

Chapter 45

Smart, Innovative and Intelligent Technologies Used in Drug Designing

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ABSTRACT

Smart and intelligent computational methods are essential nowadays for designing, manufacturing and optimizing new drugs. New and innovative computational tools and algorithms are consistently developed and applied for the development of novel therapeutic compounds in many research projects. Rapid developments in the architecture of computers have also provided complex calculations to be performed in a smart, intelligent and timely manner for desired quality outputs. Research groups worldwide are developing drug discovery platforms and innovative tools following smart manufacturing ideas using highly advanced biophysical, statistical and mathematical methods for accelerated discovery and analysis of smaller molecules. This chapter discusses novel innovative applications in drug discovery involving use of structure-based drug design which utilizes geometrical knowledge of the three-dimensional protein structures. It discusses statistical and physics based methods such as quantum mechanics and classical molecular dynamics which can also play a major role in improving the performance and in prediction of computational drug discovery. Lastly, the authors provide insights on recent developments in cloud computing with significant increase in smart and intelligent computational power thus allowing larger data sets to be analyzed simultaneously on multi processor cloud systems. Future directions for the research are outlined.

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INTRODUCTION

Rapid and steady growth of low-cost computer power in discovering and designing new drugs has become a central topic in modern biology and medical chemistry. These includes methods and techniques ranging from high-throughput screening of compounds in databases to protein inhibition through molecular dynamic and thermodynamic approaches using distributed and cloud computing. Computational drug design approaches can be divided into structure and ligand-based approaches (Reddy et al., 2007). Former approach focuses on available X-ray crystallographic protein structure, NMR-based structure or homology model obtained from known template from protein databank. Once a rigid structure of the target is available, ligand-based virtual screening identifies novel ligands by three-dimensional (3D) similarity searching or by pharmacophore protein matching (Reddy et al., 2007). Ligand based virtual screening detects compounds that are similar to the active known compounds. Next, the target compounds are identified through virtual screening following which the docking algorithms are applied to position the available compounds in the binding sites derived from several biochemical studies (Reddy et al., 2007). These compounds are then ranked according to their steric and electrostatic interactions between the receptor and ligand (Reddy et al., 2007). On the other hand, ligand-based approach is useful in absence of experimental 3D structure. Under such circumstances, known ligands are explored to understand the basic structural and chemical properties correlating with specific pharmacological properties. Design of new ligands is performed in several steps mostly by manual inspection and qualitative interpretation of ligand-binding site interactions. Ligand-based approaches use Quantitative Structure Activity Relationship (QSAR) method and pharmacophore modeling. The QSAR is a computational methodology for quantifying correlation between structures of chemical compounds and chemical/biological process (Acharya et al., 2011).

The QSAR model is applied to optimize active compounds to increase their relevant biological activities to the maximum possible level. The success of this model is closely related to the selection of appropriate molecular descriptors and its ability to generate mathematical relationships between the molecular descriptor and biological activity (Acharya et al., 2011). Some of the major statistical methods used to select molecular features are multivariate linear regression analysis (MLA), Principle Component Analysis (PCA) and Partial Least Square Analysis (PLS), all of which will be discussed in this chapter review (Acharya et al., 2011). Structure-based approaches also involve virtual screening of compound libraries which can be manifested using molecular docking approach and Molecular Dynamics (MD) simulations (Okimoto et al., 2009; Durrant & McCammon, 2011). Molecular docking allows prediction of different complex protein-ligand conformations and estimation of binding affinity using mathematical algorithms for faster conformational search of ligands. MD simulations allow the estimation of the effect of explicit and implicit water molecules around the binding site of ligand and calculation of binding free energy. The techniques involved are thermodynamic integration (TI), free energy perturbation (FEP) and molecular mechanics/Poisson-Boltzmann surface area (MM/PBSA) (Okimoto et al., 2009; Durrant & McCammon, 2011).

One of the robust methodologies currently being developed and extensively used is cloud computing in computational drug discovery. Cloud computing is a term which involves services provided over the Internet. This idea has been implemented from distributed/grid computing that integrates several individual computers to generate a super computer system of superior computational abilities (Shudong et al., 2004). Cloud computing utilizes computing resources allocated on-demand over the Internet. Use

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