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NEW TECHNIQUES IN MOLECULAR MODELLING

Anil Kumar V.*, Vandana K. and Namitha K. Baby

Department of Pharmaceutical Chemistry, National College of Pharmacy, Kozhikode 673602, Kerala, India.

***Corresponding Author: Anil Kumar V.**
Department of Pharmaceutical Chemistry, National College of Pharmacy, Kozhikode 673602, Kerala, India.

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ABSTRACT
Molecular modeling has become a valuable and essential tool to medicinal chemists in the drug design process. Molecular modeling describes the generation, manipulation or representation of three-dimensional structures of molecules and associated physico-chemical properties. Modeling is a tool for doing chemistry. Models are central for understanding of chemistry. Molecular modeling allows us to do and teach chemistry better by providing better tools for investigating, interpreting, explaining and discovering new phenomena. It involves a range of computerized techniques based on theoretical chemistry methods and experimental data to predict molecular and biological properties. Depending on the context and the rigor, the subject is often referred to as 'molecular graphics', 'molecular visualizations', 'computational chemistry', or 'computational quantum chemistry'. The molecular modeling techniques are derived from the concepts of molecular orbitals of Huckel, Mullikan and 'classical mechanical programs' of Westheimer, Wiberg and Boyd. Like experimental chemistry, it is a skill-demanding science and must be learnt by doing and not just reading. Molecular modeling is easy to perform with currently available software, but the difficulty lies in getting the right model and proper interpretation.

KEYWORDS: Auto dock, skeletal model, PASS, Ball stick model.

INTRODUCTION

Molecular modeling (MM) is one of the fastest growing fields in science. It may vary from building and visualizing simple molecules in three dimensions (3D) to performing complex computer simulations on large proteins and nanostructures. MM is a collection of computer-based techniques for driving, representing and manipulating the structures and reactions of molecules, and those properties that are dependent on these 3D structures. The techniques in MM cover several issues among them computational chemistry, drug design, computational biology, nanostructures, and material science One of the new fields in MM is the study of the self-assembly of molecules that forms nanostructures. The self-assembly processes of the single chain and the double chain surfactants are compared using Monte-Carlo simulations.

Finally, one of the main advancements in the last five years is the study of material science using MM. Advancement using a combination of DFT with periodic boundary conditions and generalized gradient approximation methods. This issue does not include peer-reviewed articles on drug design. Yet, we found that the issue drug design is an interactive topic in MM and contribute to drug discovery both in academia and in industry. Computer-aided and structure-based drug design relies on knowledge of the 3D structure of the biological target. Drug design is an iterative process that begins when a compound is identified to display an interesting biological profile and ends when its activity profile and the chemical synthesis are optimized. Today, MM permeates all aspects of drug design.

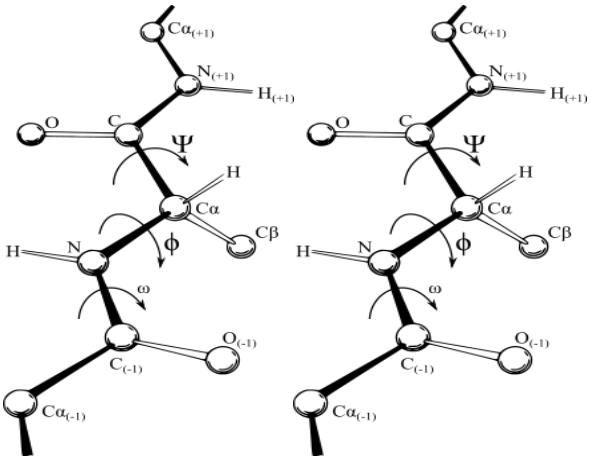

Fig. 1: The backbone dihedral angles in the molecular model of a protein.

A molecular model (Fig 1), in this article, is a physical model that represents molecules and their processes. The creation of mathematical models of molecular properties and behavior is molecular modelling, and their graphical

depiction is molecular graphics, but these topics are closely linked and each uses techniques from the others. In this article, "molecular model" will primarily refer to systems containing more than one atom and where nuclear structure is neglected. The electronic structure is often also omitted or represented in a highly sophisticated way.

Physical models of atomistic systems have played an important role in understanding chemistry and generating and testing hypotheses. Most commonly there is an explicit representation of atoms, though other approaches such as soap films and other continuous media have been useful.

