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Computational Approaches for Drug Design and Discovery Process.

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Abstract
Drug discovery is a critical issue in the pharmaceutical research as it is a very cost effective and time consuming process to produce new drug candidate. So, there is number of computational advances which have significant impact in the field of computer aided drug design over the last several years. These advances can be grouped into three basic areas: conformational modeling (of small molecules, macromolecules and their complexes), property modeling (of physical, biological and chemical properties) and molecular design (to optimize physical, biological or chemical properties). Hence, computational approaches have given a tremendous opportunity to pharmaceutical companies to identify new potential drug targets which in turn affect the success and time of performing clinical trials for discovering new drug targets.

Key Words
Drug discovery, Computational approaches, Molecular modeling.

Introduction
The drug discovery and designing is a very complex and expensive process due to the high costs of R&D and human clinical trials. In 2001 Pharmaceutical research and manufacturers of America (PhRMA) estimated the cost of total drug discovery process about $880 million over a period of 14 years from the initial research stage to the successful marketing of a new drug.[1] So, it requires an interdisciplinary approach to design effective and potential drugs. Thus, Computer aided drug design (CADD) exploits the state-of-the-art technologies to speed up the drug development process.[2] The objective of drug design is to find a lead compound that can fit into a specific site on a target protein both geometrically and chemically. After passing the preclinical and clinical trials, this compound becomes available as drug to patients.[3] The traditional approach involves random screening of chemical compounds obtained from nature or synthesized in the laboratories. The problems associated with this method are long design cycle and high cost. But modern approach involves structure based drug design with the help computational approaches which made the drug discovery process in an efficient manner.[4,5] So, the designing softwares with easy operation and improved computational tools are available to generate chemically, biologically stable and nontoxic compounds. Special emphasis is given on computational approaches for drug discovery along with salient features and applications of the softwares in drug designing.[6,7,8]

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Facts about Drug Discovery Process [9,10,11]
There are a number of factors that affect the drug discovery and development process. The important factors are given below:

a. **Medicinal objective:** Targeting the disease state to develop potential drug candidate.
b. **Ability of Medicinal chemist:** The attributes of the Medicinal chemist will influence the outcome of new drugs on the basis of knowledge of chemistry of lead molecule and biology of disease state.
c. **Screening facilities:** A successful and rapid mass screening mainly depends on the capacity to evaluate a large number of compounds and detect potentially clinically useful drugs in a very short period of time.
d. **Drug development facility:** Good facilities with interdisciplinary efforts by chemistry, biology, pharmacy and medical groups are necessary for drug development.
e. **Cost of new drug:** The following three factors affect the cost of drug development.

- **Number of compounds synthesized:** Of the about 5000-10,000 compounds studied, only one drug reaches the market.
- **Nature of the lead molecule:** Cost of production will be high if the lead molecule is prepared by an expensive route.
- **Standards required for new drugs:** The standards required by regulatory authorities prior to release of a drug into the market have increased dramatically. In the discovery phase, each drug cost about $350 million. The Food and Drug Association processes I, II and III cost another $150 million. This brings the total to about $500 million for each drug put on to the market for consumers.

Modes of Drug Design [12,13]

Now days, after knowing the detail information of the target and lead molecule, a drug are designed with the help of computational tools. This can potentially save pharmaceutical companies, government and academic laboratories alike from pursuing the "wrong" leads. So, it is important to know the following ideal features of a drug molecule.

1. Drug must be safe and effective
2. Drug should have good bioavailability
3. Drug must be metabolically stable and with a long half-life
4. Drug should be nontoxic with minimal or no side effects
5. Drug should have selective distribution to target tissues or disease state

Computational tools used for drug design [14,15,16]

The software that is available for drug design, discovery and development process originates from different sources. These include commercial companies, academic institutions, open source software or in-house development. These software packages also differ in terms of cost, functionality and efficacy, and automation. The salient features of generally used drug design software are given below.

Affinity

- Automated, flexible docking
- Uses the energy of the ligand/receptor complex to automatically find the best binding modes of the ligand to the receptor (energy-driven method)

Argus lab

Argus Lab is a molecular modeling, graphics, and drug design program for Windows operating systems. Argus Lab is freely licensed. It does not need to sign anything. It consists of a user interface that displays the graphical structure of the molecules and runs quantum mechanics calculation using Argus Computing Server16. By using Argus lab we can able to build an atom, build molecules using templates, to change the structure of an atom and bond types, and to build new structures from the pre-existing structures.

