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Computational Drug Design and Molecular Dynamic Studies-A Review

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Abstract

Drug designing and molecular dynamic studies were an intense, lengthy and an inter-disciplinary venture. At present, a new approach towards the use of computational chemistry and molecular modeling for *in-silico* drug design. Computational *in-silico* drug design skills are used in bioinformatics, computational biology and molecular biology. Drug designing using *in-silico* methods is cost effective in research and development of drugs. Currently, a vast number of software's used in drug design. *In-silico* drug designing and molecular dynamic studies can be performed by using different methods namely homology modeling, molecular dynamic studies, energy minimization, docking and QSAR etc. By using *in-silico* drug designing we can produce an active lead molecule from the preclinical discovery stage to late stage clinical development. The lead molecules which are developed will help us in selection of only potent leads to cure particular diseases. Therefore *in-silico* methods have been of great importance in target identification and in prediction of novel drugs.

Keywords: Drug design; Homology modeling; Molecular docking; QSAR; MD simulation

Introduction

Computational methodologies used for prediction and deep understanding of complex scientific facts has accelerated our knowledge gain and had tremendous impact in our societal growth. Presently, almost there are no discipline of science which is not using applied computational methodologies for better understanding and integrated studies.

There was a time when all the scientific disciplines were considered individually among the experts. Recent development in the application science and technology has shown that science is interdisciplinary in nature today. More or less each discipline is borrowing one or the other application from other to gain a deep and fruitful insight.

Life and medical science been immensely benefitted by the application of computational analysis. After the great achievement of human genome mapping, implementation of computational techniques has risen enormously.

We have observed application of computational techniques in molecular sequence analysis, understanding complex interactions of genes and non-coding regions [1,2], estimating the protein molecules and mapping their important features and performing comparative studies [3-5] for understanding complex biological phenomenon and in various other aspects of cell and molecular biology.

In this regard, ample investigations and growth has been observed in understanding the protein molecules and their interactions with other molecules through computational approach during last few decades. Development of advanced algorithms and availability of high end computation yielded a lot in this issue and allowed us to witness one of the greatest technological developments in this century [6].

In-silico drug design and development is a very intricate, time consuming process. *In-silico* methods can help in identifying drug targets via computational tools. They can also be used to analyze the target structures for possible binding active sites, generate candidate molecules, check for their drug likeness, dock these molecules with the target, rank them according to their binding affinities, further optimize the molecules to improve binding characteristics. In *in-silico* drug designing many factors are responsible for the unsuccessful of many drugs molecules which are developed by computations methods using different bioinformatics software's. hence, the developed models were not tested like *in-vivo* methods so there are few demerits in *in-silico* developed drugs such as lack of effectiveness, side effects, poor pharmacokinetics, and marketable reasons. The expenditure of this process has risen significantly during the past 34 yrs [7].

Drug discovery is most prominent process in current days and that begin with target and lead discovery, followed by lead optimization and pre-clinical *in vitro* and *in vivo* studies to recognize the potent compounds for which assure the main criteria for drug development [8]. To develop a drug through an in-vivo and in-vitro methods take long time and with high expenditure [9,10]. For that reason *in-silico* drug designing is useful to predict the active molecules and we will get an idea about the drug discovery process. The drug discovery through pharmaceutical industry, will take approximately years to bring a drug from discovery to market (12-14 years) and costing up to $1.2-$1.4 billion dollars [11]. The way of drug discovery by pharmaceutical industry is a time-consuming multi-step processes against a battery of *in vivo* biological validations and further investigating the active candidates for their pharmacokinetic properties (ADME), metabolism and potential toxicity (efficacy). Today, the process of drug discovery has been revolutionized with the advent of genomics, proteomics, bioinformatics [12] and efficient technologies like, combinatorial chemistry, high throughput screening (HTS), virtual screening, de novo design, *in vitro*, *in silico* ADMET screening and structure-based drug design.