The construction of physical models is often a creative act, and many bespoke examples have been carefully created in the workshops of science departments. There is a very wide range of approaches to physical modelling, and this article lists only the most common or historically important

Molecular models have inspired molecular graphics, initially in textbooks and research articles and more recently on computers. Molecular graphics has replaced some functions of physical molecular models, but physical kits continue to be very popular and are sold in large numbers. Their unique strengths include: Cheapness and portability; Immediate tactile and visual messages and easy interactivity for many processes (e.g., conformational analysis and pseudo rotation).

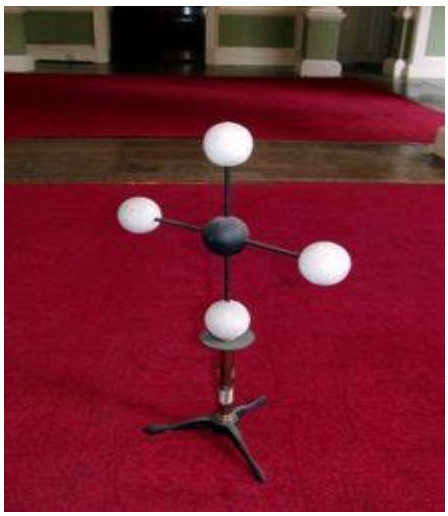

Fig. 2: Hofmann's model for methane.

John Dalton represented compounds as aggregations of circular atoms, and although Johann Josef Loschmidt did not create physical models, his diagrams based on circles are two-dimensional analogues of later models. August Wilhelm von Hofmann is credited with the first physical molecular model around 1860 (Fig. 2). Note how the size of the carbon appears smaller than the hydrogen. The importance of stereochemistry was not then recognized and the model is essentially topological (it should be a 3-dimensional tetrahedron).

Jacobus Henricus van't Hoff and Joseph Le Bel introduced the concept of chemistry in space stereochemistry in three dimensions. Van't Hoff built tetrahedral molecules representing the three-dimensional properties of carbon.

Models based on spheres

Repeating units will help to show how easy it is and clear it is to represent molecules through balls that represent atoms.

Fig. 3: Sodium chloride lattice.

Sodium chloride (NaCl) lattice (Fig 3), showing close-packed spheres representing a face-centered cubic AB lattice similar to that of NaCl and most other alkali halides. In this model the spheres are equal sizes whereas more "realistic" models would have different radii for cations and anions.

The binary compounds sodium chloride (NaCl) and caesium chloride (CsCl) have cubic structures but have different space groups. This can be rationalized in terms of close packing of spheres of different sizes. For example, NaCl can be described as close-packed chloride ions (in a face-centered cubic lattice) with sodium ions in the octahedral holes. After the development of X-ray crystallography as a tool for determining crystal structures, many laboratories built models based on spheres. With the development of plastic or polystyrene balls it is now easy to create such models.

Models based on ball-and-stick

The concept of the chemical bond as a direct link between atoms can be modelled by linking balls (atoms) with sticks/rods (bonds). This has been extremely popular and is still widely used today. Initially atoms were made of spherical wooden balls with specially drilled holes for rods. Thus carbon can be represented as a sphere with four holes at the tetrahedral angles A problem with rigid bonds and holes is that systems with arbitrary angles could not be built. This can be overcome with flexible bonds, originally helical springs but now usually plastic. This also allows double and triple bonds to be approximated by multiple single bonds.

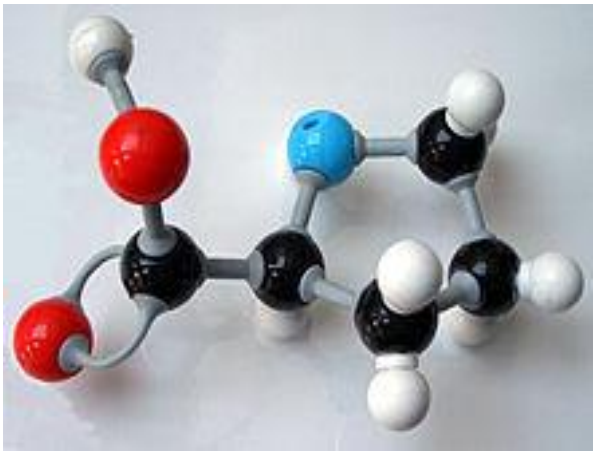

Fig. 4: A modern plastic ball and stick model. The molecule shown is proline.

Model represents a ball and stick model of proline. The balls have colours: blackrepresents carbon (C); red, oxygen (O); blue, nitrogen (N); and white, hydrogen (H). Each ball is drilled with as many holes as its conventional valence (C: 4; N: 3; O: 2; H: 1) directed towards the vertices of a tetrahedron (Fig 4). Single bonds are represented by (fairly) rigid grey rods. Double and triple bonds use two longer flexible bonds which restrict rotation and support conventional cis/trans stereochemistry.