Auto Dock

Auto Dock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure. Current distributions of AutoDock consist of two generations of software such as AutoDock 4 and AutoDock Vina. Auto Dock 4 again consists of two main programs such as autodock and autogrid. AutoDock performs the docking of the ligand to a set of grids describing the target protein Autogrid pre-calculates these grids. Auto Dock Vina does not require choosing atom types and pre-calculating grid maps for them. Instead, it calculates the grids internally, for the atom types that are needed, and it does this virtually instantly. AutoDock 4 is free and is available under the GNU General Public License. AutoDock Vina is available under the Apache license, allowing commercial and non-commercial use and redistribution. AutoDock has various applications in the field of:

- X-ray crystallography
- Structure-based drug design
- Lead optimization
- Virtual screening (HTS)
- Combinatorial library design
- Protein-protein docking
- Chemical mechanism studies

Bigger

- Bimolecular complex Generation with Global Evaluation and Ranking
- Efficient protein-docking algorithm
- Predicts the structure of binary protein complexes from the unbound structures
- Search the complete binding space and select a set of candidate complexes

- Evaluates and rank each candidate according to the estimated probability of being an accurate model of the native complex
- Integrated in CHEMERA, a molecular graphics and modeling program for studying protein structures and interactions

Combibuild

- Structure-based drug design program created to aid the design of combinatorial libraries
- Screens a library possible reactants on the computer, and predicts which ones will be the most potent
- Successfully applied to find nanomolar inhibitors of Cathepsin D

FRED

- Accurate and extremely fast, multiconformer docking program
- Examines all possible poses within a protein active site, filtering for shape complementarity and optional pharmacaphoric features before scoring with more conventional functions

FlexiDock

- Simple, flexible docking of ligands into binding sites on proteins
- Fast genetic algorithm for generation of configurations
- Rigid, partially flexible, or fully flexible receptor side chains provide optimal control of ligand binding characteristics
- Conformationally flexible ligands
- Tunable energy evaluation function with special H-bond treatment
- Very fast run times

Flex X

FlexX is one of the most established protein-ligand docking Tools. The technology is based on a robust incremental construction algorithm. The ligand is decomposed into pieces and then flexibly built up in the active site, using a variety of placement strategies. The poses are scored based on a variety of different scoring functions, and all possible data, incl. details about interactions made available for analysis by the user. There is an extension of Flex X called Flex E with flexible receptors, which has shown to produce better results with significantly lower running times. [17]

Complementary to FlexX

The several modules available that will enhance the integration of FlexX into your modeling toolbox are given below

- **FlexX-Pharm:** Docking under receptor-based pharmacophore constraints. Easily define interaction constraints with a few mouse clicks; or define spatial constraints optionally using SMARTS substructure expressions.
- **FlexX-Ensemble:** Extend your docking to include receptor flexibility. This module (formerly FlexE) simultaneously docks into an ensemble of active site conformations and thus allows for an induced fit while placing the ligand.
- **FlexX-Screen:** Docking at warp Speed. Due to several algorithmic tweaks, FlexX-Screen is up to 10 times faster than FlexX, with about the same accuracy. Indispensable for ultrahigh throughput structure based design.
- **FlexXC:** Combinatorial libraries can be docked even more efficiently using this module.
- **FlexX-Permute:** Automatically dock all tautomers, isosters etc.
- **PyFlexX:** The Python version of FlexX provides even more powerful scripting capabilities.

GOLD

GOLD is a Flexible protein-ligand docking program for predicting how flexible molecules will bind to proteins. GOLD uses a genetic algorithm methodology for protein-ligand docking and allows full ligand and partial protein flexibility.

It is suitable for,

- Calculating docking modes of small molecules into protein binding sites
- Genetic algorithm for protein-ligand docking
- Full ligand and partial protein flexibility
- Energy functions partly based on conformational and non-bonded contact information from the CSD

- Choice of scoring functions: GoldScore, ChemScore and User defined score
- Virtual library screening

GOLD Suite Programs

- **Hermes:** for 3D visualisation pre- and post-docking and interactive docking setup.
- **GOLD:** for protein-ligand docking.
- **GoldMine:** for post-processing of docking results.

