COMPUTER AIDED DRUG DESIGN

31. 3D QSAR

Mukesh Doble
Professor
DEPARTMENT OF BIOTECHNOLOGY
IIT MADRAS

Structure draw:	http://chemagic.com/JSmolVMK2.htm
Zinc:	http://zinc.docking.org/
DrugBank	https://www.drugbank.ca/
Drugs.com	https://www.drugs.com/drug_information.html
sketch:	http://www.chemaxon.com/marvin/sketch/index.php
Dragon:	http://www.vcclab.org/lab/edragon/
SWISS ADME	http://www.swissadme.ch/index.php
ChemDes	http://www.scbdd.com/chemdes/
Ochem	https://ochem.eu/home/show.do
BuildQSAR	http://www.profanderson.net/files/buildqsar.php
MOPAC	http://openmopac.net/Download_MOPAC_Executable_Step2.html
Jmol	http://jmol.sourceforge.net/

http://www.vls3d.com/index.php/links/chemoinformatics/qsar

3D-QSAR analysis of the quantitative relationship between the biological activity of a set of compounds and their three-dimensional properties

1. Molecular shape analysis (MSA)

common overlap steric volume and potential energy fields between pairs of superimposed molecules correlated to the activity of series of compounds. The MSA using common volumes also provide some insight regarding the receptor-binding site shape and size.

2. Molecular topological difference (MTD)

the minimal steric (topologic) difference approach. Minimal topological difference use a 'hypermolecule' concept for molecular alignment which correlate vertices (atoms) in the hypermolecule (a superposed set of molecules having common vertices) to activity differences in the series

3. Comparative molecular movement analysis (COMMA) COMMA

3D information contained in the movement descriptors of molecular mass and charge up to and inclusive of second order

4. Self Organizing Molecular Field Analysis (SOMFA) SOMFA

dividing the molecule set into actives (+) and inactives (-), and a grid probe process that penetrates the overlaid molecules, the resulting steric and electrostatic potentials are mapped onto the grid points and are correlated with activity using linear regression

5. Comparative Molecular Field Analysis (COMFA)

a grid based technique, most widely used tools for 3D QSAR was introduced in 1988, based on the assumption that drug-receptor interactions are noncovalent, the changes in biological activities or binding affinities of sample compound correlate with changes in the steric and electrostatic fields of these molecules. These field values are correlated with biological activities by partial least square (PLS) analysis.

http://shodhganga.inflibnet.ac.in/bitstream/10603/27948/14/14_chapter8.pdf

QSAR and 3D-QSAR Software

- Tripos – CoMFA, VolSurf
- MSI – Catalyst, Serius

3D molecular fields

- A molecular field may be represented by 3D grid.
- Each voxel represents attractive and repulsive forces between a probe molecule and a target molecule.
- An interacting partner can be water, octanol or other solvents.

CoMFA 3D-QSAR

- Each grid voxel corresponds to two variables in QSAR equation: steric & electrostatic.
- The PLS technique is applied to compute the coefficients.
- Physical properties are measured for the molecule as a whole
- Properties are calculated using computer software
- No experimental constants or measurements are involved
- Properties are known as 'Fields'
- Steric field - defines the size and shape of the molecule
- Electrostatic field - defines electron rich/poor regions of molecule
- Hydrophobic properties are relatively unimportant

CoMFA molecular fields

- A grid with energy fields is calculated by placing a probe atom at each voxel.
- The molecular fields are:
  - Steric (Lennard-Jones) interactions
  - Electrostatic (Coulombic) interactions
- A probe is sp^3 carbon atom with charge of +1.0

www.clayton.edu/portals/417/.../a.../Ch%2018%20QSAR%20and%203D-

3D-QSAR

Advantages

- No reliance on experimental values
- Can be applied to molecules with unusual substituents
- Not restricted to molecules of the same structural class
- Predictive capability

Problems:

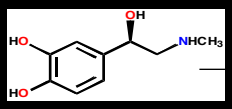
- Superposition: the molecules must be optimally aligned.
- Flexibility of the molecules.