Computational drug discovery can help in identifying potent drug molecules and targets via bioinformatics tools. They can also be used to evaluate the target structures for possible binding/active sites, generate active drug molecules, check for their dynamic and kinetic properties, the docking studies of these molecules with the target molecules will

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help us to know the affinity and efficacy of developed molecule and we rank them according to their binding affinities [13]. The molecules which are showing better activity can be modified and build to get good activity towards the target molecules, further optimize the molecules to improve binding characteristics. The use *in silico* methods will help us in all aspects of drug discovery today and forms the importance of structure-based drug design. There are plenty of programs which are helping us to build active drug molecules. Meanwhile, High-performance computing, data management software and internet are helping us to generate high quality data generated complex data and also transformation of huge complex biological data into accessible knowledge in current trends to discover a novel drug molecules [14]. The use of computational science in drug discovery increases the opportunity to succeed in many aspects like lead identification and lead optimization, developing a promising molecule against diseases. The drug discovery process using *in silico* method were easy to perform and lower cost. Major roles of computation in drug discovery are;

1. Virtual screening and de novo design (Model development) [15]
2. *In silico* ADME/T prediction (QSAR)
3. Advanced methods for determining protein-ligand binding (Docking studies)

There are various methods used in Computational Drug Design and Molecular Dynamic Studies, in which some are discussed below.

Homology Modeling

Homology modeling is also known as comparative modeling of protein. HM involves the identification of one or more recognized protein structures likely to show similarity with the structure of the query sequence, and on the making of an alignment that maps residues in the query sequence to residues in the template sequence structure [16]. The proteins which are similar with evolution have similar sequences and naturally occurring homologous proteins have similar protein structure is more conserved than expected because of the sequence conservation to generate a structural model of the target using the sequence alignment and template structure [17,18].

Important steps to do homology modeling:

Selection query sequence

Selection of template

Align the sequences (ClustalW, Discovery Studio-4.0)

Create homology models

Verify the designed model with standard structure

The Modeller is a popular tool in homology modeling, and SWISS-model repository is a database of protein structures created with homology modeling.

SWISS-MODEL is a fully automated protein structure homology-modeling server, accessible via the ExPASy web server or from the program Deep View (Swiss Pdb-Viewer). The purpose of this server is to make Protein Modeling accessible to all biochemists and molecular biologists worldwide (Tables 1 and 2).

Homology modeling, being recognized as a standard procedure to investigate the protein molecules with reasonable amount of accuracy is being used in for several disease associated proteins. The gigantic amount of literature available so far, suggests that this technique has been used for understanding proteins related to malaria [19-23], shigellosis [24,25], diabetes [26], tuberculosis [27], influenza [28], HIV [29] and several other diseases. All these reports are later on used either for further investigation purpose or experimentally gathering more information on the particular protein molecules. Thus, suggesting the importance of this technique as a better alternative resource to gather

Discovery Studio Visualization	BIOVIA determining the three-dimensional structure and properties of a macromolecule, such as enzymes, antibodies, DNA or RNA is a fundamental component to a wide range of research activities.
CADD (Computer-Aided Drug Design)	CADD is an emerging tool for research and drug development process as it reduces the time taken for the process of drug development and expense.
MOE	MOE's well known applications for protein structure prediction. It is powerful homologue identification, alignment technology and refinement methodology makes high quality sequence-to-structure predictions routinely possible.
Schrödinger	BioLuminate is a comprehensive modeling package for biologics, with advanced simulation methods deployed through an intuitive user interface that is specifically designed for biologics
ESyPred3D	Template detection, alignment, 3D modeling

Table 1: Commercial software packages for Homology Modeling.

EasyModeller	It is a graphical interface to MODELLER using Perl/Tk, which can be used as a standalone tool in windows platform with MODELLER and Python preinstalled.	It helps inexperienced users to perform modeling, assessment, visualization, and optimization of protein models in a simple and straightforward way.
Prime	Physics-based energy function	A powerful and innovative package for accurate protein structure predictions.
MODELLER	MODELLER is used for homology or comparative modeling of protein three-dimensional structures.	The user provides an alignment of a sequence to be modeled with known related structures and MODELLER automatically calculates a model containing all non-hydrogen atoms.
Yasara	Detection of templates, alignment, modeling incl. ligands and oligomers, hybridization of model fragments	YASARA Structure features a complete homology modeling module that fully automatically takes all the steps from an amino acid sequence to a refined high-resolution model using a CASP (Critical Assessment of Structure Prediction) approved protocol
HHpred	Template detection, alignment, 3D modeling	HHpred accepts a single query sequence or a multiple alignment as input. Within only a few minutes it returns the search results in an easy-to-read format similar to that of PSI-BLAST. Search options include local or global alignment and scoring secondary structure similarity. It can produce pairwise query-template sequence alignments, merged query-template multiple alignments as well as 3D structural models calculated by the MODELLER software from HHpred alignments.