GRAMM (Global RAnge Molecular Matching)

- Empirical approach to smoothing the intermolecular energy functions by changing the range of the atom-atom potentials
- Performs an exhaustive six-dimensional search through the relative translations and rotations of the molecules
- Used for protein-protein and protein-ligand docking

Haddock

- High-Ambiguity Driven protein-protein Docking
- Generates biochemical and/or biophysical interaction data such as chemical shift perturbation data resulting from nuclear magnetic resonance titration experiments or mutagenesis data introduced as ambiguous interaction restraints to drive the docking process.

Hex

- Protein docking and molecular superposition program
- Uses spherical polar Fourier correlations to accelerate docking calculations

Ligplot

- Program for automatically plotting protein-ligand interactions
- Generates schematic diagrams of protein-ligand interactions for a given PDB file
- Interactions shown are those mediated by hydrogen bonds (dashed lines between the atoms involved) and by hydrophobic contacts (represented by an arc with spokes radiating toward the ligand atoms they contact)

Situs

- Program package for modeling of atomic resolution structures into low-resolution density maps
- Software supports both rigid-body and flexible docking using a variety of fitting strategies

Accelrys

Accelrys is a software company headquartered in the US, with representation in Europe and Japan. It provides software for chemical, materials and bioscience research for the pharmaceutical, biotechnology, consumer packaged goods, aerospace, energy and chemical industries. Accelrys started in 2001 from the fusion of five companies: Molecular Simulations Inc. (MSI, itself a result of the combination of Biodesign, Cambridge Molecular Design, Polygen and, later, Biocad and Biosym Technologies), Synopsys Scientific Systems, Oxford Molecular, the Genetics Computer Group (GCG), and Synomics Ltd. Their products and technologies create solutions for several stages in the drug discovery and developmental process. [18] The different softwares produced by Accelrys are:

a. Insight II
b. Pipeline Pilot
c. Discovery Studio
d. Materials Studio
e. Accord
f. CHARMM
g. MODELLER
h. TOPKAT
i. Tsar
j. Ludi

a. Insight II

Insight II is a comprehensive graphic molecular modeling program. In conjunction with the molecular mechanics/dynamics program Discover, Insight II program can be used to build and manipulate virtually any class of molecule or molecular system. In conjunction with other Accelrys products, molecular properties can be studied.

b. Pipeline Pilot

Pipeline Pilot, is a scientific informatics software solution that aggregates and provides real time access and re-use of the volumes of disparate research data found in R&D. Data modeling in this software is done by modeling tools, statistical works with HTVS- High Through put Virtual Screening mode in which it can retrieve million compound libraries, to Standard Precise (SP) mode in which it docks hundreds to thousands of ligands

with high accuracy. From SP it switches to XP Extra Precision where the false results are changed by advanced scoring. They can also exhibit excellent range of docking accuracy across diverse range of receptors.

c. Discovery Studio

Discovery Studio is a protein modeling program that contains tools to visualize, analyse, modify and simulate protein structures. Discovery studio provides a visualizing tool ActiveX control, which provides 3D molecular structures and sharing scientific results. The sequence analysis is done by using tools such as BLAST (Basic Local Alignment Search Tool) and protein modeling by DS Modeller. It can be operated in different operating system applications such as Linux and Windows based environment.

d. Materials Studio

Materials Studio is software for simulating and modeling materials developed and distributed by Accelrys, a company specializing in research software for computational chemistry, bioinformatics, cheminformatics, molecular simulation, and quantum mechanics. Materials Studio is client server software with Microsoft Windows-based PC clients and Windows and Linux-based servers running on PCs, Linux IA-64 workstations (including Silicon Graphics (SGI) Altix) and HP XC clusters. Materials studio provides tools for modeling crystal structure and crystallization processes; determining structure property and structure activity relationship.

e. Accord

Accord is software specially designed for cheminformatics. They can capture, manage, analyze, and mine chemical data. Accord is oracle based software used for storage, retrieval, analysis of chemical structures and related biological data. Accord is user friendly and is powered by Robust and well proven chemistry engine that can be used for any type of chemistry. This software is used for carrying out sequence analysis, gene expression, prediction of ADME properties and check the toxicity profile of the drugs.

