



Molecular Docking: Transforming Drug Discovery Paradigms

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Abstract

Molecular Docking is key tool in Computer Aided Drug Designing (CADD) widely used for in-silico based drug discovery. Docking facilitates the discovery of new therapeutic compounds by predicting molecular-level interactions between ligands and targets, and by delineating structure-activity relationships (SAR), all without prior knowledge of the chemical structures of other target modulators. Molecular Docking originally envisioned to elucidate the mechanisms of molecular recognition between small and large molecules, applications of docking in drug discovery substantially evolved in recent years. Exploring the newer and emerging applications of docking, such as predicting adverse effects, polypharmacology, drug repurposing, target fishing and profiling, explores into the future potential of combining docking with emerging techniques of artificial intelligence.

Introduction:

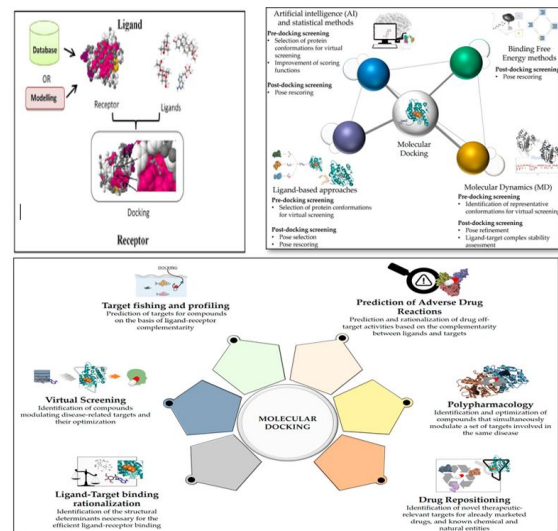
Molecular docking is to simulate the optimal conformation according to the complementarity and preorganization, which could predict and obtain the binding affinity and interactive mode between ligand and receptor. High-Throughput Screening (HTS) of large compound libraries against molecular targets has been the gold standard for discovering biologically active hits. This method is widely used in pharmaceutical industries used to characterize, metabolic, pharmacokinetic and toxicological data about new drugs. However, the high costs required to establish and maintain these screening platforms often hamper their use for drug discovery (Sliwoski *et al.*, 2014). Modern computer technology and artificial intelligence leads to rapid development of structural,

chemical, and biological data available for therapeutic targets. In-silico analysis tools comprise chemo-informatics, molecular modelling, molecular simulations significantly enable virtual screening of compounds and thus reduces initial expenses on lead identification and increases the chance for discovering desired drug candidate (D'Agostino *et al.*, 2013).

Current rational approaches in drug designing:

Molecular modelling is a tool for creating, describing and modifying the configurations and interactions of compounds, as well as the properties of these molecules that depend on their three-dimensional structures (Shoichet *et al.*, 2002). Molecular modelling classified under structure base and ligand-based approach. Structure based

approach based on 3D structure of target molecule and conformation providing ranking database based on structural and electronic complementarity of ligand of target molecule this approach is more frequently used. It helps to predict the interactions between the molecules and biological targets. Scoring functions are used for complementarity by predicting molecular orientation of a ligand and receptor (Kitchen *et al.*, 2004). Ligand based approach receptors 3D conformation is unavailable, relying on knowledge of molecules that bind to the biological target of interest. The most important and widely used tools in this approach are 3D quantitative structure-activity relationships (3D QSAR) and pharmacophore modelling. These tools can provide predictive models suitable for lead identification and optimization (Acharya *et al.*, 2014). With this approach successful binding and affinity mode of Hsp90 (Xu *et al.*, 2017) and farnesoid X receptor ligand (Kumar and Zheng, 2018) combining ligand-based approach with molecular docking. Artificial Intelligence has immense vital role in recent years machine learning algorithms implies Random Forest (RF) (Breiman, 2001) and Support Vector Machines (SVM) (Cortes and Vapnik, 1995) have been applied for improving the docking-based binding affinity predictions recently reported the development and retrospective validation of tailored SVM classification models able to improve docking posing and scoring predictions against the N-methyl-D-aspartate GluN1 receptor. Classical molecular dynamics (MD) improvised virtual screening performances for highly flexible molecules. Advanced techniques such as umbrella sampling (Torrie *et al.*, 1997), meta-dynamics (Laio *et al.*, 2002), and replica exchange. MD are used to identify additional binding pockets that could be exploited for the design of novel inhibitors such as MDM2 and MDMX inhibitors.