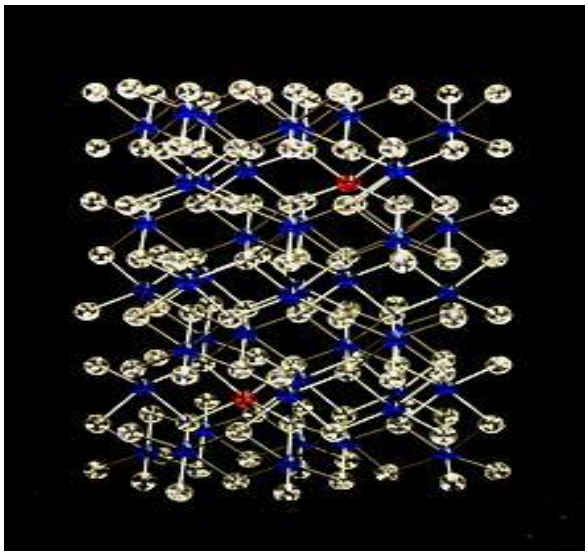

Fig. 5: Beevers ball and stick model of ruby made with acrylic balls and stainless-steel rods.

However, most molecules require holes at other angles and specialist companies manufacture kits and bespoke models. Besides tetrahedral, trigonal and octahedral holes, there were all-purpose balls with 24 holes (Fig 5). These models allowed rotation about the single rod bonds, which could be both an advantage (showing molecular flexibility) and a disadvantage (models are floppy). The approximate scale was 5 cm per ångström (0.5 m/nm or 500,000,000:1), but was not consistent over all elements.

Skeletal models

Crick and Watson's DNA model and the protein-building kits of Kendrew were among the first skeletal models. These were based on atomic components where the valences were represented by rods; the atoms were points at the intersections. Bonds were created by linking components with tubular connectors with locking screws.

André Dreiding introduced a molecular modelling kit in the late 1950s which dispensed with the connectors. A given atom would have solid and hollow valence spikes. The solid rods clicked into the tubes forming a bond, usually with free rotation. These were and are very widely used in organic chemistry departments and were made so accurately that interatomic measurements could be made by ruler.

More recently, inexpensive plastic models (such as Orbit) use a similar principle. A small plastic sphere has protuberances onto which plastic tubes can be fitted. The flexibility of the plastic means that distorted geometries can be made.

Polyhedral models

Many inorganic solids consist of atoms surrounded by a coordination sphere of electronegative atoms (e.g. PO_4 tetrahedra, TiO_6 octahedra). Structures can be modelled by gluing together polyhedra made of paper or plastic.

Composite models

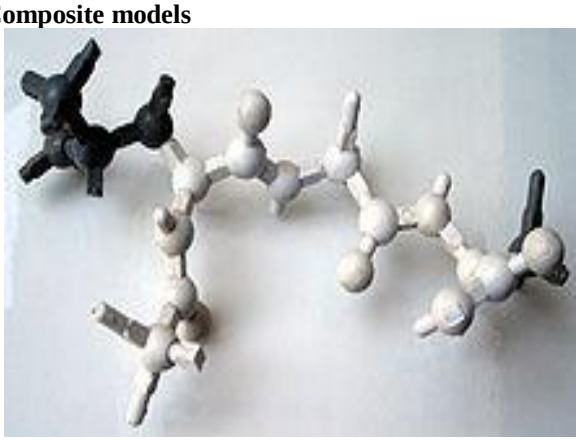

Fig. 6: A Nicholson model, showing a short part of protein backbone (white) with side chains (grey).

A good example of composite models is the Nicholson approach (Fig 6), widely used from the late 1970s for building models of biological macromolecules. The components are primarily amino acids and nucleic acids with preformed residues representing groups of atoms. Many of these atoms are directly moulded into the template and fit together by pushing plastic stubs into small holes. The plastic grips well and makes bonds difficult to rotate, so that arbitrary torsion angles can be set and retain their value. The conformations of the backbone and side chains are determined by pre-computing the torsion angles and then adjusting the model with a protractor.

Computer-based models

Fig 7: Integrated protein models.

With the development of computer-based physical modelling (Fig 7), it is now possible to create complete single-piece models by feeding the coordinates of a surface into the computer. Figure shows models of anthrax toxin, left (at a scale of approximately 20 Å/cm or 1:5,000,000) and green fluorescent protein, right (5 cm high, at a scale of about 4 Å/cm or 1:25,000,000) from 3D Molecular Design. Models are made of plaster or starch, using a rapid prototyping process.