3D-QSAR

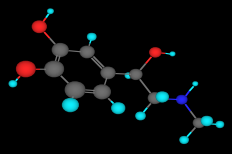
Method

www.clayton.edu/portals/417/.../a.../Ch%2018%20QSAR%20and%203D-QSAR.ppt

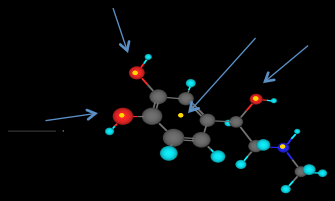
- Comparative molecular field analysis (CoMFA)
- Build each molecule
- Identify the active conformation for each molecule
- Identify the pharmacophore



3D model



Active conformation

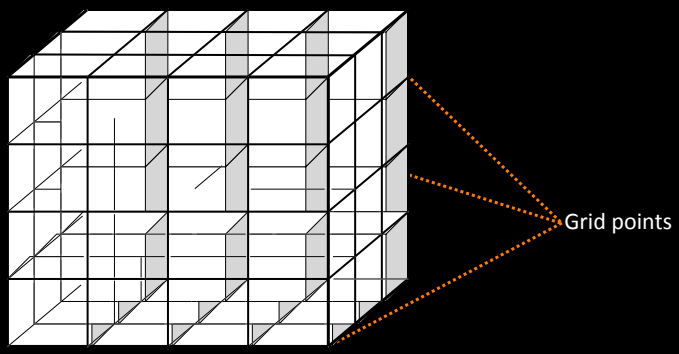


identify pharmacophore

3D-QSAR

Method

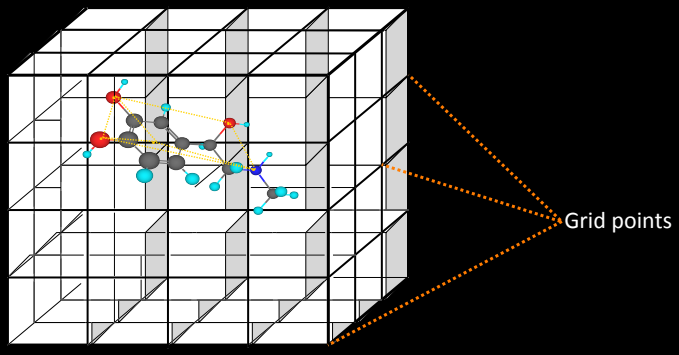
- Place the pharmacophore into a lattice of grid points



- Each grid point defines a point in space

3D-QSAR
Method

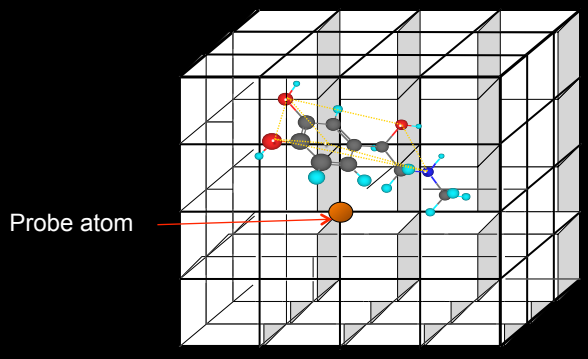
- Position molecule to match the pharmacophore



- Each grid point defines a point in space

3D-QSAR
Method

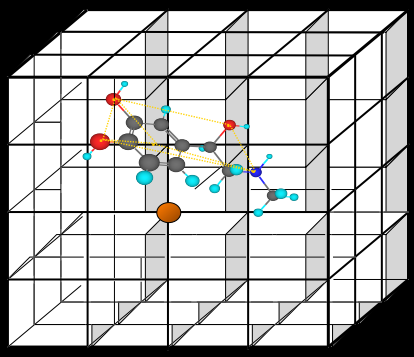
- A probe atom is placed at each grid point in turn



- Probe atom = a proton or sp^3 hybridised carbocation

3D-QSAR
Method

•A probe atom is placed at each grid point in turn



•Measure the steric or electrostatic interaction of the probe atom with the molecule at each grid point

3D-QSAR
Method

•The closer the probe atom to the molecule, the higher the steric energy
•Define the shape of the molecule by identifying grid points of equal steric energy (contour line)
•Favorable electrostatic interactions with the positively charged probe indicate molecular regions which are negative in nature
•Unfavorable electrostatic interactions with the positively charged probe indicate molecular regions which are positive in nature
•Define electrostatic fields by identifying grid points of equal energy (contour line)
•Repeat the procedure for each molecule in turn
•Compare the fields of each molecule with their biological activity
•Identify steric and electrostatic fields which are favorable or unfavorable for activity

3D-QSAR

Method

Tabulate fields for each compound at each grid point

Compound	Biological activity	Steric fields (S) at grid points (001-998)					Electrostatic fields (E) at grid points (001-098)				
		S001	S002	S003	S004	S005 etc	E001	E002	E003	E004	E005 etc
1	5.1										
2	6.8										
3	5.3										
4	6.4										
5	6.1										

Partial least squares analysis (PLS)

QSAR equation Activity = aS001 + bS002 +……..mS998 + nE001 +…….+yE998 + z

http://www.3d-qsar.com/
3D-QSAR.com

http://www.3d-qsar.com/pymoledit/user/mukeshd