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Short Communication

Drug Discovery by Computer Chemistry Using Molecular Docking

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Drug design plays a very important role in today's world of medical science. Significant amounts are invested each year in the private and government sectors to design new or improved drugs to target a new disease or simply to take part of an already existing market by bringing a new product. Different approaches for designing a drug may differ in methodology to achieve an accepted and marketable product. Several disciplines of science are solicited in this long process; biochemistry and organic chemistry, molecular biology, pharmacology, bioinformatics and statistics, physical chemistry and computer chemistry etc.

Before considering any new drug, the first question that needs to be answered is how we are going to affect the target of the molecular process causing the disease. It is important to minimize the impact of the drug on metabolic processes, so high specificity must define the interaction between the target and the drug. Given the limited time frame and the huge sums of money at stake, an empirical method of trial and error, such was the approach a few decades ago, is by no means the best method to influence the therapeutic target. How then to proceed in a non-empirical way?

One of the first components of the design is the target. On the one hand, it is necessary to specifically identify the therapeutic target that will positively influence the disease under study. This target in general is a constituent of a biological entity associated with the disease such as a virus, a bacterium, a parasite etc. More specifically, the component of this therapeutic target can be represented by a polysaccharide, a lipid, a protein or a nucleic acid. Among the potential targets a very important class of therapeutic targets consists of enzymes, a subclass of proteins. In about 40% of target therapeutic cases, the target is an enzyme that plays a direct or indirect role in one or more factors of a metabolic pathway that positively or negatively influences the disease.

Proteins, and more precisely enzymes, are often the chosen targets in the development of a drug for the disease under study. Once this protein is selected, how are we going to block its action? Enzymes have one or more active sites in their native conformation. Our drug must be selected so that its interaction with our target at specific locations alters this native three-dimensional conformation of the enzyme and thereby its normal functionality. If the interaction between the ligand and the target is directly at its active site, we say that the inhibition is competitive. If on the other hand, the interaction affects a place elsewhere on the enzyme but modifies the active site indirectly by a general conformational change of the enzyme, it will be said that it is a noncompetitive inhibition. In both cases, the conformational change may cause irreversible inhibition, i.e. the enzyme is chemically destroyed as in the example of aspirin on prostaglandin synthetase, or it can be reversibly inhibited that is, the enzyme is simply linked to the drug without a conformational change, as in the example of ibuprofen (Advil) on the same enzyme cited for aspirin.

It is also necessary to define the interaction at the molecular level between the drug and the target. There are several types of interaction/possible links and they will be defined for example according to the amino acid present and the groups or molecules involved in the interaction. The possible interactions may be ionic bonds, hydrogen bonds, dipole-dipole, Van der Waals or obviously a summation of several of these bonds. More specifically, an ionic interaction, the strongest of the interactions, occurs between two opposite charge ions. An ionic bond is formed between two atoms when an exchange of electrons takes place between these two. For a hydrogen bond, a hydrogen atom is covalently bonded to a highly electronegative atom such as N, O or F. The result of this interaction is a dipolar molecule, such as water. For a dipole-dipole interaction to occur between two molecules, the latter must have permanent dipoles within their structures, as is the case with two interacting

H-Cl molecules. For a van der Waals bond, the weakest of the four, it involves an attraction between two nonpolar molecules holding temporary dipoles inducing by their environment.

In general, the purpose of docking is to predict the structure of the complex formed by a ligand and its receptor. Historically, the first docking tools obeyed the so-called "lock-and-key" principle according to which the key ligand is complementary to the geometric level of the receiver's active site, which represents the lock. It has been quite clearly established that the tie-down of the ligand is a dynamic process in which the ligand but also the protein are likely to undergo significant conformational changes.

In principle, a docking program must be able to generate the modes of binding expected for ligands whose position adopted within the active site is known (in general, via the crystallographic structure of the protein co-crystallized with the ligand) in a reasonable time. For this, it is necessary that the conformational research algorithm can explore the conformational space as exhaustively as possible and efficiently. Classically, we judge the quality of docking by measuring the RMSD (Root Mean Square Deviation) on heavy atoms between the pose obtained in docking and the pose observed experimentally if it exists.

The docking method with different software is nowadays widely used in discovering new drugs from existing natural molecules. Many research projects based on use of docking have permeate discovering inhibitors of enzymes which are competitive to synthesized molecules and may give better therapeutic results. Developing of algorithms in molecular docking is necessary to perform results. The use of molecular docking is very promising in drugs discovery.

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