f. CHARMM

CHARMM (Chemistry at Harvard Macromolecular Mechanics) is the name of a widely used set of force fields for molecular dynamics as well as the name for the molecular dynamics simulation and analysis package associated with them. The CHARMM force fields for proteins include: united-atom (sometimes called "extended atom") CHARMM19, all-atom CHARMM22 and its dihedral potential corrected variant CHARMM22/CMAP. CHARMM also includes polarizable force fields using two approaches. One is based on the fluctuating charge (FQ) model, also known as Charge Equilibration (CHEQ). The other is based on the Drude shell or dispersion oscillator model.

g. MODELLER

MODELLER is a computer program used in producing homology models of protein tertiary structures as well as quaternary structures. It implements a technique inspired by nuclear magnetic resonance known as satisfaction of spatial restraints, by which a set of geometrical criteria are used to create a probability density function for the location of each atom in the protein. The method relies on an input sequence alignment between the target amino acid sequence to be modeled and a template protein whose structure has been solved. MODELLER was originally written and is currently maintained by Andrej Sali at the University of California, San Francisco.[3] Although it is freely available for academic use, graphical user interfaces and commercial versions are distributed by Accelrys. A freely available GUI to MODELLER called EasyModeller is developed by Kuntal Kumar Bhusan at University of Hyderabad,India. A new version of EasyModeller (EasyModeller 2.0) has been recently released and available for free download.

h. TOPKAT

It is a computer-assisted toxicology prediction program which is available from Accelrys.

i. Tsar

It is a a fully integrated analysis package for investigation of Quantitative Structure-Activity Relationships (QSARs).

j. Ludi

It fits molecules into the active site of a receptor by matching complementary polar and hydrophobic

groups. It suggests modifications to increase the binding affinity of ligand.

Schrodinger

Schrodinger software is drug design software using both ligand and structure-based methods. It provides accurate, reliable, and high performance computational technology to solve real world problems in life science research. It provides superior solutions and services for the design, selection, and optimization of novel drug candidates. Schrödinger's predictive models will enable drug discovery scientists to assess properties of chemical compounds early in the discovery process and to select drug candidates that have optimal profiles. The predictive power of Schrödinger's software allows scientists to accelerate their research and development activities, reduce research costs, and make novel discoveries that might not be possible with other computational or experimental approaches. [19,20]

The various products of Schrodinger are:

a. Glide
b. Prime
c. Jaguar
d. Macro Model
e. Liaison
f. QSite
g. Maestro
h. LigPrep
i. Phase
j. Strike
k. Induced Fit
l. SiteMap
m. Desmond
n. Impact

a. Glide

Glide offers the full spectrum of speed and accuracy from high-throughput virtual screening of millions of compounds to extremely accurate binding mode predictions, providing consistently high enrichment at every level. Glide offers the full solution for virtual screening from HTVS to SP to XP. Glide reliably finds the correct binding modes for a large set of test compounds. Unlike other methods for docking ligands to the rigid 3D structure of a known protein receptor, Glide approximates a complete systematic search of the conformational, orientational, and positional space of the docked ligand. Comparisons to published data on rms deviations show that Glide is nearly twice as accurate as GOLD as and more than twice as accurate as FlexX for ligands having up to 20 rotatable bonds.

b. Prime

Prime is a fully-integrated protein structure prediction program. Prime is a powerful and complete tool for generating accurate receptor models for structure-based drug design. Homology modeling and fold recognition can be done using prime. Prime allows the users to specify and adjust parameters to optimize the quality of predictions.

c. Jaguar

Jaguarn is quantum mechanics software for small molecules. It is a high performance ab-intio package for both gas and solution phase recreation, with particular strength in treating metal containing systems. Jaguar proceeds faster than the other conventional methods and it makes more possible to carry out more calculations at a single time. Jaguar computes a comprehensive array of molecular properties such as NMR, IR, pKa, partial charges, electron density, electrostatic potential and NBO analysis. It also generates potential energy surface with respect to differences in the internal coordinates.

d. Macro Model

Macro Model is a complete molecular mechanics based modeling (minimization, conformational analysis) of bioorganic systems using a variety of force fields which provides accurate results. Force field molecular modeling is used to examine molecular conformations, molecular motions and inter molecular interactions such as ligand receptor complex. It can also perform molecular dynamics at constant temperatures using mixed Monte Carlo algorithm and stochastic dynamics. They help wide range of searching methods and handling systems in the range of small molecules to entire proteins. Different types of force fields such as MM2, MM3, AMBER, AMBER 94, MMFF, and OPLS-AA are supported by Macro Model to do a wide range of research applications.