It has also recently become possible to create accurate molecular models inside glass blocks using a technique known as subsurface laser engraving. The image at right (Fig. 8) shows the 3D structure of an *E. coli* protein (DNA polymerase beta-subunit, PDB code 1MMI) etched inside a block of glass by British company Luminorum Ltd.

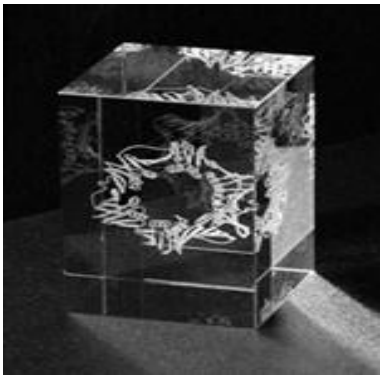

Fig 8: Protein model in glass.

Software based approaches for drug designing and development

Drug discovery include drug designing and development, is a multifarious and expensive endeavor, where least number of drugs that pass the clinical trials makes it to market. Software based drug discovery and development methods have major role in the development of bioactive compounds for over last three decades. Novel software based methods such as molecular modeling, structure-based drug design, structure-based virtual screening, ligand interaction and molecular dynamics are considered to be powerful tool for investigation of pharmacokinetic and pharmacodynamics properties of drug, and structural activity relationship between ligand and its target. Computational approaches such as docking confer interaction of small molecules with structural macromolecules and thereby hit identification and lead optimization. These methods are faster, and accurately provide valuable insights of experimental findings and mechanisms of action. In addition, appropriate implementation of these techniques could lead to a reduction in cost of drug designing and development. Currently in biomedicine sciences this software is exhibiting imperative role in the different phases of drug discovery. The review discusses working principle and successful applications of most commonly used software for drug designing and development.

To overcome these problems, it is needed to employ new and more cost effective drug discovery and designing methods (Fig 9) such as software and computer aided drug design and molecular docking. The present review highlights commonly used software used for new drug development along with their potential uses.

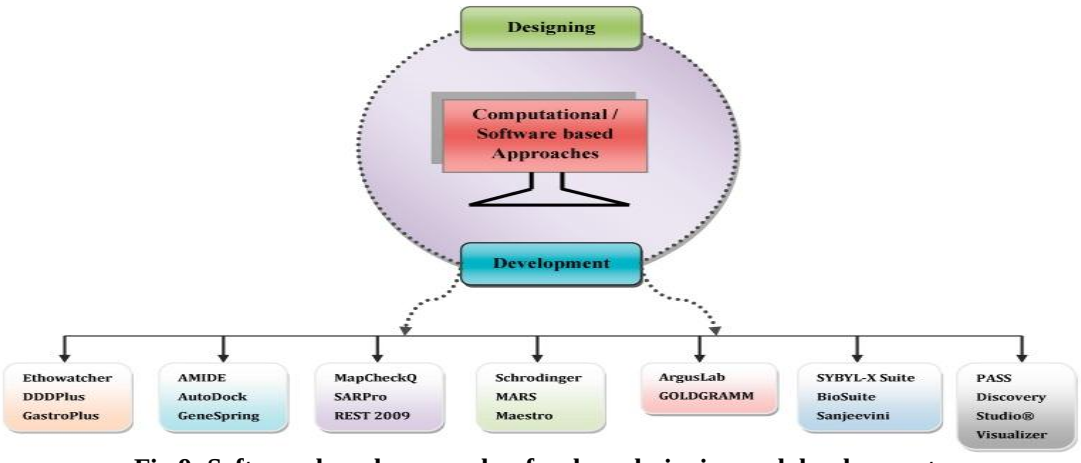

Fig 9: Software based approaches for drug designing and development.

Software for drug designing, discovery and development

The software are further categorized on the basis of task performing by the software and their working principle like software assessing pharmacokinetic parameters, ligand interactions and molecular dynamic, molecular modeling and structural activity relationship, image analysis and visualizers, data analyzer and behavior analysis software.

DDDPlus (Dose Dissolution and Disintegration software)

DDDPlus (Dose Disintegration and Dissolution Plus) is used to study disintegration and dissolution pattern of dosage form and active ingredients. It is an advanced computer program employed by formulation scientists to simulate in vitro disintegration and dissolution of active pharmaceutical ingredients (API) and excipients under different experimental conditions. In the formulation of new API, a single calibration experiment is generally required, after which DDDPlus predicts how changes in formulation or experimental parameters will affect the dissolution rate. This software provides precise information of dissolution and disintegration rate so it is not necessary to rely on conventional 'cut and try' methods to finalize a formulation design. DDDPlus allow selecting from one of 5 mathematical models and 5 dosage forms employed to illustrate dissolution of a single ingredient.

