PHARMACOPHORE MODELLING: IN NOVEL DRUG DISCOVERY

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Abstract:

Computer-Aided drug discovery techniques reduce the time and the costs needed to develop novel drugs discovery. Pharmacophore approaches represent one of the most interesting tools developed, by defining the molecular functional features needed for the binding of a molecule to a given receptor, and then directing the virtual screening of large collections of compounds for the selection of optimal candidates. Computational tools to create the pharmacophore model and to perform virtual screening are available and generated successful studies.

Keywords: Structure-based pharmacophore modeling; Ligand-based pharmacophore modeling; Virtual screening; Drug discovery; Bioinformatics; Computational biology.

Introduction:

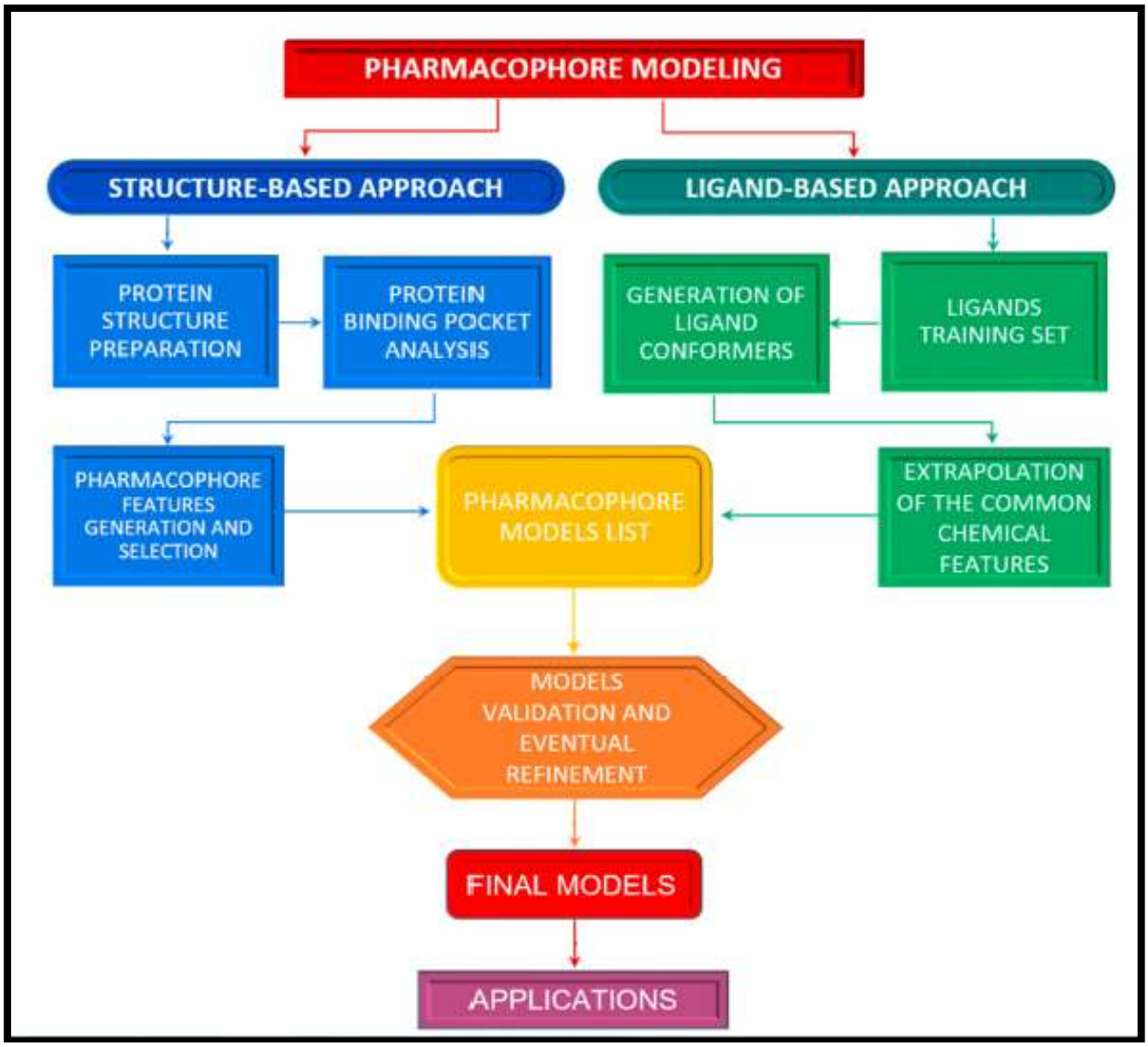
Computer-Aided Drug Discovery (CADD) investigates molecular properties to develop novel therapeutic solutions by way of computational tools and data resources. In its broadest meaning, it includes computational approaches for designing or selecting compounds as potential candidates before they are synthesized and tested for their biological activity.

