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CONTRIBUTIONS OF SOFTWARES IN DRUG DESIGN: A REVIEW

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ABSTRACT

Drug discovery encompass of drug designing and drug development. It is an expansive, extravagant strive with typical development time of 10-15 years, where least number of drugs that pass the clinical trials reach the market. Software based drug discovery have major role in the development of bioactive compounds and has potential role to design novel proteins or drugs in biotechnology or pharmaceutical field. These software's are used to analyse molecular modelling of gene, gene expression, gene sequence analysis and also for 3D structure of proteins and has crucial role in the diagnosis of lung cancer, brain cancer, breast cancer and Alzheimer disease. These methods are faster, and accurately provide valuable insights of experimental findings, mechanisms of action and appropriate implementation could lead to a reduction in cost of drug designing and development. These software's are exhibiting exigent role in the identification of a target and the discovery of some suitable drug molecule that can activate or inactivate the target. Computer aided drug design CADD or Computer assisted Molecular-designing CAMD are the computer-assisted techniques to design, discover and augment biologically active compounds. The software's such as Insight II, Discovery Studio, Materials Studio, Accord, Prime and Jaguar are designed for structure- based drug designing and the software's such as Glide, Macro Model, Auto dock and Argus lab are designed for ligand-based drug designing. These software also has prominent role in molecular dynamics, which are considered to be a powerful tool for investigation of pharmacokinetic and pharmacodynamics properties of drug and structural activity relationship between ligand and its target. Such software's are indeed useful to assist the costly, complex and highly challenging field of pharmacokinetic and pharmacodynamic that are benefitting the drug development process.

KEYWORDS: Drug design, Drug development, CAAD, Software.

INTRODUCTION

Drug discovery encompass of drug designing and drug development. It is an expansive, extravagant strive with typical development time of 10-15 years, where least number of drugs that pass the clinical trials reaches the market. Software based drug discovery have major role in the development of bioactive compounds and has potential role to design novel proteins or drugs in biotechnology or pharmaceutical field. It is an extravagant process due to the high costs of R&D and human clinical tests. Discovery of a new drug encompass the identification of a target and the discovery of some suitable drug candidates that can block or activate the target. Drug designing or rational drug design is a method of finding new medications based on the biological receptors and target molecules, which involves the designing of small molecules which is complementary to the biological receptor to which they bind and interact to cause the pharmacological actions. Clinical trial is the most time taking and costly phase in drug development, which is done in order to acquire the necessary government approvals.

Flourishing drug discovery, development and launch of single new drug into the market require high costs and nearly 12 years. High cost, insufficient and lengthy time duration, high level of risk, uncertainty in the results, and highly complex procedures are the main obstacles in the development of new drug. To overcome these obstacles, there is a requirement of employing a new and more cost effective drug discovery and designing procedures like software and computer aided drug design and molecular docking.

Software and model based tools have become a critical factor for the drug discovery and development in pharmaceutical industry, playing a key role in expanding new bio-active drugs across a range of therapeutic field. Execution of these techniques can minimise the numbers of animals needed in the preclinical stages of drug discovery, easy handling of huge data, and enhance the accuracy of study results. Right use of these software and computer based modern methods have minimise the several obstacles in the procedures of drug discovery and facilitated the development of a new drug. Modern

medicinal chemistry techniques like molecular modelling, structure-based drug design, structure-based virtual screening, ligand based modelling and molecular dynamics are the tools to understand the pharmacokinetic and pharmacodynamic properties, and structural activity relationship of ligands with its target. Combine application of modelling such as ligand based computer aided drug designing (CADD) and simulations provide a strong tool for modernizing clinical study design and analysis.

