FACULTY OF ENGINEERING AND TECHNOLOGY

Department of Biotechnology

DIRECTDRUG DESIGN

In the direct approach, the three dimensional features of the known receptor site are determined from X-ray crystallography to design a lead molecule.

In direct design the receptor site geometry is known; the problem is to find a molecule that satisfies some geometry constraints is also a good chemical match.

After finding good candidates according to these criteria a docking step with energy minimization can be used to predict binding strength.

Molecular Modeling Applications

The starting point for many computer assisted molecular modeling studies is generally a two-dimensional drawing of a required molecule. These diagrams can range from note-book sketches to electronically stored connection tables in which one defines the types of atoms in the molecule, their hybridization and how they are bonded to each other. Then the two-dimensional structures are transformed into three-dimensional representations to study chemical properties. However, more accurate molecular structures may be available from the Cambridge X-ray crystallographic database (about 50,000 structures). Various applications of computer assisted molecular modeling techniques are reviewed here.

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Generation of Chemical Structures

Molecular structures may be generated by a variety of software. The 3D structures of molecules may be created by several common building functions like make-bond, break-bond, fuserings, delete-atom, add-atom-hydrogens, invest chiral center, etc. Computer modeling allows chemists to build dynamic Models of compounds which in turn allows them to visualize moleculargeometry and demonstrate chemical principles.

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Generation of Conformations

The most active area of theoretical research using molecular orbital theory has been in the prediction of the preferred conformation of molecules. Most molecules exist in multiple conformations. The preferred conformation of a molecule is a structural characteristic feature that arises as a response to the Force of attraction and repulsion. The shape should be considered primarily in determining the interaction of the molecule with the receptor. The minimization energy is a function of bond angles, bond lengths, torsion angles and non-covalent interactions. By varying these parameters in a systematic way and calculating the total energy as a sum of orbital energies, one can determine a minimum energy structure for example, by using conjugated gradient algorithm working under universal force field.

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Docking (Molecular Interactions)

Modeling the interaction of a drug with its receptor is a complex problem. Many forces are involved in the intermolecular association: hydrophobic, dispersion, or van der Waals, hydrogen bonding, and electrostatic. The major force for binding appears to be hydrophobic interactions, but the specificity of the binding appears to be controlled by hydrogen bonding and electrostatic interactions. Modeling the intermolecular interactions in a ligand-protein complex is difficult because there are so many degrees of freedom and insufficient knowledge of the effect of solvent on the binding association.

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Determination of Molecular Properties

Molecular properties are important indicators of various chemical molecules including pharmaceuticals. Molecular properties are normally categorized as physical, chemical and biological. The three major computational methods used for calculation of properties of molecules are:

1) *Empirical (molecular mechanics): Molecular mechanics methods* are less complicated, fast, and are able to handle very large systems including enzymes.

2) *Molecular dynamics: Molecular dynamics simulations have* been used in a variety of bimolecular applications.

3)*Quantum mechanics: Quantum mechanics is one of the* oldest mathematical formalisms of theoretical chemistry.

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Determination of Drug Excipient Interactions

Molecular modeling technique became popular to study the drug-excipient interaction which helps to visualize the type and site of interaction on a computer monitor. It was reported in a study that seven glucose units were combined to get a well shaped energy minimized conformation. The cavity depth, diameter of a wider and narrower rim were calculated and compared to the literature values using DTMM package. Similarly, norfloxacin, ciprofloxacin, etc. structures were built to get energy minimized conformation. The dimensions of these molecules were measured and compared to literature values. The drug molecules were allowed to penetrate through the cavity and the probability of penetration was observed. Finally, the success in the formation of inclusion complex of betacyclodextrin with norfloxacin, ciprofloxacin, tinidazole and methotrexate was reported.

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Lead Generation

A lead is any chemical compound which shows biological activity. It is not the same as a drug molecule, but its generation is an important step in drug discovery process. It is the process of identifying potential drug compounds or Leads that interact with a target with sufficient potency and selectivity. Lead generation is a complex process, which involves two basic steps:

***i) Lead finding: Here the task is to find a chemical compound*, which has a desired biological activity.**

***ii) Lead optimization: Lead optimization involves elaborating* around the basic lead structure to build in all the desirable properties, such as safety, solubility, etc.**

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Determination of Properties of Pharmacophoric Pattern

A pharmacophoric pattern may be defined as geometrically arranged functionality possessed by a set of active compounds having some mechanism of action. Identification of pharmacophores is specially useful for designing receptor agonists and antagonists, enzyme inhibitors, etc. Molecular modeling approach has been particularly rewarding indopamine agonists, antagonists and for drugs acting on histamine and morphine receptors.

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Conclusions

Molecular modeling, an inexpensive, safe and easy to use tool, helps in investigating, interpreting, explaining and identification of molecular properties using three-dimensional structures. Since different models yield different results, it is necessary to have a small number of standard models which are applicable to very large systems.

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MCQs

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