Chapter 28
Molecular Docking Technique to Understand Enzyme-Ligand Interactions

Kailas Dashrath Sonawane
Shivaji University, India

Maruti Jayram Dhanavade
Shivaji University, India

ABSTRACT

Molecular docking has advanced to such an extent that one can rapidly and accurately identify pharmaceutically useful lead compounds. It is being used routinely to understand molecular interactions between enzyme and ligand molecules. Several computational approaches are combined with experimental work to investigate molecular mechanisms in detail at the atomic level. Molecular docking method is also useful to investigate proper orientation and interactions between receptor and ligand. In this chapter we have discussed protein-protein approach to understand interactions between enzyme and amyloid beta (Aβ) peptide. The Aβ peptide is a causative agent of Alzheimer's disease. The Aβ peptides can be cleaved specifically by several enzymes. Their interactions with Aβ peptide and specific enzyme can be investigated using molecular docking. Thus, the molecular information obtained from docking studies might be useful to design new therapeutic approaches in treatment of Alzheimer's as well as several other diseases.

BACKGROUND

Large numbers of three-dimensional structures of biomolecules are being uploaded in the various structural databases. These 3-D structures along with molecular models may be used in the docking process to understand proper interactions between receptor and ligand molecules. Molecular docking method is useful to investigate proper orientation and interactions between protein-protein, protein-ligand and DNA-protein molecules. In this chapter we have discussed protein-protein approach to understand interactions between human cathepsin B and *Aβ* peptide a causative agent of Alzheimer's disease with the help of AutoDock. Docking methodology and procedure has been discussed with proper figures.

DOI: 10.4018/978-1-5225-1762-7.ch028

INTRODUCTION

Molecular docking has become a useful technique in structure-based drug design (Sousa, 2006). We can predict the preferred orientation of receptor and ligand bound to each other to form a stable complex (Lengauer & Rarey, 2006). The molecular docking is a multistep process which starts with the representation followed by docking algorithms to identify best matched conformation to receptor structure. The docking algorithms complemented by scoring functions which is used for evaluation of interactions between ligand and receptor based on shape and electrostatic complementarities (Kitchen, et al., 2004). The two main features of molecular docking technique are conformation search algorithm and scoring function estimates the binding affinity between molecules. There are three types of docking such as protein-protein (Sonawane & Barage, 2004; Tseng, et al., 2007; Barage, et al., 2014), protein-ligand (Jalkute, et al., 2014; Jalkute, et al., 2015) and DNA-protein (Parulekar, et al., 2013) which may apply depending upon the receptors and ligands used in the docking experiments. There are two types of docking approaches used such as rigid docking and flexible docking. In rigid docking approach both the protein and ligand are considered as rigid bodies whereas in the flexible-ligand docking, receptor and ligand kept flexible. Most of the molecular docking programs treat protein as a rigid molecule and ligand as a flexible molecule. For molecular docking studies several docking programs such as AutoDock (Morris, et al., 2009), HEX (Macindoe, et al., 2010), PatchDock (Duhovny, et al., 2002; Schneidman-Duhovny, et al., 2005), Ludi (Böhm, et al., 1992), Glide (Halgren, et al., 2004), etc. are being used with appropriate docking algorithms and scoring functions.

In this chapter to understand the protein-protein docking we have taken an example of docking between cathepsin B from human with *Aβ* peptide (Musil, et al., 1991; Crescenzi, et al., 2002; Dhanavade, et al., 2013; Dhanavade, et al., 2014). Amyloid plaque formation is the pathological hallmark in the Alzheimer's disease (Hardy & Selkoe, 2002; Glenner & Wong, 1984). The Aβ peptides (1–42) are the main constituent of amyloid plaques in Alzheimer's disease (Gouras, et al., 1998; Masters et al., 1985; Tanzi, et al., 2005). There are various enzymes such as IDE, NEP, ECE, ACE, MMP-9, and plasmin are known to degrade Aβ peptides (Iwata, et al., 2001; Qui, et al., 1998; Tucker, et al., 2000; Yin, et al., 2006; Zou, et al., 2007; Cimerman, et al., 1999). Similarly, certain bacterial enzymes like aminopeptidase from *Streptomyces grieus* KK565 (SGAK), Nattokinase from *Bacillus subtilis* Natto, and Angiotensin Converting Enzyme (ACE) from *Stigmatella aurantiaca* has potential to degrade Aβ peptide (Jalkute, et al., 2015; Yoo, et al., 2010; Hsu, et al., 2009). The Aβ peptide degradation is well studied experimentally but their cleavage mechanism is yet to be understood properly. Hence, in such situation molecular docking studies between respective enzyme and ligand plays an important role to understand molecular mechanism in detail at the molecular level. The detailed procedure of docking is explained and then the results are analyzed to understand the degradation of Aβ peptide by cathepsin B from human. Finally the importance of molecular docking studies is discussed.

MATERIALS

Downloading AutoDock and AutoGrid

Download freely available version of AutoDock and AutoGrid software (Morris, et al., 2009) for Windows operating system from the AutoDock webpage (http://autodock.scripps.edu/downloads/autodock-