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A REVIEW ON PHARMACOPHORE MODELLING

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ABSTRACT

Computational methods are well-established tools in the drug discovery process and can be employed for a variety of tasks. Common applications include lead identification and scaffold hopping, as well as lead optimization by structure-activity relationship analysis and selectivity profiling. In addition, compound-target interactions associated with potentially harmful effects can be identified and investigated. This review focuses on pharmacophore-based virtual screening campaigns specifically addressing the target class of hydroxysteroid dehydrogenases. Many members of this enzyme family are associated with specific pathological conditions, and pharmacological modulation of their activity may represent promising therapeutic strategies. On the other hand, unintended interference with their biological functions, e.g., upon inhibition by xenobiotics, can disrupt steroid hormone-mediated effects, thereby contributing to the development and progression of major diseases. Besides a general introduction to pharmacophore modelling and pharmacophore-based virtual screening, exemplary case studies from the field of short-chain dehydrogenase/reductase (SDR) research are presented. These success stories highlight the suitability of pharmacophore modelling for the various application fields and suggest its application also in futures studies.

Keywords: Structure-Based Pharmacophore Modelling, Ligand-Based Pharmacophore Modelling, Virtual Screening, Drug Discovery, Bioinformatics, Computational Biology.

I. 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 [1]. 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 [2]. 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 [2], 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.

The concept of a pharmacophore was coined in the 19th century when Langley first suggested that certain drug molecules might act on particular receptors. Only later, with the discovery of Salvarsan by Paul Elrich, the selectivity of drug–target interactions were recognized. Several years of experimentation confirmed its therapeutic effect. This discovery had found support in the statement of Emil Fisher who, following his research, had defined the concept "Lock & Key" in 1894, according to which a ligand and its receptor fits like a key with its lock to interact with the on top of each other through a chemical bond [3]

Pharmacophore Modelling:

The concept of “pharmacophores” dates back to the late 19th century, when Paul Ehrlich suggested that specific groups within a molecule are responsible for its biological activity [4,5]. The pharmacophore definition, as currently used, was developed over time, with many researchers actively participating in the process (for a detailed history of pharmacophores, please refer to Güner and Bowen [5]). However, Schueler provided the basis for our modern understanding of a pharmacophore [5,6], which is defined by the International Union of

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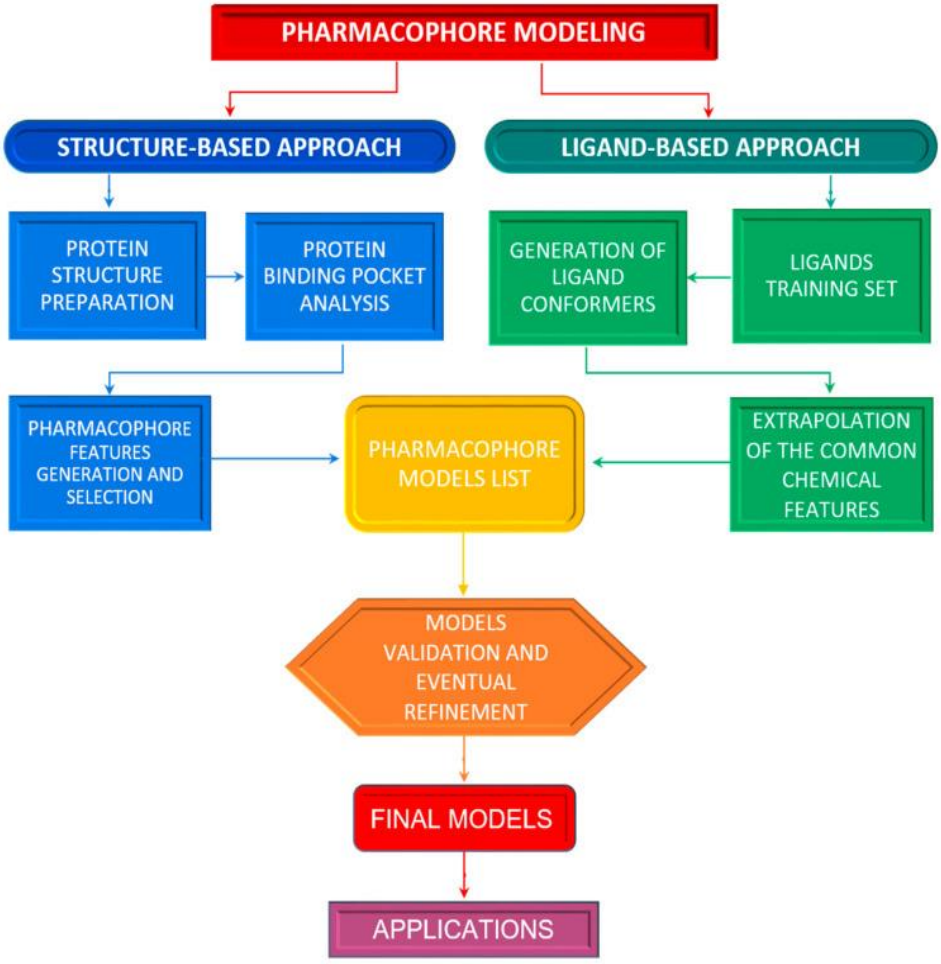
Pure and Applied Chemistry (IUPAC) as "the ensemble of steric and electronic features that is necessary to ensure the optimal supra-molecular interactions with a specific biological target structure and to trigger (or to block) its biological response" [7].