e. Liaison

It predicts ligand binding free energies using the linear interaction approximation.

f. QSite

It couples Jaguar's QM capabilities with classical molecular mechanics allowing efficient description of chemical reactions in enzyme active sites. The

hybrid QM/MM model can also be used for the prediction of binding afinities in cases where classical force fields are unreliable (e.g. significant anisotropic polarization).

g. Maestro

Maestro is the unified interface for all Schrödinger software. Impressive rendering capabilities, a powerful selection of analysis tools, and an easy-to-use design combine to make Maestro a versatile modelling environment for all researchers. Schrodinger is proud to make Maestro available to academic users at no charge. Maestro is a powerful and versatile molecular modeling environment, and the portal to the most advanced science in computational chemistry.

h. LigPrep

It generates and cleans up 3D models of bioorganic molecules. This tool is also able to generate 3D structures of possible tautomers and stereoisomers based on 2D representation of the molecule.

i. Phase

It facilitates ligand-based drug design by identifying a pharmacophore based on structures of active compounds

j. Strike

It facilitates ligand-based drug design via quantitative analysis of structure-activity relationships.

k. Induced Fit

It combines the capabilities of Prime and Glide to take into account possible changes in the protein structure upon ligand binding.

l. SiteMap

It identifies possible binding sites, setting up the target protein for subsequent docking studies.

m. Desmond

It is highly parallel molecular dynamics simulation program for macromolecules

n. Impact

It is a molecular mechanics program specifically designed to handle large macromolecular simulations. The program effortlessly treats simulations on ligand-protein systems in solvation or *in vacuo* enabling the study of large systems in a timely manner.

SYBYL

SYBYL is a general molecular modelling program written by Tripos. The SYBYL suite of computational informatics software is designed to enhance the drug discovery workflows and decision-making of today's computational chemists and molecular modelers. SYBYL provides the fundamental components for understanding molecular structure and properties with an emphasis on the discovery of lead candidates. SYBYL applications include validated solutions for key computational chemistry and molecular modelling tasks such as ligand-based design, receptor-based design, structural biology, library design, and cheminformatics. SYBYL, the heart of Tripos expert molecular modeling environment, provides the fundamental components for understanding molecular structure and properties with a special focus on the creation of new chemical entities. [21]

1. **Almond: Calculate and Utilize Alignment Independent Molecular Descriptors.** This new generation of 3D molecular descriptors is useful in 3D-QSAR, virtual screening, and design of combinatorial libraries.
2. **Distill:** Distill clusters compounds according to their common substructures and displays the results to reveal structure-activity relationships.
3. **Molconn-Z:** Molconn-Z5 calculates structural descriptors for use with statistical methods in order to create QSAR and QSPR models that predict biological activity or physical properties of new molecules.
4. **ClogP/CMR:** The ClogP/CMR6 application provides highly accurate calculated logP and molar refractivity values.
5. **VolSurf:** VolSurf predicts ADME properties using pre-calculated models; computes unique, ADME-relevant descriptors; and creates QSAR models of bioactivity or property.
6. **HQSAR:** Hologram QSAR (HQSAR) uses molecular holograms and PLS to generate fragment based structure-activity relationships.
7. **GALAHAD:** GALAHAD7 allows researchers to automatically develop pharmacophore hypotheses and structural alignments from a set of molecules that bind at a common site.

