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Pharmacophore modeling using Discovery Studio



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Use of Pharmacophore model in drug discovery

Ligand-based pharmacophore modeling

- Ligand-based pharmacophore modeling has become a key computational strategy for facilitating drug discovery in the absence of a macromolecular target structure.
- It is usually carried out by extracting common chemical features from 3D structures of a set of known ligands representative of essential interactions between the ligands and a specific macromolecular target.
- In general, pharmacophore generation from multiple ligands (usually called training set compounds) involves two main steps: The first approach has the advantage of lower computing cost for conducting molecular alignment at the expense of a possible need for a mass storage capacity. The second approach does not need mass storage but might need higher CPU time for conducting rigorous optimization.



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Structure-based pharmacophore modeling

- Structure-based pharmacophore modeling works directly with the 3D structure of a macromolecular target or a macromolecule– ligand complex. The protocol of structure-based pharmacophore modeling involves an analysis of the complementary chemical features of the active site and their spatial relationships, and a subsequent pharmacophore model assembly with selected features.
- The structure-based pharmacophore modeling methods can be further classified into two subcategories: macromolecule– ligand-complex based and macromolecule (without ligand)-based.



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Pharmacophore-model-based virtual screening

- Once a pharmacophore model is generated by either the ligand-based or the structure-based approach, it can be used for querying the 3D chemical database to search for potential ligands, which is so-called 'pharmacophore-based virtual screening' (VS). Pharmacophore-based VS and docking-based VS represent the mainstream of VS tools at the present time.
- In contrast to its counterpart, the docking-based VS method, pharmacophore-based VS reduces the problems arising from inadequate consideration of protein flexibility or the use of insufficiently designed or optimized scoring functions by introducing a tolerance radius for each pharmacophoric feature. In the pharmacophore-based VS approach, a pharmacophore hypothesis is taken as a template.
- The purpose of screening is actually to find such molecules (hits) that have chemical features similar to those of the template.



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Pharmacophore-based de novo design

- Besides the pharmacophore-based VS described above, another application of pharmacophore is de novo design of ligands. The compounds obtained from pharmacophore-based VS are usually existing chemicals, which might be patent protected.
- In contrast to pharmacophore-based VS, the de novo design approach can be used to create completely novel candidate structures that conform to the requirements of a given pharmacophore.
- The first pharmacophore-based de novo design program is NEWLEAD, which uses as input a set of disconnected molecular fragments that are consistent with a pharmacophore model, and the selected sets of disconnected pharmacophore fragments are subsequently connected by using linkers (such as atoms, chains or ring moieties).



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- Actually, NEWLEAD can only handle the cases in which the pharmacophore features are concrete functional groups (not abstract chemical features).
- Other shortcomings of the NEWLEAD program include that the sterically forbidden region of the binding site is not considered and that, as in traditional de novo design programs, the compounds created by the NEWLEAD program might be difficult to chemically synthesize. Other programs such as LUDI4 and BUILDER can also be used to combine identification of structure-based pharmacophore with de novo design.
- They, however, need the knowledge of 3D structures of the macromolecular targets.



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- To overcome drawbacks of the current pharmacophore-based de novo design software, we have developed a new program, PhDD (a pharmacophore-based de novo design method of drug-like molecules). PhDD can automatically generate drug-like molecules that satisfy the requirements of an input pharmacophore hypothesis.
- The pharmacophore used in PhDD can be composed of a set of abstract chemical features and excluded volumes that are the sterically forbidden region of the binding site. PhDD first generates a set of new molecules that completely conform to the requirements of the given pharmacophore model.
- Then a series of assessments to the generated molecules are carried out, including assessments of drug-likeness, bioactivity and synthetic accessibility. PhDD was tested on three typical examples: pharmacophore hypotheses of histone deacetylase, CDK2 and HIV-1 integrase inhibitors.



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- The test results showed that PhDD was able to generate molecules with completely novel scaffolds. A similarity analysis with the use of Tanimoto coefficients demonstrated that the generated molecules should have similar biological functions to the existing inhibitors, although they are structurally different.