Table 2: Software's which are available online free for academics.

scientific information in lack of experimental data.

Molecular Docking

Molecular docking is a method in which we can predict the preferred orientation of one molecule to a second, when the one molecule binds with the second molecule (it may be protein or ligand molecule) to form a stable complex structure. Docking indicate ligand binding to its receptor or target protein. Molecular docking is mainly used to predict the stable drug interactions by inspecting and modeling drug molecular interactions between drug molecule and target receptor molecules. They are used to develop several ligand conformations and orientations and the most suitable ones are selected for further research [30] (Tables 3 and 4).

There are several molecular docking tools available that includes AutoDock, FRED, eHITS, and FTDock, etc.

Docking studies are known for providing deep information on the interaction types of a ligand and a macromolecule, especially a protein. At present there are novel algorithms which are highly computational intensive and allow understanding the microenvironment during an interaction with the presence or absence of water molecules. Flexibility has been increased along with the increased computation possibilities. Apart from small molecule docking [31], protein-protein [32], protein-DNA [33] or protein-RNA [34] can also be studied considering the cellular level complexities associated on a case by case basis. Studying a complex interaction using a distributed computation has become a regular practice in within the scope of computational chemistry or computational biology.

Quantitative Structure Activity Relationship (QSAR)

Quantitative structure-activity relationships methods are used to show a relationship of structural and/or property descriptors of compounds with their biological activities [35]. These descriptors explaining the properties like steric, topologic, electronic, and hydrophobic of numerous molecules, have been determined through empirical methods, and only more recently by computational methods [36,37] (Tables 5 and 6).

A QSAR generally takes the form of a linear equation [38]:

{Biological Activity = Const + (C1 P1) + (C2 P2) + (C3 P3) + ...}

Discovery Studio is a comprehensive life science modeling and simulation suite of applications focused on optimizing the drug discovery process. Capabilities include, small molecule simulations, QM/MM, pharmacophore modeling, QSAR, protein-ligand docking, protein homology modeling, sequence analysis, protein-protein docking, Comparative Molecular Field Analysis [39], antibody modeling, etc.

QSAR studies were initiated with nominal number of descriptors and were computed till two dimensional data model only. Presently, improvement in the algorithms and the computing facilities and speed made it possible to calculate for multiple dimensions along with crucial

Program	Description	Web service	License
ADAM	Prediction of stable binding mode of flexible ligand molecule to target macromolecule	Not Available	Commercial
DockingServer	Integrates a number of computational chemistry software	Available	Commercial
DockVision	Based on Monte Carlo, genetic algorithm, and database screening docking algorithms	Not Available	Commercial
eHiTS	Exhausted search algorithm	Not Available	Commercial
FlexX	Incremental build based docking program	Not Available	Commercial
Glide	Exhaustive search based docking program	Not Available	Commercial
GOLD	Genetic algorithm based, flexible ligand, partial flexibility for protein	Not Available	Commercial
ICM-Dock	Docking program based on pseudo-Brownian sampling and local minimization	Not Available	Commercial
Lead finder	Program for molecular docking, virtual screening and quantitative evaluation of ligand binding and biological activity	Not Available	Commercial
LigandFit	CHARMm based docking program	Not Available	Commercial
LIGIN	Molecular docking using surface complementarity	Not Available	Commercial
Surflex-Dock	Based on an idealized active site ligand (a protomol)	Not Available	Commercial

Table 3: Commercial software packages for docking studies.

Program	Description	Web service
Score	The Score service allows to calculate some different docking scores of ligand-receptor complex	Freeware
Q-Dock	Low-resolution flexible ligand docking with pocket-specific threading restraints	Freeware
HADDOCK	Makes use of biochemical and/or biophysical interaction data such as chemical shift perturbation data resulting from NMR titration experiments, mutagenesis data or bioinformatics predictions. Developed for protein-protein docking, but can also be applied to protein-ligand docking.	Freeware
GEMDOCK	Generic Evolutionary Method for molecular docking	Freeware
FTDOCK	Based on Katchalski-Katzir algorithm. It discretises the two molecules onto orthogonal grids and performs a global scan of translational and rotational space	Freeware
Blaster	Combines ZINC databases with DOCK to find ligand for target protein	Freeware
AutoDock	Automated docking of ligand to macromolecule by Lamarckian Genetic Algorithm and Empirical Free Energy Scoring Function	Freeware
DOCK	Based on Geometric Matching Algorithm	Freeware for academic use
AutoDock Vina	New generation of AutoDock	Open source

Table 4: Software packages available free for docking studies.

stochastic modeling and accuracy in prediction ability.