The computer-assisted techniques used to design, discover and optimize biologically active compounds are Computer aided drug design CADD or the Computer assisted drug design or the Computer assisted Molecular-designing CAMD. CADD is used not only to the design the potential compounds but also to minimise the steps of going from an "Idea to Drug" and also find out new leads. The recent update in CADD are finding out the ligands that will interact with the receptor that is present at the target site or the site of action. Binding of a ligand to the receptor involves various types of interactions like the hydrophobic, electrostatic and hydrogen bonding interactions. CADD reduces the fight of a ligand in a receptor site and is dependent on the quantity of data that is available on the ligand and the receptor.

A computer needs software for its functions such as programs. This software makes our work simpler and faster. 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 modelling and structural activity relationship, image analysis and visualizers, data analyser and behaviour analysis software Various companies such as Accelrys, Schrodinger, Auto Dock and Argus Lab offering drug designing software.

Software for drug designing, discovery and development

Serial No	Software Name	Parameter	Uses
1	DDDPlus	Pharmacokinetic parameters	Dissolution and disintegration study
2	GastroPlus		In-vitro and in vivo correlation for various formulations
3	MapCheck		Compare dose or fluency measurement
4	AutoDock		Evaluate the ligand-protein interaction
5	Schrodinger		Ligand-receptor docking
6	GOLD	Ligand interactions and molecular dynamic	Protein-ligand docking
7	BioSuite		Genome analysing and sequence analysing
9	ArgusLab		Molecular docking calculations and molecular modelling package
10	GRAMM		Protein-protein docking and protein-ligand docking
13	PASS		Create and analysis of SAR models
14	AMIDE (A Medical Image Data Examiner)	Image analysis and Visualizers	Medical image analysis in molecular imaging
16	Imaging Software Scge-Pro		Cytogenetic and DNA damage analysis
20	REST 2009 Software		Analysis of gene expression data
21	Ethowatcher	Behavioural study	Behaviour analysis
22	MARS (Multimodal Animal Rotation System)		Animal activity tracking, enzyme activity, nanoparticle tracking and delivery study

Accelrys

It is a software company which cater software's especially for drug discovery and materials science. Their products and technologies create solutions for several stages in the drug discovery and developmental process4. The different software's produced are Insight II, Pipeline Pilot, Discovery Studio, Materials Studio, Accord.

DDD Plus

DDD Plus (Dose Disintegration and Dissolution Plus) is a key to study about disintegration and dissolution pattern of dosage form and active ingredients. It can be used to model and simulate the in vitro dissolution of active pharmaceutical ingredients (API) and formulation excipients under various experimental conditions in seconds, and begin making informed decisions to help improve your chances for success.

Gastro Plus

Gastro Plus (simulation software for drug discovery and development),simulates intravenous, oral, oral cavity, ocular, intranasal and pulmonary absorption, pharmacokinetics, and pharmacodynamics in human and animals. Use with either compartmental or physiologically based pharmacokinetics (PBPK Plus), Apply competitive and/or time-dependent inhibition kinetics by parent and/or metabolite, Simulate DDIs for any species, Account for enzyme expression level differences in various populations and Built-in tool to easily calculate the fraction metabolized from in vitro assays. It is used to transporter-based drug-drug interactions, Metabolic and/or transporter induction.

Map Check
The Map Check analogize absolute dose measurements of both systems with ion chamber results. It analogize IMRT QA process of Sunnuclear's Map Check and Varian's Portal Dosimetry it is used for IMRT verification, Small detectors identify MLC and Dose based EPID IMRT QA done by using Map Check.

Auto Dock
Auto Dock is a key to find ligand and protein (bio-macromolecular targets) interactions. Continuous advancement in bimolecular X-ray crystallography gives structural information of complex biomolecules such as protein and nucleic acids which could be recruited as targets for new drug molecules in controlling human, animal and plant diseases and disorders, and understanding of fundamental aspects of biology, used for the Identification of aromatic rings and to explore the conformational states of a flexible ligand, using the maps generated by Auto Grid to evaluate the ligand-protein interaction at each point in the docking simulation.