Pharmacophoric modelling is based on the theory that having common chemical functionalities, and maintaining a similar spatial arrangement, leads to biological activity on the same target. The chemical characteristics of a molecule capable of creating interactions with its ligand are represented in the pharmacophoric model as geometric entities such as spheres, planes and vectors. The most important pharmacophoric feature types are: hydrogen bond acceptors (HBAs); hydrogen bond donors (HBDs); hydrophobic areas (H); positively and negatively ionizable groups (PI/NI); aromatic groups (AR); and metal coordinating areas (Figure 1). Additional size restrictions in the form of a shape or exclusion volumes (XVOL)—forbidden areas—can be added to represent the size and the shape of the binding pocket [8].

II. STRUCTURE-BASED PHARMACOPHORE MODELLING

The structure-based approach owns its name to the fact that the three-dimensional structure of a macromolecule target is the essential prerequisite to obtaining a structure-based pharmacophore. The 3D structure of a protein provides significant details at the atomic level that can be very useful for the design or discovery of new drugs. As previously outlined, a pharmacophore is an abstract picture showing the stereo-electronic features, which make a ligand bioactive toward a specific target, and this type of information can be extracted from the 3D structure of the protein target in its hollo or apo form. Typically, the workflow of the structure-based approach (Figure 2, left side of the flow) consists of different steps: protein preparation, identification or prediction of ligand binding site, pharmacophore features generation, and the selection of relevant features for ligand activity [9,10].

Molecular docking is another method to study in silico the interaction of a known active compound towards a specific receptor and derive protein-ligand complexes from the most favourable binding poses [11].



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III. APPLICATIONS OF PHARMACOPHORE-BASED VS

In the course of a VS run, a pharmacophore model is screened against large chemical libraries, and molecules mapping the model are collected in a virtual hit list. These molecules fulfil the requirements of the model and therefore have a high likelihood to be active in the experimental testing. Accordingly, VS can be used to filter promising compounds out of large compound collections and enrich active molecules in chemical databases selected for experimental investigations. VS is considered a valuable support for classical HTS campaigns [12,13]

3.1 Pharmacophore Models Validation:

Once one or more pharmacophore models have been computed, a validation step is crucial before their implementation for practical purposes. Pharmacophore validation could be performed by exploiting several methods, such as the goodness of hit list (GH), receiver operating characteristic (ROC) curves construction, Fischer's method, or other statistical analysis, which relies on screening a test set and decoy set (if needed) to evaluate the model ability to distinguish active and inactive molecules and provide an estimation of its quality [14].

The GH scoring method consists of calculating the percentage of sensitivity, the percentage of the yield of actives the enrichment factor and the Güner–Henry score, which gives an evaluation of the efficiency of the screening dataset search and can vary from 0 to 1 where 1 is the value for the ideal model [15]. The ROC curve shows the enrichment power of a model plotting the sensitivity against 1—specificity (the false positive rate). The area under this curve (AUC) gives a measure of the pharmacophore's performance and it is useful for multiple model's evaluation. AUC can vary from 0 to 1, where 1 corresponds to an ideal case in which all the active compounds are detected at first, 0 to the collection of the inactive ones at first and 0.5 to random results [16]. Fisher's randomization test validation method is instead used to analyse the significance of the statistical correlation between structure and biological activity [17].

3.2. Applications In Toxicology:

3.2.1. Anti-Target Screening:

Although the actual virtual screening process is analogous to lead identification, anti-target screening pursues a different aim. Lead identification focuses on the discovery of ligands for therapeutically relevant targets, whereas anti-target screening aims at predicting the interaction of molecules with macromolecules mediating potentially harmful effects (so-called anti-targets). These investigations support the identification of (serious) adverse events already at an early stage in drug development. This strategy is powerful, as recently shown by Kratz et al. [18], who successfully applied pharmacophore models to identify inhibitors of the human ether-a-go-go-related gene (hERG) potassium channel, thereby predicting the cardiotoxic potential of the investigated molecules [18].