8. **GASP:** GASP8 performs pharmacophore elucidation without requiring prior knowledge of pharmacophore elements or constraints.
9. **Tuplets:** Tuplets facilitates the retrieval of compounds from molecular structure databases that are likely to exhibit biological activity. Additionally, Tuplets can be used to prioritize virtual combinatorial libraries for pharmaceutical research and can provide a biasing descriptor to allow the design of focused combinatorial libraries.
10. **DISCOtech:** DISCOtech10 performs pharmacophore elucidation from a set of active compounds. Starting from a set of representative conformers for each molecule, DISCOtech considers all possible mappings of features to create a set of alignments, each of which is a hypothesis for the pharmacophore and its geometry.
11. **Surflex-Dock:** Surflex-Dock9 offers unparalleled enrichments in virtual high-throughput screening combined with state-of-the-art speed, accuracy, and usability.
12. **CScore:** CScore uses multiple types of scoring functions to rank the affinity of ligands bound to the active site of a receptor.
13. **EA-Invento:** EA-Inventor2 is a new and different approach to de novo design. It enables researchers to invent new compounds, new R-groups around a fixed scaffold, or new scaffolds.
14. **LeapFrog:** LeapFrog uses a receptor site or a CoMFA model as the basis for de novo ligand design, and can be used to optimize lead compounds or to generate novel structures.
15. **RACHEL:** RACHEL performs automated combinatorialoptimization of lead compounds by systemically derivatizing user-defined sites on the ligand.
16. **Biopolymer:** Biopolymer delivers an extensive set of tools for building, predicting, visualizing, and manipulating the 3D structure of proteins, peptides, nucleic acids, and polysaccharides.
17. **ProTable:** ProTable uses SYBYL's MolecularSpreadsheet to analyze and evaluate protein structures. ProTable creates Ramachandranplots, assesses deviation of local geometries and sidechain rotameric states from standard protein values, and determines the energetic and structural properties of each residue.
18. **SiteID:** SiteID provides analysis and visualization tools to identify potential binding sites within or at the surface of macromolecules.
19. **Composer:** Composer12 builds 3D models of proteins from sequence using knowledge-based homology modeling methods. For a given protein sequence, Composer searches a database of known structures to find homologous proteins. Composer aligns regions of the sequences that have topological equivalence and completes construction of a 3D model by adding sidechains using rule-based substitution tables and suitable loop fragments of high-resolution protein structures.
20. **FUGUE:** FUGUE13 recognizes distant structural homologs of a target sequence by sequencestructure comparison. It assesses the compatibility between a target sequence and structural profiles of all known protein structural families. The key elements of FUGUE are environment-specific substitution tables, structure-dependent gap penalties,automated alignment method selection.
21. **GeneFold:** GeneFold14 identifies a protein's function from its amino acid sequence. Sequence homology and threading methods are used to recognize protein folding patterns. GeneFold threads a new sequence through known protein structures and calculates how well the sequence matches.
22. **MatchMaker:** MatchMaker14 uses an inverse-folding method to predict the 3D structure of a protein from its amino acid sequence. By comparing a new protein sequence to its topology fingerprint database, MatchMaker assesses the ability of a sequence to adopt characteristic topologies.
23. **Legion/CombiLibMaker:** Legion and CombiLibMaker2 provide the capability for building and storing combinatorial libraries of compounds. Libraries of compounds can be defined and enumerated with full control of stereochemistry.
24. **OptDesign:** Starting from a virtual combinatorial library (cSLN file), OptDesign selects compounds that balance the practical constraints of combinatorial library design, such as cost and ease of synthesis, with diversity and representativeness, thereby performing true double-objective optimization.

