius[2].

APPLICATIONS

- The information generated from 3-D hypothetical receptor models built around template molecules has been used to produce highly predictive QSAR models.
- The receptor surface models generated using high resolution computers graphics are visually intuitive and can be used for activity prediction of new candidate structures.
- A receptor surface model is non atomistic model that uses explicit surfaces to characterize the shape of active site.
- Receptor surface models used for surface analysis of some anti-inflammatory benzimidazole derivatives.
- Receptor surface models used quantitatively in QSAR studies of corticosteroids binding & dopamine beta-hydroxylase inhibition.
- GERM :- These models used to produce predictive models for a high potency sweetner receptor. These models work for a very diverse set of structures (peptides, ureas, guanidines, amio acids)



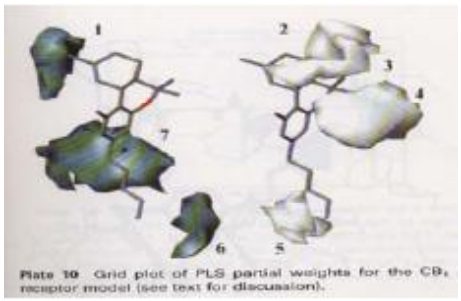


Plate 10 Grid plot of PLS partial weights for the CB_1 receptor model (see text for discussion).

- Receptor surface models are simple to understand.
- Three dimentional structure of cannabinoid receptor is still unknown and its knowledge is available on the nature of ligand-receptor interactions with the help of receptor model.

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