Bioinformatics and computational tools offer an in silico approach to reducing costs and times, i.e., the factors that influence the progress of the research and, in the specific field of drug development, limit the possibilities of fighting more pathologies. To date, in vitro screening is expensive and time-consuming, and alternatives are highly desirable. Virtual Screening (VS) is a CADD method that involves in silico screening of a library of chemical compounds, to identify those that are most likely to bind to a specific target.

In this way, it is possible to reduce the impact of these limiting factors on drug discovery, meeting the needs due to health emergencies, as well as the spread of personalized medicine. This process can be speeded up using pharmacophore models used as the query with which compound libraries can be searched to pull out molecules of interest with desired properties. Indeed, pharmacophore-based methods are widely used tools in CADD and are of great interest in the chemo-informatics field , since they find many applications in drug discovery projects including not only the virtual screening but also scaffold hopping, lead optimization, ligand profiling, target identification, multi-target drug or de novo drug design.

Pharmacophore modelling divided into two types.

1. Structure based approach
2. Ligand based approach



Pharmacophore models can be generated using two different approaches depending on the input data employed for model construction, :

1. “structure-based” pharmacophore modelling.
2. “ligand-based” pharmacophore modelling.

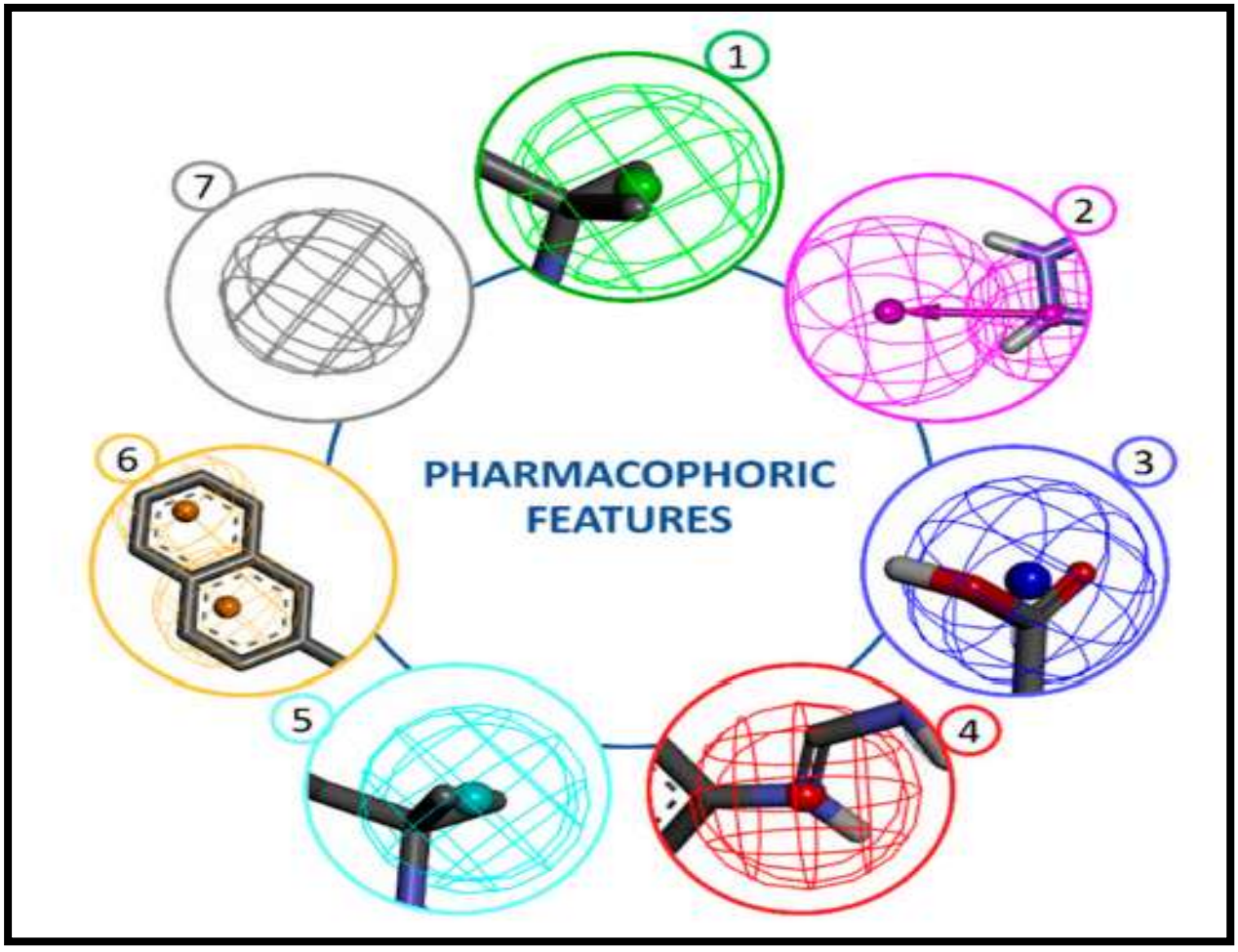
1. “structure-based” pharmacophore modelling :

The structure-based approach uses the structural information of the target proteins like enzymes or receptors, to identify compounds that can potentially be used as a drug.