Applications:

Adverse Drug Reactions (ADR) Prediction:

Most of the drug candidates fail in clinical trial due to side effects with unexpected off-targets. To assess safety of drug in post marketing surveillance (pharmacovigilance) large number of computational approaches are used to assist this task. It requires sufficient bioactivity data and adverse effect for model training and requires time. Molecular docking, requiring only the target's structural information, is valuable for predicting potential side effects of compounds early in clinical and pre-clinical development or for marketed drugs lacking comprehensive drug labels and bioactivity records. Reverse Docking used for screening and identifying the adverse drug reactions. SIDER database for ADR is used for screening of 43 drugs approved by FDA for the treatment of Gulf War Illness (GWI)-related symptoms. RD screening was conducted to identify potential side effects for a series of anti-HIV drugs.

Reverse Screening for Target Fishing and Profiling:

Reverse docking (RD) assesses binding affinity of a molecule by using Protein Data Bank (PDB), Therapeutic Target Database (TTD), sc-PDB, Pocketome, providing useful information for comparing protein cavities, better describing the ligand-protein pharmacophoric properties and for target identification via pocket-based virtual screening, and to benchmark docking screenings. In RD screenings, potential targets of a ligand can be ranked according to scoring functions implemented in commonly used docking programme Glide (Friesner *et al.*, 2004). Some natural products with anti-cancer targets investigated with this approach such as MEK1, EGFR and Aurora A.

Polypharmacology:

Pharmaceutical industry focused on the development of highly selective drugs to avoid side effects high attrition rates of drug candidates in late clinical trials led to polypharmacology. It refers to identification of ligands that hit a set of selected, therapeutic-relevant targets. Molecular Docking provides identification of chemical scaffolds that efficiently and simultaneously binds to a pool of selected targets of interest. Selection of protein conformations improves success rate of drug design whenever dealing with targets with structurally distant binding sites. Several studies reporting the identification of multi-target ligands are based on the combination of docking screening with pharmacophore modelling. Identification of the first Hsp90/B-Raf dual inhibitors, demonstrating that substructure pre-filtering and pharmacophore-guided docking can be efficiently combined to search for polypharmacology ligands that bind to structurally unrelated targets. Combination of MD, probe mapping, and docking

approaches to investigate selectivity of multi-target ligands towards a set of bioaminergic G-protein-coupled receptors (Selvam *et al.*, 2013). Web tools and platforms such as Computational Analysis of Novel Drug Opportunities (CANDO), DRAR-CP and DPDR-CPI are extensively used for polypharmacology.

Drug Repurposing (Repositioning):

Drug Repurposing represents the new approach to find novel therapeutic uses for already approved drug. In silico repositioning approaches with reverse screening identify novel targets for known ligands based on their structural complementarity (Kharkar *et al.*, 2014). Docking facilitates virtual screening database of approved drugs, natural products, synthetic compounds for discovering one or more biological targets of interest in affordable time. Extensive structure-based studies on nine different Mycobacterium tuberculosis InhA structures to evaluate whether the entacapone and tolcapone drugs, approved for the treatment of Parkinson's disease, might be repurposed against tuberculosis (Kinnings *et al.*, 2009). Recent studies discovered anti-parasitic drug mebendazole is also an anti-angiogenic VEGFR2 inhibitor, docking successfully discovered that the COX-2 inhibitor celecoxib and dimethyl celecoxib bind to Cadherin-11, which is a protein mediating calcium-dependent cell-cell adhesion that plays a crucial role in rheumatoid arthritis thus molecular docking provides much precise approach for drug repurposing and consumes less time. (Dakshanamurthy *et al.*, 2012).

Conclusion:

Molecular Docking is unique In-Silico tool to assist drug discovery and designing. Being versatile tool, it has been widely used in

drug repurposing, polypharmacology and adverse effect prediction, identification of novel chemical scaffolds. Recent advancements on Graphics Processing Units (GPUs) have also provided remarkable improvements, both in data-driven drug discovery and in molecular dynamics simulations. Considering the high attrition rates characterizing drug discovery, the possibilities offered by docking in combination with the approaches outlined here will be important to reduce time and costs in both the development of clinical candidates with better safety profiles (target profiling and ADRs findings) and for the identification of novel applications of already known drugs (target profiling and drug repositioning). Further efforts should be directed toward a better integration of the different approaches with the publicly available information reported in these databases. This is expected to provide novel valuable opportunities in future drug discovery and development and, in particular, in the design of challenging and innovative drugs (i.e., multi-target ligands), as well as in assisting ligand profiling and repositioning.

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