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Virtual screening using Pharmacophore model in Discovery Studio

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Pharmacophore-model-based virtual screening:-

- Once a pharmacophore model is generated by either the ligandbased 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.

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- 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.
- Some of these hits might be similar to known active compounds, but some others might be entirely novel in scaffold.
- The searching for compounds with different scaffolds, while sharing a biological activity is usually called 'scaffold hopping'.
- The screening process involves two key techniques and difficulties: handling the conformational flexibility of small molecules and pharmacophore pattern identification.

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- The strategies for handling the flexibility of small molecules in pharmacophore-based VS are very similar to those used in pharmacophore modeling.
- Again, the flexibility of small molecules is handled by either pre-enumerating multiple conformations for each molecule in the database or conformational sampling at search time. Pharmacophore pattern identification, usually called ‘substructure searching’, is actually to check whether a query pharmacophore is present in a given conformer of a molecule.
- The frequently used approaches for substructure searching are based on graph theory, which include Ullmann, the backtracking algorithm, and the GMA algorithm.

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- Pharmacophore-based VS can be very time-consuming, especially in cases of screening large chemical databases with flexible molecules, which is currently a key challenge in pharmacophorebased VS.
- A commonly used method to speed up the screening process is the multilevel searching approach. In this approach, a series of screening filters are applied to the molecules in an increasing order of complexity so that the first filters are fast and simple, whereas successive ones are more time-consuming but are applied only to a small subset of the entire database.
- However, the most challenging problem for pharmacophorebased VS is that in many cases, few percentages of the virtual hits are really bioactive; in other words, the screening results bear a higher 'false positive' rate and/or a higher 'false negative' rate. Many factors can contribute to this problem, including the quality and composition of the pharmacophore model and whether and how much the macromolecular target information is involved.

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- First, the most apparent factor is associated with the deficiency of a pharmacophore hypothesis. To address this problem requires a comprehensive validation and optimization to the pharmacophore model. Various validation methods such as cross-validation and test set method have been suggested, which were reviewed recently by Triballeau et al.. The validation process is usually associated with model optimization.
- Lately, Sun et al. have developed a genetic algorithm-guided pharmacophore query optimization program, in which the optimization is carried out by automatically adjusting the position and tolerance radius of each pharmacophoric feature. The final query has been validated by using a test set method, which shows a considerably improved hit rate. Second, because the pharmacophore model used for 3D query is generally one of the subgraphs of the full pharmacophore map, screening with this pharmacophore query might not retrieve molecules that match other subgraphs except for the selected one, which is probably an important reason for the higher false negative rate in some studies.

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- Third, the flexibility of target macromolecule in pharmacophore approaches is handled by introducing a tolerance radius for each pharmacophoric feature, which is unlikely to fully account for macromolecular flexibility in some cases. Some recent attempts to incorporate molecular dynamics simulations in pharmacophore modeling have suggested that the dynamics pharmacophore models generated from MD simulation trajectories show considerably better representation of the flexibility of pharmacophore.
- Another factor that might lead to the high false positive rate is that the steric restriction by the macromolecular target is not sufficiently considered in pharmacophore models, although it is partly counted for by the consideration of excluded volumes.

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- In addition, most of the interactions between ligand and protein are distance sensitive – particularly the short-range interactions, such as the electrostatic interaction, for which a pharmacophore model is difficult to account for.
- An efficient approach is the synergistic combination of pharmacophore-based VS and docking-based VS. Because inherent limitations of each of these screening techniques are not easily resolved, their combination in a hybrid protocol can help to mutually compensate for these limitations and capitalize on their mutual strengths. Various combined virtual screening strategies and their validity have been well reviewed by Talevi et al. , Kirchmair et al. and Muegge.
- This approach has also been routinely used in our group, with which we have successfully obtained several real hits validated experimentally for inhibition against protein kinases Aurora-A, Syk and ALK5.