Moreover, there are literature evidences for such successful studies for different diseases with number of drug molecules [40]. Studies have been conducted on the pollutant molecules and their impact on environmental and health issues.

QSAR analyses eventually allowed us to quantify the relationship of the important factors involved in contributing towards the functional activity for a series of molecules. Thus, providing an initial understanding towards the activity of the molecules and focusing on particular aspects of the experimentations through reduced number of target molecules. Industrially this approach has been tremendously helpful in advanced drug designing and accelerated the process of drug discovery through reducing the time required for screening the molecules experimentally [41].

Molecular Dynamic (MD) Simulation

Molecular dynamics is an effective procedure and depends on the molecular motion simulation by solving Newton's equations of motion for each atom and increasing the speed and position of each atom by a small increase of the time duration [42]. MD simulations characterize alternative methods to sample configuration space, based on the above mentioned rule. That is shared with temperatures using "reasonable", this means that only the local area around the sampled point, and only relatively small barriers are overcome. Generation may be different, minimum may be accomplished by selecting configuration appropriate times during the simulation and thus minimize these structures. MD methods utilize the inherent dynamics of the system to search deformation modes of low energy and can be used for sampling of the conformational space of a large confined system [43].

At present there are few molecular dynamics software programs are available for *in-silico* research and simulations. Every program has different features and their own eminence. Here is a brief introduction to three of the most popular molecular dynamics packages - Amber, CHARMm and Gromacs - which we have been supporting in recent years [44] (Table 7).

Molecular dynamics simulations are the state-of-the-art techniques aiding in understanding a large molecule functionally as well as structurally in a real-time scenario. Experimentally it is not always possible capturing the molecular interactions sequentially, capturing a particular snapshot of the molecular reaction is comparatively easy. Thus, molecular simulation of the events helps in understanding the reactions in a sequential manner following the biophysical limits so far understood.

Interactions are being studied in an aqueous medium considering the type of interactions under study and the requirement or major focus of the study on a case by case basis. A large series of molecular simulations can be done through these methodologies which are described in the following section.

Software	Availability	Applicability
ADMET Predictor	Commercial	Qualitative and quantitative prediction
ACD ToxSuite (ToxBoxes);	Commercial	ER binding affinity prediction.
Derek	Commercial	Classification models (different levels of QSAR)
Leadscope	Commercial	Classification models for developmental and reproductive toxicity studies.
MolCode Toolbox	Commercial	Quantitative prediction of rat ER binding affinity and AhR binding affinity.
MultiCASE (MC4PC)	Commercial	Computational toxicity predictions
PASS	Commercial	Prediction of Activity Spectra of Substances
TIMES (COREPA)	Commercial	Classification models for the prediction
TOPKAT (Accelrys)	Commercial	Classification models for developmental and reproductive toxicity studies.

Table 5: Software for developmental and reproductive toxicity.

Software	Availability	Applicability
CAESAR	Freely available	Specifically dedicated for validation of QSAR models: bio-concentration factor, skin sensitization, carcinogenicity, mutagenicity, Developmental toxicity
Endocrine Disruptor Knowledge Base (EDKB)	Freely available	Quantitative models to predict ER binding reported here may be applied to other receptors and/or reversible binding mechanisms involved in endocrine disruption
T.E.S.T.: The Toxicity Estimation Software Tool	Freely available	Developmental toxicity estimation of chemicals using QSAR
OSIRIS property explorer	Freely available	Predict physico-chemical and toxicological molecular properties, which need to be optimized when designing pharmaceutically

Table 6: Software's used online for QSAR studies.

Software	Full Name	Availability
AMBER	Assisted Model Building with Energy Refinement (Amber Molecular Dynamics Package)	Commercial
CHARMM	Chemistry at HARvard Macromolecular Mechanics	Commercial
GROMACS	Groningen Machine for Chemical Simulations (High performance MD)	Free version
NAMD	NAnoscale Molecular Dynamics program (It is a mlecular graphics program VMD for simulation setup and trajectory analysis, but is also file-compatible with AMBER, CHARMM, and X-PLOR)	Free version
LAMMPS	Large-scale Atomic/Molecular Massively Parallel Simulator	Open Source
VMD	Visual Molecular Dynamics (Molecular visualization program for displaying, animating, and analyzing large bio-molecular systems using 3-D graphics and built-in scripting)	
FoldX	FoldX is an empirical force field that was developed for the rapid evaluation of the effect of mutations on the stability, folding and dynamics of proteins and nucleic acids.	Open Source

Table 7: Commercial software's used in molecular dynamic studies.

