

Molecular Docking: A Smart Tool Accelerating the Search for New Medicines

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ABSTRACT

Molecular docking is a computational method widely used to identify potential drug candidates through virtual screening. It predicts the most favourable binding position between a small molecule or ligand and receptor and the scoring functions help to identify the most promising molecule. Some common tools for molecular docking are AutoDock, AutoDock Vina, GOLD, MP-Dock, Cluspro, HADDOCK etc. It involves three basic steps; protein/receptor preparation, ligand preparation, and protein-ligand docking. The docked complex can then be visualized with tools such as PyMOL or UCSF chimera while 2D interaction and the hydrogen bond length can be obtained using programs like LigPlot or DimPlot. Therefore, in silico screening through docking prior to experimental validation can save time and resources.

INTRODUCTION:

Molecular docking is a computational technique that predicts the interaction between a protein and a small molecule at the atomic level (Sahoo *et al.*, 2022). The target protein whose binding site being studied is the receptor while the molecule being tested for interaction to the

receptor is the ligand. A receptor can be an enzyme, membrane receptor, ion channel, transport protein etc. Ligands are often small molecules such as a drug, peptide, hormone, neurotransmitter, metabolite, or small organic compound. In recent years, molecular docking has emerged as an essential tool in drug

discovery specially for virtual screening of possible therapeutic compounds (Agu *et al.*, 2023; Kitchen *et al.*, 2004). With molecular docking, the conformation of small molecule within a target binding site of a protein can be predicted with a substantial degree of accuracy (Meng *et al.*, 2011). There are several tools, either free or commercial for molecular docking such as AutoDock, AutoDock Vina, DOCK, Surflex, GOLD, MCDock, LeDock, LigandFit, MOE-Dock, MP-Dock, Cluspro, HADDOCK, HDOCK etc. Among these, AutoDock Vina is commonly used for docking small molecules to its protein receptor. For protein-protein, protein-peptide, protein-DNA, and protein-RNA interactions, HADDOCK (High Ambiguity Driven DOCKing) is widely used (Martins *et al.*, 2026). While the algorithms used in molecular docking generates the potential orientation of protein-ligand interaction, a separate scoring functions evaluate the fit and binding energy of a docked pose. It measures the hydrogen bonds and hydrophobic interactions as well as the steric clashes. In molecular docking, a lower energy (more negative) indicates more stable complex and stronger binding affinity. Thus, molecular docking can be used for screening of large number of compounds to predict the most promising candidates for the target protein before undergoing wet lab experiments. This article summarizes the basic concepts of molecular docking and its applications.

Essentials of molecular docking

Molecular docking involves three basic steps, i.e., protein/receptor preparation, ligand preparation, and protein-ligand docking (Venkatesan *et al.*, 2010). The technique requires a high-resolution 3D structure of the target protein which can be retrieved from Protein Data Bank (PDB) database or generated using SWISS MODELLER or other tools. The protein structure is refined through a series of steps such as protonation of ionizable residues, energy minimization, removal of

water molecules and bound ligands etc to make it suitable for the docking process. The small ligands can be obtained from PubChem or Zinc database or can be generated using ChemDraw or ChemSketch. If the ligand is a peptide, the 3D structure can be generated using tools like PEPFOLD. The selected ligands are then prepared by generating conformers, assigning charges, and optimizing their geometry (Agu *et al.*, 2023; De Azevedo and Filgueira, 2010). Then the protein-ligand docking can be carried out either through site directed docking or blind docking. In site-directed docking, the binding pocket in the protein is identified and the ligand is docked. Whereas, in blind docking, the ligand is docked with the complete protein structure (Pujadas *et al.*, 2008). After docking, the best docked protein-ligand complex based on the energy score is selected and the hydrogen bonds, hydrophobic and electrostatic interactions are analysed. The 3D structure of the docked complex can be visualized with molecular visualization system such as PyMOL or UCSF chimera while 2D interaction and the bond length can be analysed using programs like LigPlot or DimPlot.

Applications of molecular docking in drug discovery

Molecular docking has been widely applied in virtual screening of compounds to identify the most possible drug candidate for a target protein, for example, identification of potent inhibitors of bacterial DNA gyrase (Gaba *et al.*, 2010; Boehm *et al.*, 2000). Once the best ligand is identified, molecular docking can be used for further optimization to improve its binding affinity and selectivity and also to design new analogs (Eweas *et al.*, 2014). This technique can be used for designing activators of enzymes involved in the degradation of environmental pollutants to boost bioremediation efficacy (Suresh *et al.*, 2008). It can be used to elucidate the structure of

proteins by generating a homology model based on the binding modes of small molecules (Ferreira *et al.*, 2015). Molecular docking can also be used to predict the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties to screen out undesirable compounds (Das *et al.*, 2020). In combination with molecular dynamic simulations, molecular docking can be used to understand the dynamic behaviour and the stability of the protein-ligand complex (Dhanik *et al.*, 2013). With various applications, molecular docking has become a crucial tool in the process of drug discovery as it can significantly reduce the resources, time and labour required in identification of potential drug candidate as compared to conventional laboratory experiments.

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