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Review Article

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A COMPHREHENSIVE STUDY ON DOCKING ANALYSIS OF PHYTOCONSTITUENTS

***Anita A., Dr. Kalpana Diwekar and Dr. Geetha K. M.**

Dayananda Sagar University, Bangalore 560078.

***Corresponding Author: Anita A.**

Dayananda Sagar University, Bangalore 560078.

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ABSTRACT

The process of drug discovery involves technical and prolonged procedures to find a perfect lead molecule and compels us to source newer methods discovering biological targets by the knowledge of computational tools, molecular docking which is a part of molecular biology and CADD offers the solution, The review aims a brief write up on usage of molecular docking for various screening of compounds and hypothesis of ligand binding with receptor complex to form a stable complex and finally through 3d conformation get a perfect lead optimization which is targeted mainly on phytoconstituents. The computational technique to find out a special arrangement with the help of a software to pedict a ligand –receptor complexes having minimum energy, maximum specificity and efficacy is also called *in silico* approach. As the study of phytoconstituents is still under explored therefore it's an effort to co-relate and encourage research based on it.

KEYWORDS: Computer aided drug design, Target, Three dimensional molecule, ligand, phytoconstituents.

INTRODUCTION

The experimental category of cellular biology is basically divided into three broad category i) *IN VITRO* - (meaning within the glass)where there is total control on the on the outside environment of an organism and it is performed within the glass as per the procedure ,ii) *IN VIVO-(*within the living)where the experimental procedures are performed using whole living organism rather than in dead or half dead organism[1,2] *(iii)IN SILICO*-means to perform on a computer screen or by computer simulation, it was used in workshop titled "cellular automata" and pedro miramontes a mathematician use the term *in silico* for his experiment on dna/rna molecular evolution, signifies the total usage of biological experiment in computerized form.[3] The basis of drug discovery utilizes the usage of various technique required for the confirmation of a structure are infra red spectroscopy x-ray crystallography and nuclear magnetic resonance which can faintly establish a three dimensional Structure of the molecule too which also Is referred as bimolecular targets which leads us to a long pathway for *in silico* discovery of drug molecules[4] with the help of various database the hypothetical conformers are produced then compared for the maximal activity.

In case of a failure the process continues till a suitable docked conformer is obtained, the binding orientation has a minimal error but for the cases of binding free energy and experimental binding tendency usually produces more difficulty which is usually overpowered by different scoring functions like consensus scoring ,all the negative results are compared with score in the same docking position to eliminate the error.[5]

Various databases available are for small ligand library are CSD (Cambridge Structural Database), ACD (Available Chemical Directory), MDDR (MDL Drug DataReport) and NCI (National Cancer Institute Database, KiDB TRACER, GPCR DB TRACER DB.

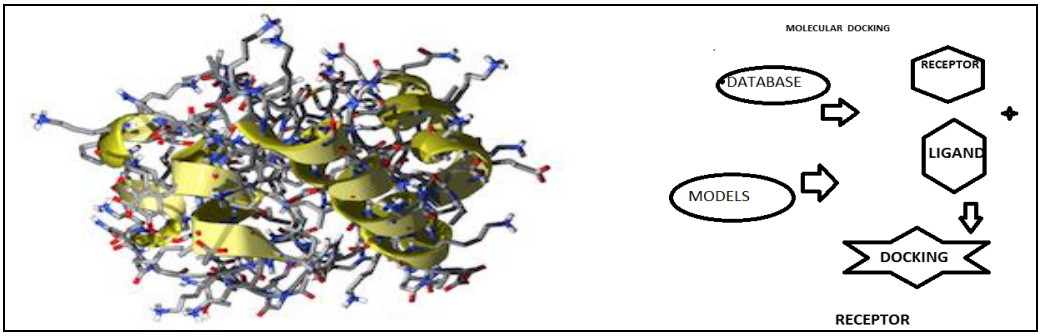

Fig. 1: Computational approaches to molecular recognition. (LIGAND AND BASE).