GastroPlus (simulation software for drug discovery and development)

GastroPlus is a mechanistically based simulation software package that simulates intravenous, oral, oral cavity, ocular, intranasal and pulmonary absorption, pharmacokinetics, and pharmacodynamics in human and animals.

Model parameters can be fitted to data for a single record, or across multiple records simultaneously. The program will run one simulation for each record each time and it changes the values of one or more model parameters. Typically, hundreds of iterations will be performed, each with N simulations, where N is the number of records whose observations are being used to compare predicted and observed values. Objective function weighting is user-defined, and includes the most common weighting schemes.

MapCheck

The MapCheck compare absolute dose measurements of both systems with ion chamber results. It compares IMRT QA process of Sunnuclear's MapCheck and Varian's Portal Dosimetry.

The MapCheck system create verification plan for each field, export calculated dose map (Frontal) to MapCheck for each field, calibrated diode array prior to collecting data. Standard deviation increases with plan complexity. The average measured dose is independent of plan complexity. It is user friendly software for data analysis, easier commissioning process and generates comprehensive report.

AutoDock

AutoDock is an automated program employed to predict ligand and protein (bio-macromolecular targets) interactions. Continuous advancement in bimolecular X-ray crystallography helps to provide structural information of complex biomolecules such as protein and nucleic acids. These structures could be employed as targets for new drug molecules in controlling human, animal and plant diseases and disorders, and understanding of fundamental aspects of biology.

- Multiple steps are employed for Auto Dock calculations:
- Preparation of coordinate files using Auto Dock tools.
- Precalculation of atomic affinities using Auto Grid.
- Docking of ligands using Auto Dock.
- Analysis of results using Auto Dock Tools.
- Coordinate file preparation.

AutoDock4.2 is optimized to use a model containing protein and ligand that includes polar hydrogen atoms, but not hydrogen atoms bonded to carbon atoms. An extended PDB format, termed PDBQT, is used for coordinate files, which includes atomic partial charges and atom types. The current AutoDock force field uses several atom types for the most common atoms, including separate types for aliphatic and aromatic carbon atoms, and separate types for polar atoms that form hydrogen bonds and those that do not. PDBQT files also include information on the torsional degrees of freedom. AutoGrid calculation

Analysis using AutoDock tools

AutoDock Tools encompass of different techniques for analyzing the results of docking simulations, comprising tools for clustering results by conformational similarity, visualizing confirmations, ligand protein interactions, and affinity potentials created by AutoGrid. It is involved in the identification of aromatic rings and used to explore the conformational states of a flexible ligand, using the maps generated by AutoGrid to evaluate the ligand-protein interaction at each point in the docking simulation.

Schrodinger

Schrodinger software has wide range of applications that can solve most of the challenges these bio-molecules will bring. It highlights particular advances in molecular modeling, molecular dynamics, ligand-receptor docking, and biologics that were designed to handle these challenges. Structure based properties of molecule such as understanding of conformational changes and hydrophobicity of structures can be analyzed by this software.

The molecular dynamics simulations software is employed to study a series of stabilized stapled α-helical peptides at different temperatures. The predicted α-helical propensities derived from the simulations were in good agreement with the experimentally observed circular dichroism melting curves. The local flexibility of key residues could be related to differences in affinity of the stapled peptides binding to MDM2. These simulations explore new approaches for the α-helical stapled peptides designing and development of potent inhibitors of α-helical protein–protein interfaces. The main advantages are in Molecular dynamics simulation studies, Quantum mechanics and for the prediction of binding affinity.

GOLD (Genetic Optimization for Ligand Docking)

GOLD (Genetic Optimization for Ligand Docking) is a genetic algorithm to provide docking of flexible ligand and a protein with flexible hydroxyl groups. This software uses a scoring function which is based on favorable conformations found in Cambridge Structural Database and on empirical results on weak chemical interactions. Different values of the genetic algorithm parameters are used to control the balance between the speed of GOLD and the reliability of its predictions. It gives reliable results and correct atom typing for both protein and ligand.

