

3D-Pharmacophore Based VIRTUAL SCREENING IN DRUG DISCOVERY



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3D based similarity

- Shape-based ROCS (Rapid Overlay of Chemical Structures) Silicos-it.com (Shape it)
- Computationally more expensive than 2D methods
- Requires consideration of conformational flexibility
 - -Rigid search based on a single conformer
 - -Flexible search
 - Conformation explored at search time
 - Ensemble of conformers generated prior to search time with each conformer of each molecule considered in turn
 - How many conformers are required?

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Multiple actives known: pharmacophore searching

 IUPAC Definition: "An ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response"



In drug design, the term 'pharmacophore' refers to a set of features that is common to a series of active molecules
Hydrogen-bond donors and acceptors, positively and negatively charged groups, and hydrophobic regions are typical features

We will refer to such features as 'pharmacophoric groups'



3D-Pharmacophores

- A three-dimensional pharmacophore specifies the spatial relation-ships between the groups
- Expressed as distance ranges, angles and planes





Workflow of Pharmacophore modeling



Selected Pharmacophore model

Many Actives and Inactives known : Machine learning methods

SAR Modeling

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- Use knowledge of known active and known inactive compounds to build a predictive model
- Quantitative-Structure Activity Relationships (QSARs)
 - Long established (Hansch analysis, Free-Wilson analysis)
 - Generally restricted to small, homogeneous datasets eg lead optimization.
- Structure-Activity Relationships (SARs)
 - "Activity" data is usually treated qualitatively
 - Can be used with data consisting of diverse structural classes and multiple binding modes
 - Some resistance to noisy data (HTS data)
 - Resulting models used to prioritize compounds for lead finding (not to identify candidates or drugs)



Protein Ligand Docking



Computational method which mimics the binding of a ligand to a protein.

It predicts ..

a) the **pose** of the molecule in the binding site

b)The binding affinity or score representing the strength of binding



Pose and Binding Site

- Binding Site (or "active site")
- the part of the protein where the ligand binds .
- generally a cavity on the protein surface.
- can be identified by looking at the crystal structure of the protein bund with a known inhibitor.

- Pose ("binding mode")
- the geometry of the ligand in the binding site
- Geometry- location , orientation and conformation of the molecule



Protein Ligand Docking

- How does a ligand (small molecule) bind into the active site of a protein?
- Docking algorithms are based on two key components
 - search algorithm
 - to generate "poses" (conformation, position and orientation) of the ligand within the active site
 - scoring function
 - to identify the most likely pose for an individual ligand
 - to assign a priority order to a set of diverse ligands docked to the same protein – estimate binding affinity



The search space

- The difficulty with protein–ligand docking is in part due to the fact that it involves many degrees of freedom
 - The translation and rotation of one molecule relative to another involves six degrees of freedom
 - These are in addition the conformational degrees of freedom of both the ligand and the protein
 - The solvent may also play a significant role in determining the protein–ligand geometry (often ignored though)
- The search algorithm generates poses, orientations of particular conformations of the molecule in the binding site
 - Tries to cover the search space, if not exhaustively, then as extensively as possible
 - There is a tradeoff between time and search space coverage



Dock Algorithms

- DOCK: first docking program by Kuntz et al. 1982
- Based on shape complementarity and rigid ligands
- Current algorithms
 - Fragment-based methods: FlexX, DOCK (since version 4.0)
 - Monte Carlo/Simulated annealing: QXP(Flo), Autodock, Affinity &

LigandFit (Accelrys)

- Genetic algorithms: GOLD, AutoDock (since version 3.0)
- Systematic search: FRED (OpenEye), Glide (Schrödinger)



DOCK (Kuntz et al. 1982)

- Rigid docking based on shape
- A negative image of the cavity is constructed by filling it with spheres
- Spheres are of varying size
- Each touches the surface at two points
- The centres of the spheres become potential locations for ligand atoms.





DOCK

- Ligand atoms are matched to sphere centers so that distances between atoms equals distances between sphere centers.
- The matches are used to position the ligand within the active site.
- If there are no steric clashes the ligand is scored.
- Many different mappings (poses) are possible
- Each pose is scored based on goodness of fit
- Highest scoring pose is presented to the user







Energetics of protein-ligand binding

a) Ligand-receptor binding is driven by

electrostatics (including hydrogen bonding interactions)

- dispersion or van der Waals forces
- hydrophobic interactions

 desolvation: surfaces buried between the protein and the ligand have to be desolvated

Conformational changes to protein and ligand

 ligand must be properly orientated and translated to interact and form a complex

loss of entropy of the ligand due to being fixed in one conformation.
b) Free energy of binding

$$\Delta G_{bind} = \Delta G_{solvent} + \Delta G_{conf} + \Delta G_{int} + \Delta G_{rot} + \Delta G_{t/r} + \Delta G_{vib}$$



Conclusions

- Wide range of virtual screening techniques have been developed
- The performance of different methods varies on different datasets
- Increased complexity in descriptors and method does not necessarily lead to greater success.
- Combining different approaches can lead to improved results.
- Computational filters should be applied to remove undesirable compounds from further consideration.



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THANK YOU