All these simulation tools in general uses some force field parameters which contains energy functions, bonded and non-bonded interaction specifications, type of water model to be used, biophysical and biochemical constraints to be maintained.

During the simulation different boundary conditions such as periodic, spherical, cylindrical is generally taken care of by the simulation algorithm. Pressure and temperature is maintained throughout the simulation as per the specifications provided depending on the requirement of the study.

Various types of simulations can be done through these advanced simulations programs including RMSD of the molecule with each time step, coarse grain simulation, steered molecular dynamics analysis [45], targeted molecular dynamics simulations, free energy based calculations etc.

Virtual High-Throughput Screening

Virtual screening is a computational technique where large libraries of compounds are evaluated for their potential to bind specific sites on target molecules such as proteins, and well-matched compounds tested [46,47] (Table 8). The research in the drug discovery process involves virtual screening (VS) which is a computational method used for the rapid exploration of large libraries of chemical structures in order to identify those structures that are most likely to bind to a drug target, usually a protein receptor or enzyme (Figure 1).

Virtual high throughput screening will help us to develop prominent molecules for drug discovery [48]. By using vHTS we can design drug molecules using two types of methods,

a. Structure based drug design: Structure based drug design also known as direct drug designing process. In this the structure of drug molecule (3D structure) is known. The 3D structure can build by using NMR crystallography or X-ray crystallography. If the crystal structure of a protein molecule is not known then we can precede it by building a homology modeling to develop drug molecules.

b. Ligand based drug design: Ligand based drug design also known as In-direct drug design. In which the process of drug designing depends on the other molecules which binds to the targeted receptor. It can be designed by designing pharmacophore models which are having the similar structure features of the standard one [49,50].

Chemical Libraries	Description
ZINC	It is a curated collection of commercially available chemical compounds, with 3D coordinates, provided by the Shoichet Laboratory in the Department of Pharmaceutical Chemistry at the University of California, San Francisco (UCSF).
NCI	250251 open structures ready for searching.
ChEMBL	It is a database of small molecules. Includes interactions and functional effects of small molecules binding to their macromolecular targets, and series of drug discovery databases.
PubChem	Database of chemical compounds maintained by the National Center for Biotechnology Information (NCBI), along with bioassays results. Allows similar compounds search (2D and 3D).
Chemspider	Collection of chemical compunds maintained by the Royal Society of Chemistry. Includes the conversion of chemical names to chemical structures, the generation of SMILES and InChI strings as well as the prediction of many physicochemical parameters.

Table 8: Databases used in virtual high throughput screening.

In-Silico Drug Designing Process

The use of bioinformatics tools and computational methods spread through all the aspects of drug discovery today and forms the core of structure-based drug design [51]. High-performance computing, data management software and internet are facilitating the access of huge amount of data generated and transforming the massive complex biological data into workable knowledge in modern day drug discovery process. The process of drug design is an iterative one and often proceeds through multiple cycles before an optimized lead goes into phase I clinical trials. Using computer algorithms, compounds or fragments of compounds from a database are positioned into a selected region of the structure. The use of complementary experimental and informatics techniques increases the chance of success in many stages of the discovery process, from the identification of novel targets and elucidation of their functions to the discovery and development of lead compounds with desired properties. These compounds are scored and ranked based on their steric and electrostatic interactions with the target site and the best compounds are tested with biochemical assays. In the second cycle, structure determination of the target in complex with a promising lead from the first cycle, one with at least micro molar inhibition *in vitro*, reveals sites on the compound that can be optimized to increase potency. Additional cycles include synthesis of the optimized lead, structure determination of the new target: lead complex, and further optimization of the lead compound. After several cycles of the drug design process, the optimized compounds usually show marked improvement in binding and, often, specificity for the target.