25. **Selector:** Selector characterizes, compares, and samples sets of compounds. Selector can create diverse or representative subsets, filter compound lists based on properties, find compounds similar to a lead compound, and mcompare the diversity of sets of compounds.
26. **DiverseSolutions:** DiverseSolutions2 assesses the chemical diversity of a population of molecules, selects diverse or representative subsets, and compares the diversity of two or more different populations of molecules.
27. **UNITY:** UNITY is a search and analysis system for exploring chemical and biological databases. UNITY's 2D searching capabilities offer exact, substructure, and similarity searching.
28. **Concord:** Concord sets the industry standard for extremely rapid conversion of 2D (or crude 3D) input to accurate, geometry-optimized 3D structures.
29. **Confort:** Confort2 is a powerful conformational analysis tool that performs exhaustive yet rapid analysis of drug-sized molecules. It can be used to identify the global minimum energy conformer, all local minima within a userspecified energy range, or a maximally diverse subset of conformers.
30. **ProtoPlex:** ProtoPlex2 provides a mechanism for making accurate and realistic structural representations of chemical compounds. ProtoPlex allows users to control the protonation, deprotonation, or tautomerization for each chemical class of proto-centers
31. **MM3:** MM315 is one of the most highly respected, peer reviewed software systems available for performing molecular mechanics calculations.
32. **MM4:** MM415 is the latest in a well-known series of molecular mechanics programs for generating high quality geometries and energies for calculating small molecule structures. MM4 offers increased accuracy in calculating molecular structures, performing conformational analyses, and computing spectroscopic and thermodynamic properties.
33. **StereoPlex:** StereoPlex2 generates multiple stereoisomers of each input compound structure according to a user-specified limit on the number of stereoisomers and a user-specified priority rule which tells the program which stereoisomers to generate if the complete set would exceed the user's limit.
34. **AMPAC:** Rapidly Calculate Transition States and Spectral Properties Using Semiempirical Quantum Mechanics
35. **HiVol:** HiVol works within the SYBYL environment to facilitate the exploration of a high volume of data such as that generated by highthroughput synthesis or screening.
36. **GSSI:** GSSI2 is a novel, general approach to modeling solution-phase properties through a fairly rigorous yet efficient consideration of solute-solvent interactions. It is useful for predicting various partition coefficients and membrane permeability coefficients in support of ADME-related efforts.
37. **HSCF:** HSCF is a unique semiempirical molecular orbital (MO) "information server."
38. **Hint:** Hint provides tools to visualize and calculate the relative strengths of non-covalent interactions between and within biological molecules. It calculates 3D hydropathy fields and 3D hydropathic interaction maps and estimates LogP for modeled molecules or data files.
39. **ZAP:** ZAP uses the Poisson-Boltzmann equation to calculate the electrostatic potential surrounding a molecule in a medium of varying dielectric.

VLifeMDS

VLifeMDS is a comprehensive and integrated software package for computer aided drug and molecular discovery. With its flexible architecture, VLifeMDS is ready to meet demands from a structure based design approach as well as a ligand based design approach. VLife's offerings have a range of applications in life sciences and allied sectors, including pharmaceutical, biotechnology, agri-biotechnology, chemical, petrochemical, cosmetics, nutraceutical and healthcare. [22]

VLife's includes following drug design soft wares

a. **VLife Molecular Design Suite (VLifeMDSTM):** A comprehensive integrated suite of discovery products with modular functionalities for molecular modeling, simulation, analysis, visualization, interpretation and prediction.
b. **QSARProTM:** Specialty software for Quantitative Structure Activity Relationship with multiple methods for variable selection, statistical regression and visualization.

c. **ChemXplorTM:** Software focused on chemoinformatics database generation and database search based on molecular structures, descriptors, fingerprints.
d. **BioPredictaTM:** Specialty software for protein modeling and interaction studies
e. **VLifeBase:** For molecule draw, visualization and analysis
f. **VLife Engine:** For all molecular operations and key activity of conformer generation
g. **ProModel:** For homology modeling with options for manual and automated template based modeling
h. **VLifeDock:** For docking studies with multiple scoring functions and options for rapid and high precision docking
i. **GQSAR:** To obtain site specific clues for new molecule design and optimization.
j. **VLifeQSAR:** For 2D/ 3D QSAR with multiple variable selection options and regressions methods
k. **VLifeAutoQSAR:** For an automated workflow of the entire QSAR modeling and for a consensus based result on the best model.
l. **VLife SCOPE:** To optimize lead design based on interaction between the molecule and interacting residues in the active site.
m. **ChemDBS:** For exploring databases with multiple search options including property, fingerprint and pharmacophore based.
n. **MolSign:** For pharmacophore generation and application in optimization and searches.
o. **ProViz:** For calculating and visualizing molecular properties on the surface of a molecule
p. **LeadGrow:** For creating combinatorial library with a choice of substitutions.
q. **LeadGrow+:** An extension to the combinatorial library generation capability that ensures that molecules which can be synthesized can only be generated in a library.
r. **ConfAlys:** Generate conformers systematically or with Monte Carlo method. Get the results in the W orkSheet with row, column & function based operations (Plot, Comparison, Correlation etc.).
s. **MolBuild (Engine):** Draw the molecular structures and Visualize molecules in various models, colors, scales and orientations.
t. **BioPredicta:** Construct proteins / polypeptides / DNA / RNA just by choosing amino/nucleic acid residues and secondary structure. Edit protein structures using mutation, insertion, deletion, excising, joining, renumbering of residues etc.
u. **CombiLib:** Generate combinatorial libraries of molecules with structural templates. Construct and save your own templates and substituents for further use. Choose functional groups for substitution at each site.
v. **Chem Phore:** Pharmacophore identifcation is carried out. Enhance your searches using receptor or pharmacophore based queries. Identify the pharmacophoric points for an active site of receptor just by picking.