2. "ligand-based" pharmacophore modelling :

The ligand-based approach consists of the development of 3D pharmacophore models and modelling quantitative structure-activity relationship (QSAR) or quantitative structure-property relationship (QSPR), using only the physicochemical properties of known ligand molecules for drug Development.

The choice of the best approach to use depends on several factors such as data availability, data quality, computational resources and also the intended use of the generated pharmacophore models. In the following paragraphs, we describe both strategies and their implementation in virtual screening is provided below to guide the nonexperts on this topic in their application by explaining the basic concepts these methods are based on.

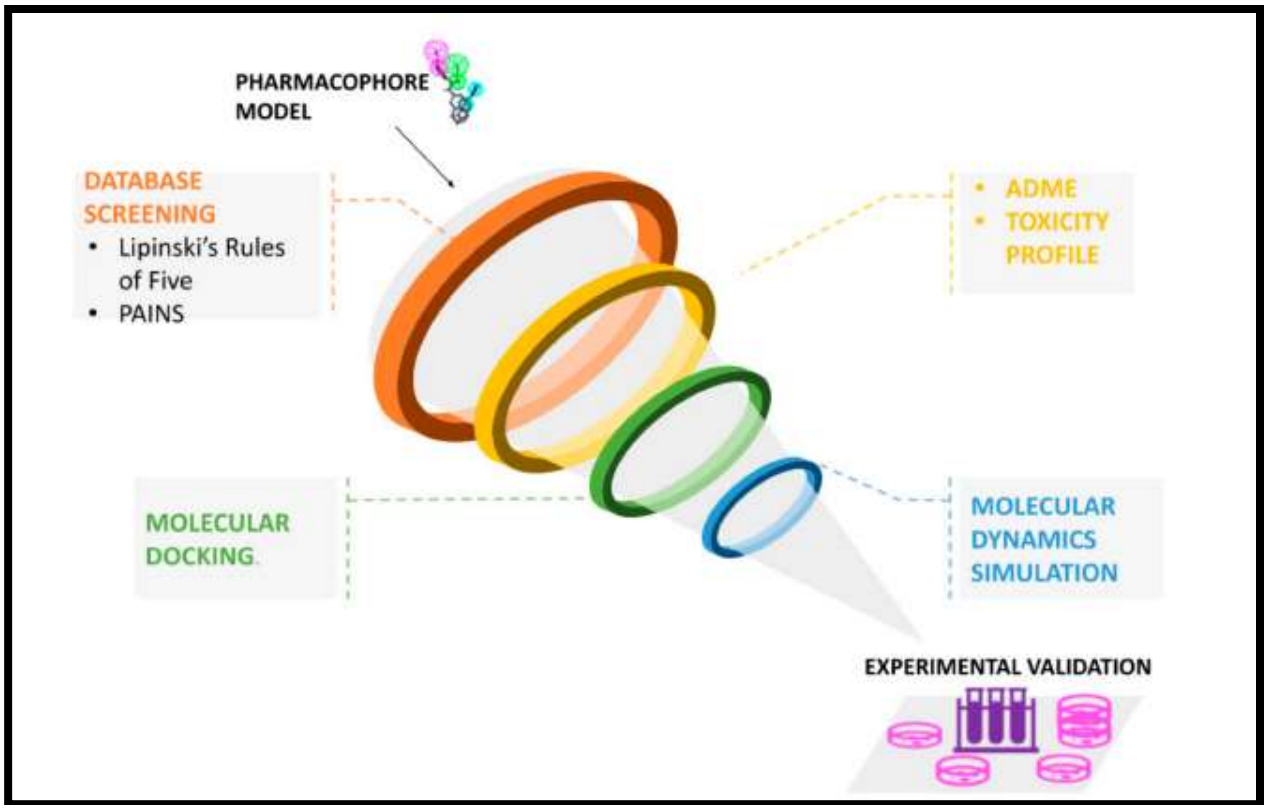


Pharmacophore Numbers	Pharmacophoric Features
1	Hydrogen Bond Acceptor (HBA)
2	Hydrogen Bond Donor (HBD)
3	Negative Ionizable (NI)
4	Positive Ionizable (PI)
5	Hydrophobic (H)
6	Aromatic (AR)
7	Exclusion Volume (XVOL)

Pharmacophore-Based Virtual Screening:

Among the strategies for the identification of new bioactive substances, VS techniques play a prominent role. VS tools are important in drug discovery as they increase the speed of the bioactive molecule discovery process through computational simulations by selecting from large libraries the compounds that are most likely to interact with the identified target. In addition, VS identifies compounds that may be toxic or have unfavorable Pharmacodynamic (for example, potency, affinity, selectivity) and pharmacokinetic (for example, absorption, metabolism, and bioavailability) properties.