3.2.2. Parallel Screening:

Parallel screening represents an extension to lead identification and anti-target screening protocols. It investigates not a single target but a whole collection of macromolecules with the aim of obtaining activity profiles of compounds of interest in order to prioritize further investigation. Thus, the focus of this technique shifts from the target of interest to the compound of interest, which is screened against a collection of pharmacophores, representing a plethora of different targets. Parallel screening has the potential to identify macromolecular interaction partners of the investigated molecule, thereby providing novel insight into its biological activities. These activities may include beneficial (i.e., therapeutic) and harmful (i.e., toxic) effects. Therefore, the results support the evaluation of a compound both with regard to the occurrence of adverse events and potential novel application fields (whenever this aspect represents the main aim of the parallel screening, this technique is also referred to as drug repurposing or drug repositioning). In the attempt to explore the biological activity of loliginid, a lignan isolated from the alpine plant Edelweiss (Leontopodium alpinum), the compound was screened against the Intelligent pharmacophore collection in the course of a parallel screening [19]. Among the proposed targets, was cholesteryl ester transfer protein (CETP), a target involved in lipoprotein metabolism, was shown to be activated by loliginid in subsequent experimental testing. On the other side, loliginid was also predicted to inhibit the cytochrome P450 (CYP) isoforms 1A2, 2C9, and 3A4 [20],

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Importance Of Pharmacophore in Drug Design:

It is important feature to design new drug for treatment of the intended disease. Pharmacophore defined as the essential geometric arrangement of atoms or functional groups necessary to produce a given biological response. The strict IUPAC definition of a pharmacophore is: A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response. According to definition, the interactions of bioactive molecules with their targets are represented via three-dimensional (3D) arrangement and this arrangement has some feature that defines interaction type. These interaction types include formation of hydrogen bonds, charged interactions, metal interactions, or hydrophobic and aromatic contacts. So, how can pharmacophore help in designing of drug? Pharmacophore provide information in drug design and as a 3D query in searching databases containing drug-like small organic molecules to identify active and specific inhibitor. Pharmacophore is the essential to understand the interaction between the receptor and ligand. Drug design is a step-by-step process very important in biopharmaceutical field. Therefore, scientist using computer-based pharmacophore modelling to select the bioactive substance. Drug design is of two types; 1) structure-based drug design and 2) ligand-based drug design, ligand-based drug design relies on the knowledge of known bioactive molecule that bind to the biological target. Ligand based drug design uses pharmacophore features (hydrogen bonds, charged interactions, metal interactions, or hydrophobic and aromatic contacts) to design drugs. Pharmacophore modelling is done by online available bioinformatics tools, local research and platform. This new computational strategy is characterized by a multi-step design process: 1) screening of a specific biological target for a crystal structure in database, 2) pharmacophore modeming and virtual computational screening, by using public domain databases of bioactive compounds in order to find a promising molecule that could become a new potential medicine. 3) molecular and biological evaluation, to check the compounds selected by virtual screening, for their biological properties to trace their origin and underline their most important physical-chemical features, an enzyme-catalysed metabolic pathway predictor server to highlight and identify their biosynthetic-metabolic pathways and investigating the biotransformation of best candidates, analysing their metabolites and their potential biological activity. Then, ADMET/toxicity predictor server is applying the Lipinski-five rule filters is used to calculate the bioavailability the ADMET/toxicity properties. After this evaluation, a molecule with good bioavailability, good predicted bioactivity and good ADMET properties are considered as hit compound or drug. Pharmacophore approach accelerated drug designing process. Nowadays, personalised medicines have been developing according to patients' genetic profile on the basis of pharmacophore approach

IV. CONCLUSION

The pharmacophore concept was first put forward as a useful picture of drug interactions almost a century ago, and with the rise in computational power over the last few decades, has become a well-established CADD method with numerous different applications in drug discovery. Depending on the prior knowledge of the system, pharmacophores can be used to identify derivatives of compounds, change the scaffold to new compounds with a similar target, virtual screen for novel inhibitors, profile compounds for ADME-tox, investigate possible off-targets, or just complement other molecular methods. While there are limitations to the pharmacophore concept, multiple remedies are available at any time to counter them. Given this versatility, it is expected that pharmacophore modeming will maintain a dominant role in CADD for the foreseeable future, and any medicinal chemist should be aware of its benefits and possibilities.

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