Biosuite

BioSuite is a versatile, comprehensive, portable, scalable software suite, catering to the needs of scientists and academicians and to the bioinformatics industry. The Bio-Suite package is divided into four main modules: Genomics, Protein modeling and Structural analysis, Simulations and Drug Design. This software suite has been developed in such a way that it can be used for genome analysing, sequence analysing, 3D modelling, simulation, manipulation, structural changes, drug design, pathway modelling, SNP analysis and comparative genomics. The suite runs on platforms such as Compaq, IBM Aix, SGI, Linux clusters and the operating systems of Unix and Linux flavours, the official said. The 3D structure manipulations in the module will help in building molecules, side chain placements and stereo chemical editing and the drug design model will help in developing de-novo designs with high throughput screening of chemical databases, the official claimed. [23]

Conclusion

Drug designing softwares has potential role to design novel proteins or drugs in biotechnology or pharmaceutical field. The drug designing softwares are used to analyze molecular modeling of gene, gene expression, gene sequence analysis and 3D structure of proteins. In addition, drug designing area has important role in the diagnosis of diseases such as lung cancer, brain cancer, breast cancer and Alzheimer disease. This review article summarizes the structure based drug designing and ligand based drug designing softwares and their applications in the field of medicinal research.

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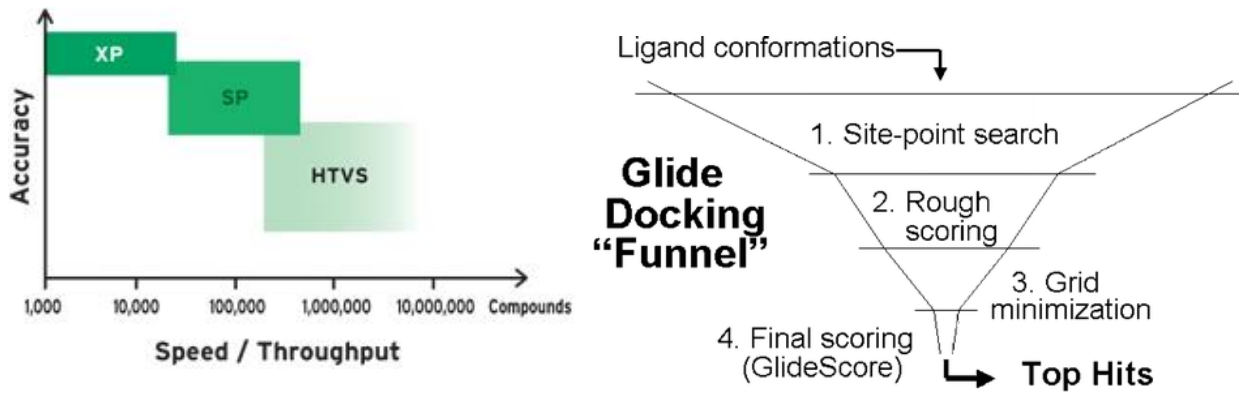

Fig: 1: Application of Glide for virtual screening from HTVS to SP to XP with its Docking funnel.

Table: 1 List of drug design software packages.

Sl. No.	Name of Software	Types of Software	Company /institution	Application	Websites
1.	Insight II, Discovery studio	Structure based	Accelrys	Graphical molecular modelling and de novo drug design.	http://www.accelrys.com /products
2.	Bio-suite	Structure based	Tata consultancy services	Genomics, Protein modeling, structural analysis, simulation and drug design.	http://www. Atc.tcs.com/biosuite
3.	Phase,Glide, Liasion	Ligand based	Schrodinger	Pharmacophore modeling, Ligand receptor docking.	http://www. Schrodinger.com
4.	Rachel, GALAHAD, HQSAR	Ligand-based and receptor-based design,	Tripos	Computational informatics software for drug discovery	http://www.tripos.com
5.	Sanjeevini	Structure based	IIT, Delhi	Active site directed drug design	http://www.scfbioitd.in/research/drugdesign.htm
6.	VLifeAutoQSAR	Structure based as well as a ligand based design	VLifeMDS	Pharmacophore generation, homology modeling	www.vlifesciences.com

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