MOLECULAR DOCKING

The various interactive reaction involving high amount of energy between a target and ligand through virtual simulation is called as molecular docking which actually has a capacity to predict the best ligand formation with least energy with orientation on to the binding site[6], The method in molecular biology which predicts the formation a target bound small molecule which later on forms a stable complex having preferred orientation simply called as lock and key, is also known as docking, the methodology, deals with complex no of steps including the first one being the active site of a molecule which serves as a target being accessed with the help of docking algorithm to small molecules. The assessment of continuous target interaction and compound are due to the scoring functions of the algorithm of docking mainly the design are made for evaluation purpose.

Aim of the the docking process are basically covered into three category 1) From the compound library selection of the suitable library 2) Known ligand is used as reference to predict the binding mode of ligand in question 3) Based on the binding affinity and scoring algorithm functions Which are calculated for minimal energy to choose the best compound which probably going to the drug target. This also basically follows induced fit theory. Computer aided drug designing (CADD) also has its fundamental pillar as Molecular docking, the interaction between ligand and small molecule is also analysed by it.

Various naturally occurring phytochemicals having specific therapeutic property are clearly understood and documented by computational method efficiently and economically compared to normal conventional way which is time consuming, high cost maintainence and unpredictable bioavailability due to high intrinsic activity. Phtochemicals which have specific actions, the computational methods are favoured as it involves selection of specific molecule compound which selects potential target like protein or enzyme by molecur docking and then the analysis of pharmacophore begins with the virtual screening of the ligand from the library. The development of efficient techniques like nanoparticles, liposomes, phospholipid micelle is due to the elucidation of of molecular target and the phytoconstituents Successful elucidation of molecular targets and mechanisms of phytochemicals are most efficient way to to develop the formulations from phytoconstituents.[7]

Latest study related to plants physiology suggest using traditional methodology to develop drugs may take a long duration and susceptible to failure rates, in such cases[8] Computational methods become a choice of drug discovering process from phytoconstituents as they have capacity to bind with multiple targets from the several available and show various effects[9], it is also a viable option due to availability of the medicinal plant database along with their structure and individual therapeutic uses from the previous researches.the interaction between the target and the ligand is studied by process of molecular simulation.

PHYTOCONSTITUENTS COMPUTATIONAL WORK FLOW: It also follow the same molecular docking principles, starting the extraction of chemical constituents or biological molecules manually or computationally, sorces from books reports papers followed by biological network are put to operation for suitable functions to collect suficient information to move towards next step for kinetic parameters and selection of proteins molecule from database and apply docking methodology followed by simulation of biological network the output offers to predict the efficacy and toxicity levels of the phytoconstituents present at system level new designing can also be studied along.