GOLD is a part of GOLD Suite software that also includes two additional software components, Hermes and GoldMine. GOLD provides all the functionality required for docking ligands into protein binding sites from prepared input files. The Hermes visualize is used for the preparation of input files for docking with GOLD, visualization of docking results and calculation of descriptors. The input files like the addition of hydrogen atoms, including those necessary for defining the correct ionization and tautomeric states of protein residues are obtained from Hermes. The Hermes visualizer is also employed for interactive docking setup such as for defining the binding site and the setting of constraints. Gold Mine is a tool for the analysis and post-processing of docking results. GOLD will likely be used in conjunction with a modeling program to create and edit starting models. It is used for Protein-Ligand Docking by using Genetic Algorithm and for binding mode predictions.

BioSuite

BioSuite together utilize the functions of macromolecular sequence and structural analysis, chemo informatics and algorithms for aiding drug discovery. It is organized into four major modules containing 79 different programs making it one of the few comprehensive suites that cater to a major part of the spectrum of bioinformatics applications. The four major modules Genome and Proteome Sequence Analysis, 3D Modeling and Structural Analysis, Molecular Dynamics Simulations and Drug design, are made available through a convenient graphics-user interface along with adequate documentation and tutorials.

The Genome and Proteome Sequence Analysis module of BioSuite deals with the applications relating to the analysis of the nucleic acid and protein sequences, not only of individual molecules, but also of complete genome and proteome sequences. This module would enable to annotate genomes, predict protein secondary structures, derive a phylogenetic relationship among organisms and compare two genomes for similarities at the gene or protein level.

The 3D modeling and analysis module has capabilities to build, analyze and predict three dimensional structures of macromolecules and macromolecular complexes. The 'Simulations' module essentially simulates the behavior of a molecule, in terms of its three-dimensional structure.

Molecular modeling and structural activity relationship

Maestro

Maestro is freely available, full-featured molecular visualization software. Maestro is a powerful tool for interpreting, managing, and sharing the results of computational experiments. It helps for building, visualizing, and sharing 3-dimensional chemical models.

Maestro is the linchpin of Schrodinger's computational technology. It is powerful and versatile tool for the molecular modeling in the field of computational chemistry. It manages organization and analysis of obtained data. Maestro's intuitive interface makes setting up calculations easy and straightforward. The computed results are automatically returned and incorporated into projects for further study. Maestro's vast array of visualization options makes it possible to glean insight into molecular properties as well as detailed intermolecular interactions. It is used in the quantitative structural analysis and in the visualization of vibrational modes, molecular orbital, or electron density and molecular properties.

ArgusLab

ArgusLab is a molecular modeling, graphics, and drug design program for Windows operating systems. Conformational analysis such as geometry optimization study was performed on a window-based computer using ArgusLab.

This software works on the principle of quantum mechanics and helps to predict potential energies, molecular structures, geometry optimization of structure, vibration frequencies of coordinates of atoms, bond length, bond angle and reactions pathway. ArgusLab calculate minimum potential energy using geometry convergence function. The main advantages are in molecular docking calculations, It is used to build molecules, Building of molecules using template structure, and for molecular modeling Package.

GRAMM (global range molecular matching)
GRAMM software is used for protein docking. It predicts structure using atomic coordinates of the two molecules. It produces list of high-score (low-energy) ligand positions which further used as it is or refined by other techniques. This software does not use a statistical sampling, but rather performs an exhaustive search to get all configurations of the complex with the high-score steric fit. This software performs an exhaustive 6-dimensional search through the relative translations and rotations of the molecules. The molecular pairs may be two proteins, a protein and a smaller compound and two trans membrane helices etc. It is used for high-resolution of molecules for inaccurate structures in cases of large conformational changes. Thus, the docking of high-resolution structures with small conformational changes yields an accurate prediction, while the docking of ultralow resolution structures will produce only the gross features of the complex. It is mainly applied in protein-protein docking and protein-ligand docking.

SYBYL–X Suite
SYBYL-X gives information to understand and balance the competing SAR's for each of the multiple criteria which successful drug candidate must meet. It visualizes and explores relationships between multiple properties with the analysis tools in the new Molecular Data Explorer (MDE) in SYBYL-X and obtains insights into data in least time. It provides new ways to approach life science molecular discovery projects, while extending the unrivaled.

SYBYL-X explore different insights of drug interaction mechanism with its receptor to identify potential new binding interactions that will provide 'step jumps' in potency, or to identify options for improving ADME or physical properties without disrupting key receptor interactions. It is used in molecular modeling from sequence through lead optimization, Ligand Based Design, Structural Based Design and to build a Protein Model.