Pharmacophore models can be successfully applied to filter large collections of compounds to find the so-called hits, i.e., novel molecules matching the Pharmacophoric features required to be potentially active against a specific target. Since a pharmacophore does not represent exact chemical groups but chemical functionalities and their spatial relationships, the retrieved hits usually include structurally different compounds, making pharmacophore useful tools for scaffold hopping.



The first step in virtual screening is to consult a database that contains a large number of compounds annotated with information about the 3D structure, known target, and in some cases the purchasability. Some of the free databases include the Protein Data Bank (PDB), PubChem, ChEMBL, Zinc, and Drugbank. Moreover, there are some commercially available databases such as the MDL Drug Data Report. Usually, due to the presence of a multitude of compounds in these repositories, the strategy adopted by many researchers is to filter the data by applying different parameters to reduce the computational cost of the pharmacophore searching. This may be obtained through the exclusion of compounds that are too big for the ligand pocket, the use of Lipinski's Rule of Five or standard metrics for lead-likeness, and removing compounds deemed to be pan-assay interference compounds (PAINS) In addition, a combination of filtering for desired pharmacological and adsorption, distribution, metabolism, excretion, and toxicological (ADMET) properties is advisable to be applied early in the virtual

screening process. These filters should be considered suggestions, not mandatory, and they can be applied depending on the specific case. As an example, the Rule of Five is not an absolute rule, as many drugs go under the “beyond the rule of five”.

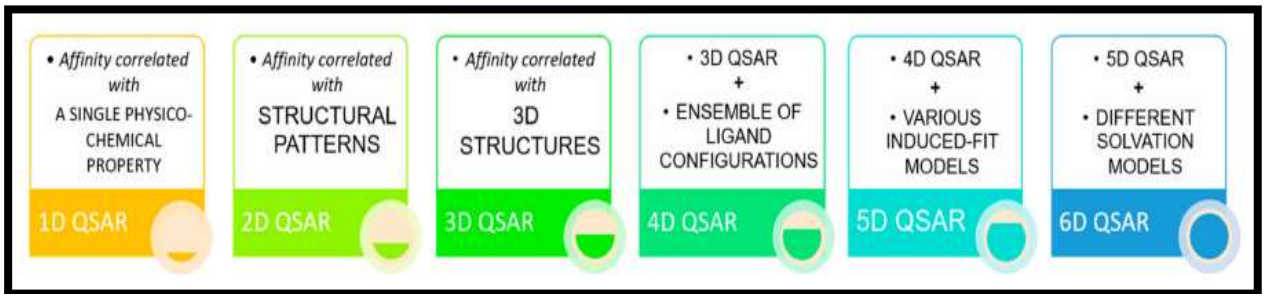


Figure- QSAR Classification

Sr.No	QSAR	Parameters
1	1D-QSAR	Single physico-chemical property of the ligand
2	2D-QSAR	Affinity is correlated with structural patterns
3	3D-QSAR	3D structure of the ligand and its interactions
4	4D-QSAR	ensemble of ligand configurations in 3D-QSAR
5	5D-QSAR	Induced-fit models
6	6D-QSAR	Different Solvation Models

Conclusion:

Pharmacophore modelling is a very useful tool for many applications in Drug discovery or drug design. However, despite its strength, this method is not free of limitations that have implications in virtual screening increasing the rate of false positives and/or false negatives, and that should be in mind to find proper solutions, when possible, and to have a critical view of the results.

Future Perspectives:

CADD approaches have been successfully developed to improve the ability to discover new drugs. The increasing computational power of hardware opens the perspective of many more applications, also by increasing the availability of protein target structures through deep learning and AI-based prediction tools. The deep learning approaches have been also recently applied to drug-target interaction. However, the experimental steps needed to validate the compound activity and safety remains time-consuming and will always slow down the whole drug discovery process. From this point of view, the pharmacophore Modelling followed by the virtual screening of databases of approved drugs, in the drug repurposing perspective, represents the most advanced rational approach, and the most promising way to find novel therapies.

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