COMPUTER-AIDED DRUG DESIGN

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Abstract: Drug design, sometimes referred to as rational drug design or more simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target.[1] The drug is most commonly an organicsmall molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of small molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it.

Introduction: Drug design frequently but not necessarily relies on computer modeling techniques.[2] This type of modeling is often referred to as computer-aided drug design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the biomolecular target is known as structure-based drug design.

In addition, these drugs should also be designed so as not to affect any other important "off-target" molecules or antitargets that may be similar in appearance to the target molecule, since drug interactions with off-target molecules may lead to undesirable side effects. Sequence homology is often used to identify such risks.

There are two major types of drug design. The first is referred to as ligand-based drug design and the second, structure-based drug design.

Ligand-based: Ligand-based drug design (or indirect drug design) relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target.[3] In other words, a model of the biological target may be built based on the knowledge of what binds to it, and this model in turn may be used to design new molecular entities that interact with the target.

Structure-based: Structure-based drug design (or direct drug design) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy.[4]

Active site identification: Active site identification is the first step in this program. It analyzes the protein to find the binding pocket, derives key interaction sites within the binding pocket, and then prepares the necessary data for Ligand fragment link. The basic inputs for this step are the 3D structure of the protein and a pre-docked ligand in PDB format, as well as their atomic properties. Both ligand and protein atoms need to be classified and their atomic properties should be defined, **basically, into four atomic types:**

hydrophobic atom: All carbons in hydrocarbon chains or in aromatic groups.

H-bond donor: Oxygen and nitrogen atoms bonded to hydrogen atom(s).

H-bond acceptor: Oxygen and sp^2 or sp hybridized nitrogen atoms with lone electron pair(s).

Polar atom: Oxygen and nitrogen atoms that are neither H-bond donor nor H-bond acceptor, sulfur, phosphorus, halogen, metal, and carbon atoms bonded to hetero-atom(s).

The space inside the ligand binding region would be studied with virtual probe atoms of the four types above so the chemical environment of all spots in the ligand binding region can be known. Hence we are clear what kind of chemical fragments can be put into their corresponding spots in the ligand binding region of the receptor

Ligand fragment link: Before the first fragment, i.e. the seed, is put into the binding pocket, and other fragments can be added one by one, it is useful to identify potential problems

The pre-placed seeds ensure high binding affinity and their optimal conformation determines the manner in which the ligand will be built, thus determining the overall structure of the final ligand. This strategy efficiently reduces the calculation burden for fragment construction. On the other hand, it reduces the possibility of the combination of fragments, which reduces the number of possible ligands that can be derived from the program. The two strategies above are widely used in most structure-based drug design programs. They are described as "**Grow**" and "**Link**". The two strategies are always combined in order to make the construction result more reliable.[6][7][9]

Structure-based drug design attempts to use the structure of proteins as a basis for designing new ligands by applying accepted principles of molecular recognition. The basic assumption underlying structure-based drug design is that a good ligand molecule should bind tightly to its target. Thus, one of the most important principles for designing or

obtaining potential new ligands is to predict the binding affinity of a certain ligand to its target and use it as a criterion for selection.

Computer-aided drug design uses computational chemistry to discover, enhance, or study drugs and related biologically active molecules. The most fundamental goal is to predict whether a given molecule will bind to a target and if so how strongly. Molecular mechanics or molecular dynamics are most often used to predict the conformation of the small molecule and to model conformational changes in the biological target that may occur when the small molecule binds to it. Semi-empirical, ab initio quantum chemistry methods, or density functional theory are often used to provide optimized parameters for the molecular mechanics calculations and also provide an estimate of the electronic properties (electrostatic potential, polarizability, etc.) of the drug candidate that will influence binding affinity.