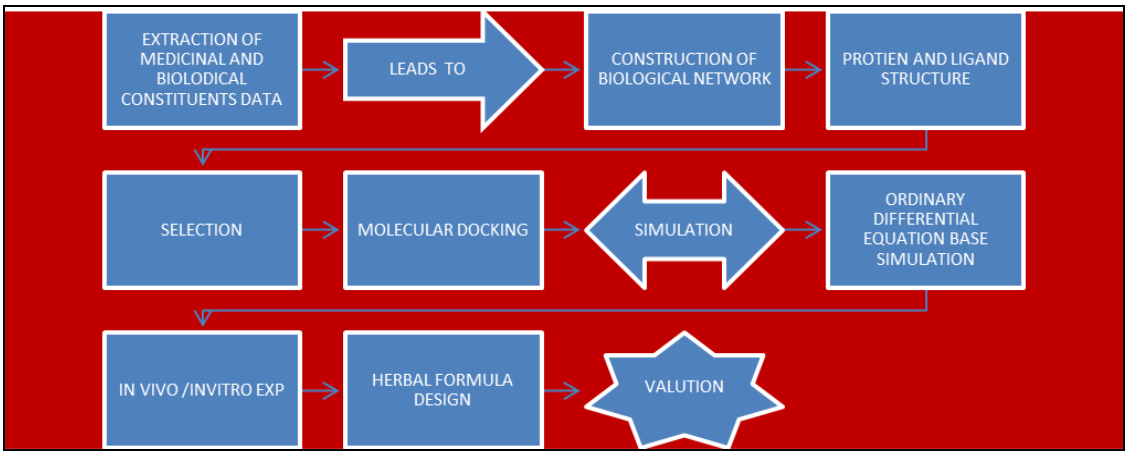

Fig 2: Process of Phytoconstituents Docking.

TYPES OF DOCKING

The types of molecular docking are usually rigid based or flexible based involving ligand and target following the simulating procedures[10] like flexible ligand docking where target is rigid ligand is flexible, rigid body docking where both ligand and target are rigid and flexible docking where both interacting molecule are flexible, Tools like DOCK, GOLD, FLEX,and ICM are

generally used for high end docking simulations, search algorithms like genetic algoritm, fragment based algoritm, molecular algoritm and montecarlo algoritm are comprehensively utilized docking tools.

AUTOMATED DOCKING ALGORITHM

Algorithmic approaches is Finding useful ways of representing the molecules and molecular properties the interaction between ligand and receptoris explored by the conformational spaces available, it is also done in two phases as hard and soft docking, basically docking itself is classified as into two types: 1)Qualitative- energy calculations – to deretmine the global minimum energy which seeks the free energy measurement and is hybrid to compliment the geometry and energy.

2) Qualitatively –geometry and the shape fitting with complimentary to the structure.

SCORING

The binding energy is modeled as follows: ΔG bind= ΔGvdw + ΔGhbond + ΔGelect + ΔG conform+ ΔG tor + ΔG,The physical phenomena like Entropy and electrostatic attraction are linked to the affinity of ligand to bind to the target and to evaluate it ,molecular docking helps it ,it does this by various suggention to improvise these rules ,usually some of them disregarded in scoring scheme,the lack of scoring functions related to accuracy and speed is the main cause of congestion in molecul;ar docking.[11] binding site is usually not accessible as the binding energy is difficult to evaluate therefore in such case the rank configuration and evaluation using scoring system does the work required.

MOLECULAR DOCKING

plays a prominent role in the initial prediction of making number of suggestions to evaluate ligand affinity linked to The physical phenomenon like entropy and electrostatic interactions but they are disregarded in scoring schemes. Hence the lack of suitable scoring function, both in terms of accuracy and speed, is the main congestion in molecular docking programming.[12] Evaluation and rank configurations using a scoring system, usually works in such cases, the binding energy is difficult to evaluate as the binding sites may not be easily accessible, the binding energy is modeled as follows: ΔG bind= ΔGvdw + ΔGhbond + ΔGelect + ΔG conform+ ΔG tor + ΔG.

SCORING FUNCTIONS

Depending on the molecular data sets used to perform regression analysis the model is designed on idea that the sum of individual uncorrelated terms that the sum of individual uncorrelated terms function, Empirical scoring are Based on binding energies and/or conformations, the experimentally determined binding energies and X -ray structural information coefficients are obtained from regression analysis .

KNOWLEDGE BASED SCORING

The general schemis →Incremental construction →Scoring function →Receptor-ligand interactions→Ligand conformational → flexibility Modeling Algorithm → Base selection →Base placement ,it defines number of atom type interaction depending on their molecular environment,also reproduces structues than binding energy with protein ligand complex ,it is modeled in a simple atomic interactions depending on their potentials ,it has unique feature of computational simplicity which permits the large compound database to be screened effectively the otherwise issue is only that derivation is essen tially based on information implicity encoded in limited sets of protein.

