Chapter 1
Role of Molecular Docking in Computer–Aided Drug Design and Development

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ABSTRACT

Molecular Docking is widely used in CADD (Computer-Aided Drug Designing), SBDD (Structure-Based Drug Designing) and LBDD (Ligand-Based Drug Designing). It is a method used to predict the binding orientation of one molecule with the other and used for any kind of molecule based on the interaction like, small drug molecule with its protein target, protein – protein binding or a DNA – protein binding. Docking is very much popular technique due to its reliable prediction properties. This book chapter will provide an overview of diverse docking methodologies present that are used in drug design and development. There will be discussion on several case studies, pertaining to each method, followed by advantages and disadvantages of the discussed methodology. It will typically aim professionals in the field of cheminformatics and bioinformatics, both in academia and in industry and aspiring scientists and students who want to take up this as a profession in the near future. We will conclude with our opinion on the effectiveness of this technology in the future of pharmaceutical industry.

1. INTRODUCTION

Computer aided drug designing or CADD, is a strategy that harnesses state of the art technology to expedite the drug development process. Traditionally the drug development /discovery (that includes random screening, serendipitous discovery and process optimization) takes nearly a decade to complete with an average expense of ~300 million dollar. CADD tends to curtail this expenditure and timeline by providing

a holistic view of a drug discovery project and enables a SWOT (strength-weakness-opportunity-threat) analysis to evaluate the viability of the program.

Molecular docking is one of the fundamental pillars of CADD. It analyzes the binding interaction between a target protein and small molecules (Lengauer & Rarey, 1996). These small molecules also referred as ligands are the potential drug candidates that are being developed against the phenotypes and the therapeutic model for which the protein in the CADD is the target (Sliwoski, Kothiwale, Meiler, & Lowe, 2014).

2. HISTORY OF CADD

The evolution of CADD began in 1900s when Emiel Fischer (in 1894) and later Paul Ehlrich (in 1909) propagated the concept of receptors and lock and key mechanism (Fischer, 1894). Lock and key concept explains the interaction of a drug and its receptor. Just as there are innumerable pairs of lock and key, where each key inserts into a specific lock to open it, drugs are designed to be tailor made for a particular receptor. Depending on the perfection of the design, the drugs its binding capacity of the drugs with the receptor excels. But just as duplicate keys can be made for a single lock, which makes the lock vulnerable, there is a chance that multiple drugs can work on single receptor thereby giving rise to undue side effects. Additionally one drug can also interact with multiple receptors again giving rise to undue side effects. It was Paul Ehlrich, who proposed the concept of "magic bullet" the elusive drug that only bind to the chosen receptor thereby exhibiting no side effects (Elrich P, 1909,1957).

Nearly 70 years later with the advent of quantitative structure activity relationship (QSAR), CADD took its next leap towards advancement. At that time only 2-dimentional medchem properties were considered and it was much later that the 3-dimentional properties came into the picture. Gradually, with the evolution of the concepts of molecular biology, protein X-ray crystallography (refer Figure 1) and multidimensional nuclear magnetic resonance spectroscopy (NMR), CADD too evolved into a more reliable and viable strategy in drug discovery.

Advancements in high performance computing, availability of 3-dimensional structure of important pharmaceutical targets, has opened new possibilities for computational drug design. An article in Fortune magazine entitled "Next Industrial Revolution: Designing Drugs by Computer at Merck" (Sliwoski et al., 2014; Van Drie, 2007) clearly postulated the beginning of a new era for drug discovery methods involving a bevy of computational approaches.

3. COMPUTER AIDED DRUG DESIGN (CADD)

Computer Aided Drug Designing (CADD) broadly focuses on two major verticals; 1) Ligand Based Drug Designing (LBDD) and 2) Structure Based Drug Designing (SBDD). These two methods depend on the information available about the protein structure and the ligands binding to them. Ligand based drug designing involved structure activity relationship studies where structure of the receptor (mostly proteins) is unknown. Ligands were tested for their activity and pharmacophore generation. Ligand based drug discovery propagates that similar ligands are assumed to bind to similar proteins and thus to have similar biological activities.

In general LBDD involved four major steps:

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