Molecular mechanics methods may also be used to provide semi-quantitative prediction of the binding affinity. Also, knowledge-based scoring function may be used to provide binding affinity estimates. These methods use linear regression, machine learning, neural nets or other statistical techniques to derive predictive binding affinity equations by fitting experimental affinities to computationally derived interaction energies between the small molecule and the target.[5][6]

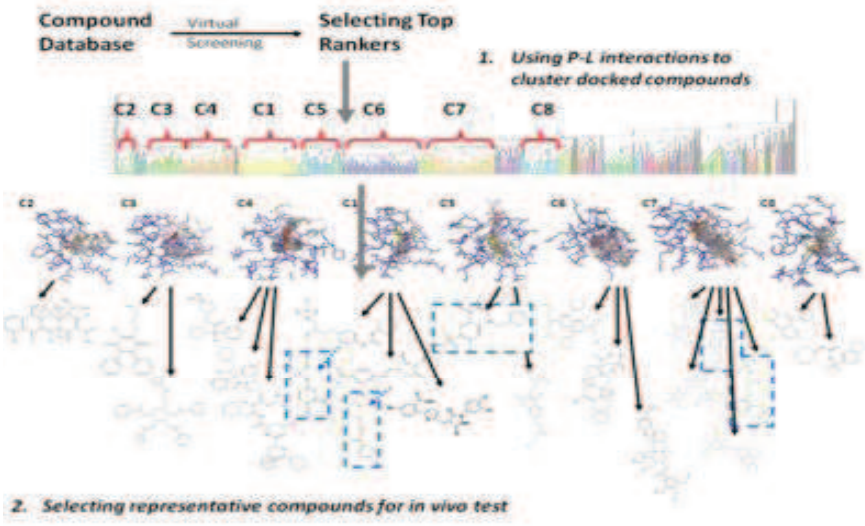
Ideally the computational method should be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized. The reality however is that present computational methods are imperfect and provide at best only qualitatively accurate estimates of affinity. Therefore in practice it still takes several iterations of design, synthesis, and testing before an optimal molecule is discovered. On the other hand, computational methods have accelerated discovery by reducing the number of iterations required and in addition have often provided more novel small molecule structures.

Drug design with the help of computers may be used at any of the following stages of drug discovery:

hit identification using virtual screening (structure- or ligand-based design)

hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)

lead optimization of other pharmaceutical properties while maintaining affinity



Flowchart of a Usual Clustering Analysis for Structure-Based Drug Design

In order to overcome the insufficient prediction of binding affinity calculated by recent scoring functions, the protein-ligand interaction and compound 3D structure information are used to analysis. For structure-based drug design, several post-screening analysis focusing on protein-ligand interaction has been developed for improving enrichment and effectively mining potential candidates:

Consensus scoring[7][8]

- Selecting candidates by voting of multiple scoring functions

- May lose the relationship between protein-ligand structural information and scoring criterion

Geometric analysis

- Comparing protein-ligand interactions by visually inspecting individual structures
- Becoming intractable when the number of complexes to be analyzed increasing

Cluster analysis[9][10]

- Represent and cluster candidates according to protein-ligand 3D information
- Needs meaningful representation of protein-ligand interactions.

Examples: A particular example of rational drug design involves the use of three-dimensional information about biomolecules obtained from such techniques as X-ray crystallography and NMR spectroscopy. Computer-aided drug design in particular becomes much more tractable when there is a high-resolution structure of a target protein bound to a potent ligand. This approach to drug discovery is sometimes referred to as structure-based drug design. The first unequivocal example of the application of structure-based drug design leading to an approved drug is the carbonic anhydrase inhibitor dorzolamide, which was approved in 1995.[21][22]

Another important case study in rational drug design is imatinib, a tyrosine kinase inhibitor designed specifically for the *bcr-abl* fusion protein that is characteristic for Philadelphia chromosome-positive leukemias (chronic myelogenous leukemia and occasionally acute lymphocytic leukemia). Imatinib is substantially different from previous drugs for cancer, as most agents of chemotherapy simply target rapidly dividing cells, not differentiating between cancer cells and other tissues.

Additional examples include:

- Many of the atypical antipsychotics
- Cimetidine, the prototypical H_2-receptor antagonist from which the later members of the class were developed
- Selective COX-2 inhibitor NSAIDs
- Dorzolamide, a carbonic anhydrase inhibitor used to treat glaucoma
- Enfuvirtide, a peptide HIV entry inhibitor
- Nonbenzodiazepines like zolpidem and zopiclone
- Probenecid
- SSRIs (selective serotonin reuptake inhibitors), a class of antidepressants
- Zanamivir, an antiviral drug
- Isentress, HIV Integrase inhibition

Traditional Drug Screening:

- Random, trial and error . Time consuming
- Very expensive
- Extremely low yield (1 in 100,000)

Computer-based Design:

- Target specific and structure-based
- Fast and automatic
- Very low cost

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