The use of complementary experimental and informatics techniques increases the chance of success in many stages of the discovery process,

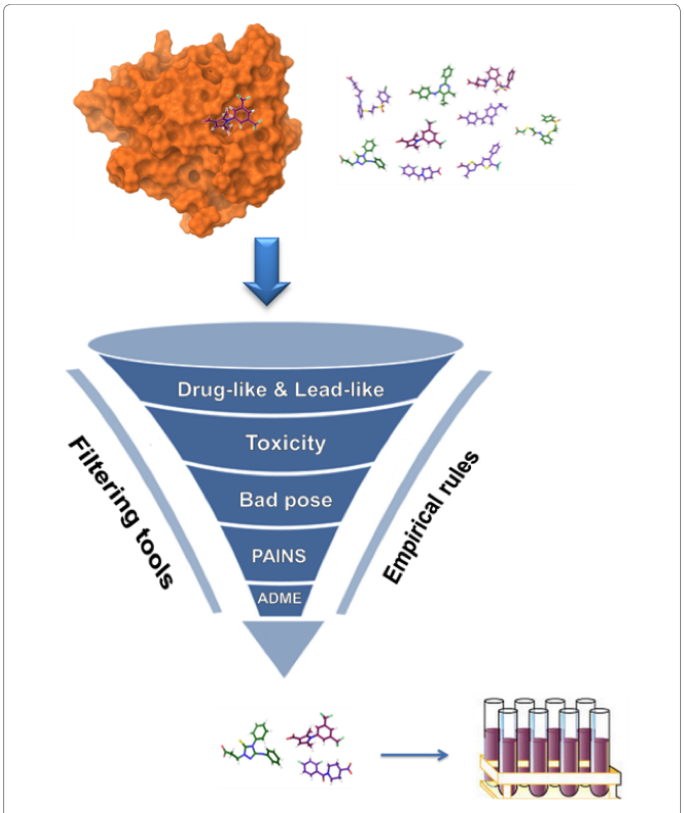

Figure 1: Process of virtual high-throughput screening.

from the identification of novel targets and elucidation of their functions to the discovery and development of lead compounds with desired properties. Computational tools offer the advantage of delivering new drug candidates more quickly and at a lower cost. Major roles of computation in drug discovery are; (1) Virtual screening & de novo design, (2) *in-silico* pharmacokinetics properties (ADME/T) prediction and (3) Advanced methods for determining protein-ligand binding.

The *in-silico* drug design is a vast field in which the different sides of basic research and practice are combined and inspire each other, modern techniques such as QSAR/QSPR, structure-based design, combinatorial library design [52], chemoinformatics, bioinformatics and the increasing number of biological and chemical databases are used in the field. Furthermore, large numbers of the available tools provide a much developed basis for the design of ligand and inhibitors with preferred specificity. The aim of this review was to discuss the process of *In-silico* drug design.

Conclusion

Drug designing is a process of choosing of novel drug candidates many necessary steps are taken to banish such drug molecules that have side effects and also represent interaction with other drugs candidates. There are vast numbers of software's which play a crucial role in *in-silico* drug designing to develop a novel proteins or drugs in the pharmaceutical field. The *in-silico* drug designing software's are used to inspect molecular modeling of gene, protein sequence analysis and 3D structure of proteins [53]. Right now *in-silico* drug designing methods have been of vast significance in target identification and in prediction of novel drugs.

In future prospects, our study has addressed a number of issues that emerged in homology modeling of proteins and provided new insights about the dynamics of the protein under different environment conditions using various programs.