Sanjeevini
This software is developed to provide a computational pathway for automating lead design. It utilizes bimolecular (protein) target and a candidate drug. Software is perform identification of potential active sites, docking and scores the candidate drug and returns four structures of the candidate drug bound to protein target together with binding free energies.

In this software the drug molecule is uploaded with target protein. On uploading, software pops-up a window which displays the results of some essential pre-tests done based on the parameters needed for the acceptable format of the drug and protein files. The software contains following modules such as Drug Preparation, Protein Preparation, Docking and Scoring, and Protein Ligand Complex. It is used for drug designing, predicts binding affinity and for the prediction of protein-ligand binding affinity.

PASS (prediction of activity spectra of substances)
This software predicts possible biological activities of new pharmaceutical substance of lead molecule based on 4366 kinds of biological activity with an average prediction accuracy of about 95%.

The prediction of biological activities in PASS is described qualitatively interns of 'yes/no' or 'active/inactive'. To know possible biological activities, the structure of new chemical compound is converted in 2D structural formulae. The molecular structure is represented in PASS by the set of unique MNA descriptors. The substances are considered to be equivalent in PASS if they have the same set of MNA descriptors. The PASS algorithm of biological activity spectrum prediction is based on Bayesian estimates of probabilities of molecules belonging to the classes of active and inactive compounds, respectively. The structural formula of a molecule, for which PASS prediction should be carried out, is presented as a MOL file. It is used to reveal new effects and mechanisms of action for known substances in corporate and personal databases, to find new leads with given biological activity profiles among the compounds from in-house and commercial databases and to select the most promising compounds from available samples for high throughput screening.

Image analysis and visualizers
AMIDE (A Medical Image Data Examiner)
AMIDE is developed in such a way that, it should provide multimodality volumetric medical image analysis. Data sets (e.g. PET, CT, and MRI) and regions of interest (ROI's) are logically organized within a tree structure so that an unlimited number of these items can be displayed, modified, and analyzed simultaneously.

The data hierarchy within AMIDE is built around a tree abstraction composed of a succession of objects such as data sets and ROI's each object in AMIDE is assigned its own Euclidean space, and the location of this local coordinate frame is defined with respect to the global coordinate frame. It is used to provides multi-modality medical image analysis to the molecular imaging research community and gives interactive "wizard" interfaces for making advanced medical imaging algorithms (e.g. factor analysis and cardiac polar maps).

Discovery Studio Visualizer
Discovery Studio Visualizer (DS Visualizer) is used for viewing, sharing and analyzing protein and small molecule data. It is a free and employed for both small molecule and macromolecule applications.

It allows data to be transferred and analyze data in several formats like graphics, 3D structures, SMILES and sequences. The required structures and sequence can

be downloaded from PDB or NCBI. Molecular properties can be explored by editing structures and performing calculations. It is used in visualization: Advanced molecular visualizations, publication quality graphics, macromolecule design, multi-domain protein sequences (e.g. Antibodies) editing and for prediction of secondary structures.

Imaging software Scge-Pro

SCGE-Pro is widely used for single cell gel electrophoresis or Comet assay. It is a collaborative project with Computer Division on development of imaging software for cytogenetic and DNA damage analysis. Genotoxicity of environmental factors such as low and high LET radiations, drugs, chemical mutagens and carcinogens is investigated by employing Comet assay.

In this imaging method fluorescence in-situ hybridization (FISH) technique is used to measure gene specific repair in relation to total DNA or loss of heterozygosis (LOH) for single gene. An intracellular DNA damage in different cell as well as repair kinetics of eukaryotic cell is investigated through these assays. Studies such as effect of 3.3 MeV proton beams on DNA damage of mouse peripheral blood leukocytes is carried out using Neutral Comet assay. It is used in clinical application such as prenatal diagnosis, DNA repair deficiency syndrome, diabetes, cancer susceptibility, genomic instability, human bio-monitoring: Aging and nutrition, environmental bio-monitoring.

Xenogen living image software

Wave Metrics IGOR Pro1, a powerful data analysis and programming tool is used for Xenogen Living Image Software. The software forms custom environment which is employed for acquisition and analysis of data. Macintosh® and Windows® both supports the software functioning. The working of software includes an image acquisition control panel, image display and analysis window, system status and dialog window, and a lab book window. Software tools are present at the top of menu bar for both IGOR Pro and Living Image software. During Igor Pro software running remaining menu items that support Living Image software remains inactive to avoid interface clutter and confusion.

GeneSpring

GeneSpring gives information related to terminology used to refer to various organizational elements in the user interface and supplies a high-level overview of the data and analysis paradigms available in the application.