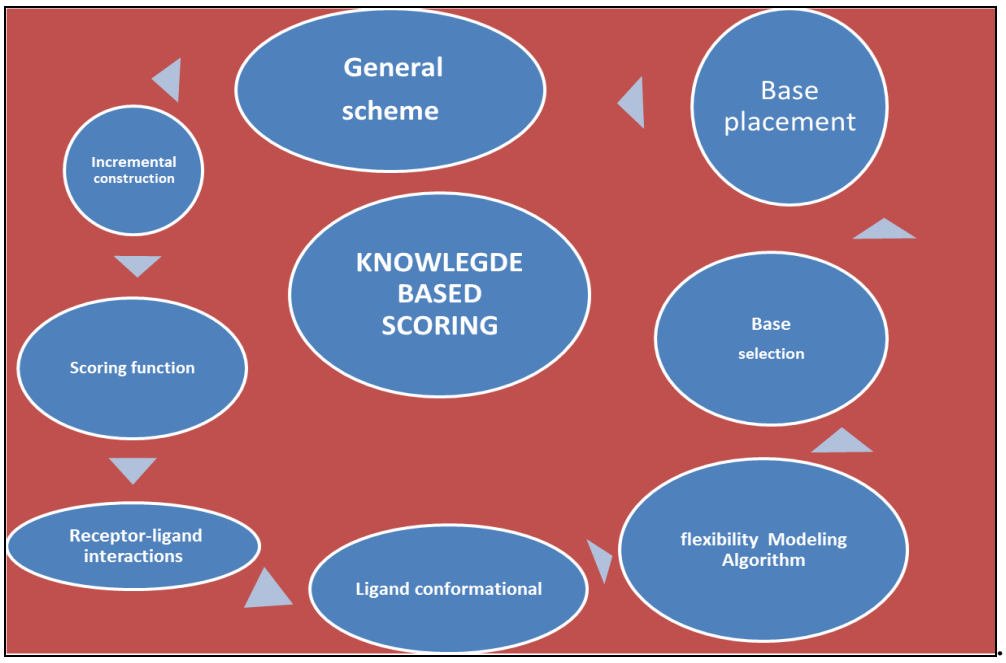

Fig 3: Scheme of Knowledge Based Scoring.

VIRTUAL SCREENING

The most important process in drug discovery is virtual screening from the large library of compounds the process of identification and compilation is done for appropriate structures ,the identified photochemical tend to bind to the computationally identified targets ,it is the major process of molecular docking leading to identification of the wanted molecule from the thousands of ligands to protein target by interacting and with least binding energy, The virtual screening process requires 3DSTRUCTURES of ligands,which are easily available, from which small databases libraries can be built which will be highly specific for targeted virtual screening[12] 2D datases are also available.

Table 4: Common virtual screening software's overview.

Softwares	References	Websites	Features
1.Molecular docking AutoDock	[13]	http://www.scrip ps.edu/pub/olson - web/doc/autod ock	The calculations are more accurate as it is based on molecular dynamics ,molecular mechanics and simulate
2. DOCK	[14]	http://www.dock.compb io.ucsf.edu	The programmes are free open acess and are widely
3.DockVision	[15]	http://www.dockv ision .com	Multiple algorithm are supported by set of applets
4.DockIt	[16]	http://www.metap horic s.com/dockit	PMF, PLP evaluation methods are followed and provide energy.
5.EHiTS	[17]	http://www.simbi osys.ca/ehits	EHiTS provides Accurate docking poses high speed through out steric hinderances it is also a flexible docking programme which coves conformational space

Shape-Similarity Screening Method: Molecules have same electrostatic properties and same shape usually exhibit mostly same activity in case pf phytoconstituents also, therefore the spatial arrangement, molecular and atomic characters are considered for the target molecule along with the pharmacophore to the library of chemical compounds form the available database,Schrodinger's The PHASE MODULE has a programme software which usually can do the shape similarity searching.