References

1. Meyer EF, Swanson SM, Williams JA (2000) Molecular modeling and drug design. Pharmacol Ther 85: 113-121.
2. Shinde SP, Banerjee AK, Arora N, Murty US, Sripathi VR, et al. (2015) Computational approach for elucidating interactions of cross-species miRNAs and their targets in Flaviviruses. J Vector Borne 52: 11-22
3. Banerjee AK, Ravi V, Murty US, Shanbhag AP, Prasanna VL (2013) Keratin protein property based classification of mammals and non-mammals using machine learning techniques. Comput Biol Med 43: 889-99.
4. Banerjee AK, Ravi V, Murty US, Sengupta N, Karuna B (2013) Application of intelligent techniques for classification of bacteria using protein sequence-derived features. Appl Biochem Biotechnol 170: 1263-81.
5. Banerjee AK, Manasa BP, Murty (2010) US Assessing the relationship among physicochemical properties of proteins with respect to hydrophobicity: a case study on AGC kinase superfamily. Indian J Biochem Biophys 47: 370-7.
6. Chothia C, Lesk AM.(1986) The relation between the divergence of sequence and structure in proteins. EMBOJ 5: 823-6.
7. DiMasi JA, Hansen RW, Grabowski HG, Lasagna L (1991) Cost of innovation in the pharmaceutical industry. J Health Econ 10: 107.
8. Bleicher KH, Bohm HJ, Muller K, Alanine AI (2003) Hit and lead generation: Beyond high-throughput screening. Nat Rev Drug Discov 2: 369-378.
9. DiMasi JA (1995) Trends in drug development costs. Drug Inform 29: 375.
10. DiMasi JA, Hansen RW, Grabowski HG (2003) The price of innovation: new estimates of drug developmentcosts. J Health Econ 22: 151-185.
11. Hileman B (2006) Accounting for R&D, Many doubt the $800 million pharmaceutical price tag. Chemical Eng News 84: 50-51.
12. Lesk AJM (2002) Introduction to bioinformatics. Oxford University Press Inc. New York.
13. Irwin J, Lorber DM, McGovern SL, Wei B, Shoichet BK (2002) Molecular Docking and Drug Discovery. Computational Nanoscience and Nanotechnology 2: 50-51.
14. Taft CA, Silva VB da, Silva CHT de P da (2008) Current topics in computer-aided drug design. J Pharm Sci 97: 1089 - 1098.
15. Hann MM, Oprea TI (2004) Pursuing the leadlikeness concept in pharmaceutical research. Curr Opin. 8: 255–263.
16. Kaczanowski S, Zielenkiewicz P (2010) Why similar protein sequences Encode similar three M dimensional structures. Theoretical Chemistry Accounts 125: 543-50.
17. Marti M, Renom MA, Stuart AC, Fiser A, Sanchez R, et al. (2000) Comparative protein structure modeling of genes and genomes. Annu Rev Biophys Biomol Struct 29: 291-325.
18. Perdo HL (2010) A systematic review on CADD: Docking and Scoring. JMPI 47-51.
19. Banerjee AK, Arora N, Murty U (2012) Analyzing a Potential Drug Target N-Myristoyltransferase of Plasmodium falciparum Through In Silico Approaches. J Glob Infect Dis 4: 43-54.
20. Banerjee AK, Arora N, Murty US (2009) Structural model of the Plasmodium falciparum thioredoxin reductase: a novel target for antimalarial drugs. J Vector Borne Dis 46: 171-83.
21. Arora N, Chari U, Banerjee A, Murty U (2006) A computational approach to explore Plasmodium falciparum 3D7 Chorismate Synthase. The Internet Journal of Genomics and Proteomics 3.
22. Arora N, Banerjee AK, Murty USN (2010) Homology Model of 2C-methyl-d-erythritol 2, 4-cyclodiphosphate (MECP) Synthase of Plasmodium falciparum 3D7. Electronic Journal of Biology 6: 52-57.
23. Banerjee AK, Arora N, Murty USN (2012) Aspartate carbamoyltransferase of Plasmodium falciparum as a potential drug target for designing anti-malarial chemotherapeutic agents. Med Chem Res 21: 2480.
24. Arora N, Banerjee AK, Murty US (2010) In silico characterization of Shikimate Kinase of Shigella flexneri: a potential drug target. Interdiscip Sci 2: 280-90.
25. Arora N, Narasu ML, Banerjee AK (2016) Shikimate Kinase of Yersinia pestis: A Sequence, Structural and Functional Analysis. Int J Biomed Data Min 5: 101.
26. Duddela S, Nataraj SP, Padmavati GV, Banerjee A, Murty USN, et al. (2010) Probing the structure of human glucose transporter 2 and analysis of protein ligand interactions. Med Chem Res 19: 836.
27. da Cunha EE, Barbosa EF, Oliveira AA, Ramalho TC (2010) Molecular modeling of Mycobacterium tuberculosis DNA gyrase and its molecular docking study with gatifloxacin inhibitors. J Biomol Struct Dyn 27: 619-25.
28. Igarashi M, Ito K, Yoshida R, Tomabechi D, Kida H, et al (2010) Predicting the antigenic structure of the pandemic (H1N1) 2009 influenza virus hemagglutinin. PloS one 5: e8553.
29. Banerjee A, Murty U (2006) Extracting the significant descriptors by 2D QSAR and docking efficiency of NRTI drugs: A Molecular Modeling Approach. The Internet Journal of Genomics and Proteomics 2.
30. Lengaure T, Rarery M (1996) Computational methods for molecular docking. Curropnin struct biol 6: 402 406.
31. Varady J, Wu X, Fang X, Min J, Hu Z, et al. (2003) Molecular modeling of the three-dimensional structure of dopamine 3 (D3) subtype receptor: discovery of novel and potent D3 ligands through a hybrid pharmacophore-and structure-based database searching approach. Journal of Medicinal Chemistry 46: 4377-4392.
32. Gray JJ, Moughon S, Wang C, Schueler-Furman O, Kuhlman B, et al. (2003) Protein-protein docking with simultaneous optimization of rigid-body displacement and side-chain conformations. Journal of Molecular Biology 331: 281-299.
33. van Dijk M, Alexandre M, Bonvin JJ (2008) A protein-DNA docking benchmark. Nucleic Acids Research 36: e88-e88.
34. Perez-Cano L, Solernou A, Pons C, Fernández-Recio J (2010) Structural prediction of protein-RNA interaction by computational docking with propensity-