This software represents a collection of samples for which arrays have been run in order to answer a specific scientific question. In this, a new experiment is created from selected project. New experiment by loading samples of a technology and performing a set of customary pre-processing steps like, normalization, summarization, and baseline transform etc. which will convert the raw data to a state where it is ready for analysis. Multiple samples are involved in the experiment with which it was created, multiple interpretations, which group these samples by user-defined experimental parameters, and all other objects created because of various analysis steps in the experiment.

QSARPro

This software identifies of relationship of a molecular activity or property with the structural parameters, analysis of such relationships and rapid predictions using reliable statistical modeling. It is employed to evaluate more than 1000 molecular descriptors including physicochemical, topological and electro-topological, information theory based, quantum mechanical, electrostatic and hydrophobic, alignment independent, MMFF atom types and so on. QSAR modeling typically involve activities such as descriptor choice and calculation, statistical evaluation of the calculated descriptors, training and test set assignment, regression and results analysis. It evaluates multiple options for classes of descriptors, test set, choice of linear or nonlinear regression and choice of regression technique to determine the option that is most suitable to a project. It is used to explore and exercise various combinations of variable selection methods and regression methods, aligning given set of molecules in the protein active site with respect to the co-crystal ligand to develop a basis for the placement of ligand and in protein-protein interaction studies.

REST 2009 Software

REST 2009 Software is a single tool for analysis of gene expression data from quantitative and real-time PCR experiments. The analysis or quantitation of relative gene expression uses expression of reference genes to normalize expression levels of genes of interest (GOI) in different samples. This method allows quantitative PCR data to be adjusted, for example to compensate for variations due to sample loading differences. This software uses a mathematic model which considers the different PCR efficiencies of the gene of interest and reference genes. The reliability of results is enhanced by comparing single reference gene and using multiple reference genes for normalization. It is used to determine whether a significant difference exists between samples and controls and for behavioral study.

Ethowatcher

Behavioral change is considered to be major parameter to diagnose range of disorders. Complex behaviors of experimental animal are associated with morphological and physiological changes. These changes are often recorded in laboratory or free-ranging animals for many purposes relevant to biological or biomedical research such as ecology, physiology, neurosciences, psychology, genetics, pharmacology and pathology. Advanced automated techniques selectively record behaviors indirectly by detecting their consequences through the

activation of pressure or infrared sensors or by image processing techniques such as those derived from video-tracking analysis.

Ethowatcher is based on C++ language and under C++ builder 5.0 environments. This software is integrated tool to build and save behavioral changes, used for 'real-time' behavioral scoring (like directly from the ongoing events in the environment or from analog video files) or 'off-line' behavioral recordings (from digital video files). The obtained digital video file may be processed for automated extraction of activity-related parameters (distance traveled, angle, velocity, approximate object area, track graph) and object (animal) tracking using digital image processing techniques. The software provides time-segmented reports on sequence, duration, frequency and latency of the scored behaviors, and on the activity related-indices and further these reports are synchronized by the same time source. It is used as a validation tool for behavior analysis in laboratory animal and for video-tracking analysis in laboratory animals.

MARS (Multimodal Animal Rotation System)

MARS is a Multimodal Animal Rotation System which captures 360° movement of an experimental animal. The software is designed in such a way that it automatically rotates a mouse to the required positions or angels to track all the relevant molecular and anatomical information of experimental animal. It also captures optical signals generated due to orientation of experimental.

Using this software automatic co-registration and capturing of multimodal and multispectral data sets from all acquired angles is possible. The software amplifies obtained signal sensitivity by quantifying the perfect image or exporting complete rotation movements or video. This software includes animal rotation device, controlling software, and multimodal visualization and co-registration software. It is used in cell tracking, Enzyme activity, Bone disease, inflammatory disease and in nanoparticle tracking and delivery.

CONCLUSION

In this review, we have discussed different software-based approaches that are playing major role in the drug designing and drug discovery now days. Successful implementation of software-based techniques provided an opportunity for the in vitro identification of biologically active agents, without bias towards known hits or leads. New methods such as docking also help to unravel multifarious mechanisms underlying complex target ligands interaction. Significant advances and application of new softwares continue to be made in the field of pharmacokinetic and pharmacodynamic are benefitting discovery and cost woes of the several biochemical industries. Several previous examples of drugs like indinavir, the HIV protease inhibitor that are output of software based drug discovery will serve as the ultimate proof that the software and software based approaches can indeed be used to assist the costly, complex and highly challenging drug designing and discovery process.

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