Databases Developers	References	Websites	Abstract
Binding DB Skaggs School of Pharmacy & Pharmaceutical Sciences, USA	[18]	http://www.bindi ngdb.org/bind/index.jsp	BindingDB has ligands which are small drug like an has interaction with protein as drug targets it is a public, web-accessible database which has a measurable binding affinity,
BioGRID (Biological General Repository for Interaction Datasets	[19]	http://www.thebiogrid.org	Post translational modifications from major model organism species has the current index is version3.4.151 and searches 63,354publicationsfor1,493,749 protein and genetic interactions,27,785 chemical associations .
DAVID (Database for Annotation, Visualization, and Integrated Discovery)	[20]	http://www.david.ncifc rf.gov	DAVID DATABASE basically list interacting proteins and its other functions also it discovers enriched functionally related ggene groups and Identifies enriched biological Themes too.
DRUGBANK Canadian Institutes of Health Research, Canada	[21]	http://www.drugbank.ca	The database contains 9591 drug entries including 2037 FDA-approved small molecule drug, Cheminformatics resource that combines detailed drug data & comprehensivedrug target information has also 241 FDA-approved biotech drugs, 96 nutraceuticals and over 6000 experimental drugs.

Figure 5: Common druggable targets/protein databases overview.

Docking assessment: The novel compounds predicted by binding affinity is related to the connection between sampling and scoring functions which is done with a help of protocol, this assessement can be performed using different techniques, Calculation of docking accuracy, the enrichment factor determination, relationship between docking score and experiment respectively.

Table 5: Common visualization tool overview.

Tools	References	Websites	Features
CADLIVE (Computer-Aided Design of living systems)	[22]	http://www.cadli ve.jp	Cadlive is a comprehensive computational tool for analyzing large-scale biological network maps for constructing large-scale topological features of them, and simulating their dynamics
Cytoscape	[23]	http://www.cytos cape.org	Cytoscape is an open source software platform for visualizing biological pathway,molecular interaction networks and help in integrating these networks with gene expression profiles other state data annotations.
Graphviz	[24]	http://www.graph viz.org	Graphviz is a networking bioinformatic software engineering,database which is open source Graph visualization is a way of representing structural information as diagrams of abstract graphs and networks.The technical domain like visual interfaces databases, webdesigns and machine learning are part of it.
Pajek	[25]	http://www.mrvar .fdv.unilj .si/pajek	Pajek is a pacage of program which is available for more than 20 years where there is no limit on except on memory size on no of lines and is use for analysis and visualization of large networks.
VANTED	[26]	http://www.vante d.ipkga tersl eben.de	VANTED is an analytical tool for networks with related experimental data and is used for visualization anddistances between the ions in active site and due to induced fit models.

Accuracy of docking: the experimental observations are the standard to predict the right orientation of the ligand which quantifies the fitness of docking programme which in turn is measurable.

Enrichment factor: The success of docking screen is due to its capacity to select out large number of small molecules in top score in known sequence as compared to molecules present as duplicates from the database the calibration method provides accuracy under ROC (RECIEVER OPERATING CHARACTER), it helps in evaluation of annotated ligands of known binder from database too in case of photochemical database also.

Applications[27] apart from the most important one being drug designing molecular docking is applied to identify the "hit" target along with matching scoring function which can be used to identify the potential molecules which has affinity to bind with the particular target ,the entire class of drugs can be explored, it also gives a clear view on lead optimization to develop more potent analogs and primarily the explation of phytoconstituents along with prediction on toxicities and potency can be predicted and prediction of pollutantants degraded by enzyme can also be predicted by docking studies.[28]

Restrictive usage: Lack of synergistic computational model, low quality database pertaining to phytoconstituents, improper standardization of results and validation lack of accurate scoring function multidrug assessment actually poses limitation threat molecular docking of phytoconstituents.

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