based statistical potentials. Pacific Symposium on Biocomputing 15.

35. Bernard D, Coop A, MacKerell AD Jr (2005) Computer-Aided Drug Design: Structure-Activity Relationships of Delta Opioid Ligands. Drug Des Rev 2: 277-291.

36. Park DS, Kim JM, Lee YB, Ahn CH (2008) QSID Tool: a new three-dimensional QSAR environmental tool. Journal of Computer-Aided Drug Design 22: 873-883.

37. Myung-Eun S, So-Young P, Hyun-Jung L (2002) Comparison of QSAR Methods (CoMFA, CoMSIA, HQSAR) of Anticancer 1-N-Substituted Imidazoquinoline-4,9-dione Derivatives. Bull Korean Chem Soc 23: 417-422.

38. Wold S, Ruhe A, Wold H, Dunn WJ (1984) The collinearity problem in linear regression. The partial least squares approach to generalized inverse. SIAM J Sci Stat Compute 5: 735-743.

39. Cramer RD, Patterson DE, Bunce JD (1988) Comparative Molecular Field Analysis (CoMFA). 1. Effect of Shape on Binding of Steroids to Carrier Proteins. J Am Chem Soc 110: 5959-5967.

40. Verdonk ML, Berdini V, Hartshorn MJ, Mooij WT, Murray CW, et al. (2004) Virtual screening using protein-ligand docking: avoiding artificial enrichment. J Chem Inf Comput Sci 44: 793-806.

41. Kovesdi I, Dominguez-Rodriguez MFD, Orfi L, Naray-Szabo G, Varro A, et al. (1999) Application of neural networks in structure-activity relationships. Med Res Rev 19: 249.

42. Allen MP, Tildesley DJ (1989) Computer Simulation of Liquids, Oxford Science Publications, Oxford, UK 385.

43. Go N, Scherga HA (1970) Ring closure and local conformational deformations of chain molecules. Macromolecules 3: 178-187.

44. Tuckerman ME, Martyna GJ (2000) Understanding Modern Molecular Dynamics: Techniques and Applications. J Phys Chem B 104: 159-178.

45. Malinowski ER, Howery DG (1988) Factor Analysis in Chemistry; Wiley: New York.

46. Walters WP, Stahl MT, Murcko MA (1998) Virtual screening - an overview. Drug Discov Today 3: 160-178.

47. Verma SK, Yadav S, Singh J (2014) Virtual Screening and PharmacophoreAnalysis of Potent Antiviral Inhibitors for Viral Proteins from Ebola virus. J Appl Bioinform Comput Biol 3: 2.

48. Bohacek RS, McMartin C, Guida WC (1996) The art and practice of structure-based drug design: a molecular modeling perspective. Med Res Rev 16: 3-50.

49. Kurogi Y, Guner OF (2001) Pharmacophore modeling and three dimensional database searching for drug design using catalyst. Curr Med Chem 8: 1035-1055.

50. Hopfinger AJ, Duca JS (2000) Extraction of pharmacophore information from high-throughput Screens. Curr Opin Bio technol 11: 97-103.

51. Richard C (2005) Bioinformatics in Computer-Aided Drug Design.

52. McGregor MJ, Muskal SM (1999) Pharmacophore fingerprinting: Application to QSAR and focused library design. J Chem Inf Comput Sci 39: 569-574.

53. Soloman AK (2008) Molecular modelling and drug design. (2ndedtn) MB Publisher.