Schrodinger
Schrodinger foreground particular advances in molecular modelling, molecular dynamics, ligand-receptor docking, and biologics. Structure based properties of molecule such as understanding of conformational changes and hydrophobicity of structures can be enumerated by this software. It helps in Molecular dynamics simulation studies, Quantum mechanics and Prediction of binding affinity. The various products of Schrodinger are: Glide,Prime,Jaguar and Macro Model

GOLD
GOLD (Genetic Optimization for Ligand Docking) is a genetic algorithm to contribute docking of flexible ligand and a protein with flexible hydroxyl groups. It gives reliable results and correct atom typing for both protein and ligand. It is used for Protein-Ligand Docking by using Genetic Algorithm and also for binding mode predictions.

Flex X
It uses MIMUMBA torsion angle database for the creation of conformers. The MIMUMBA is an interaction geometry database used exactly to describe intermolecular interaction patterns. Flex X shows totally opposite behaviour to DOCK. It has a bit lower hit rate than DOCK but cater better estimates of Root Mean Square Distance for compounds with correctly predicted binding mode. Extensions of Flex X called Flex E with receptors, which has shown to produce better results with significantly lower running times.

Bio Suite
Bio Suite together make use of the functions of macromolecular sequence and structural analysis, chemo informatics and algorithms for aiding drug discovery. It is arranged into four major modules containing 79 different programs making it one of the few comprehensive suites that serve to a major part of the spectrum of bioinformatics application. Mainly used in Genome analysing and sequence analysing and also in 3D modelling, simulation, structural changes, drug design, pathway modelling, SNP analysis and comparative genomics.

Argus Lab
Argus Lab includes molecular modelling, graphics, and drug design program for Windows operating systems. Conformational analysis such as geometry optimization study was done on a window based computer using Argus Lab. Uses are Molecular docking calculations, to build molecules, Building of molecules using template structure and for molecular modelling Package.

GRAMM
GRAMM(global range molecular matching) software is a key for protein docking and envision the structure using atomic coordinates of the two molecules. It bring about list of high-score (low-energy) ligand positions which further used as it is or refined by other techniques. It is used for protein-protein docking and protein-ligand docking.

PASS
PASS (prediction of activity spectra of substances) software envision the possible biological activities of new pharmaceutical substance of lead molecule based on comparison of library of existing structures. Reveal new effects and mechanisms of action for known substances in corporate and personal databases, Find new leads with given biological activity profiles among the compounds from in-house and commercial databases, Select the most promising compounds from available samples for high throughput screening are its uses.

AMIDE
AMIDE (A Medical Image Data Examiner) is generated in such a way that, it should cater multimodality volumetric medical image analysis. It Provides multi-modality medical image analysis to the molecular imaging research community.

SCGE-Pro
SCGE-Pro is a key for single cell gel electrophoresis or Comet assay. Genotoxicity of environmental factors such as low and high LET radiations, drugs, chemical mutagens and carcinogens is found out by employing Comet assay. Prenatal diagnosis, DNA repair deficiency syndrome, diabetes, cancer susceptibility, genomic instability, Human bio- monitoring: Aging and nutrition, Environmental bio-monitoring: Aquatic or terrestrial conditions, Genotoxicity evaluation of radiation and chemicals in human and animal models and Clinical and molecular epidemiology, agricultural sciences, radiation biology are the areas where they are used.

REST 2009 Software
REST 2009 Software is a single device for analysis of

gene expression data from quantitative and real-time PCR experiments. The quantitation of relative gene expression uses expression of reference genes to normalize expression levels of genes of interest (GOI) in different samples and allows quantitative PCR data to be adjusted, for example to compensate for variations due to sample loading differences. It is used to determine whether a significant difference exists between samples and controls.

Ethowatcher

Behavioural change is a major criterion to diagnose range of disorders. This software helps to build and save behavioural changes, used for 'real-time' behavioural scoring or 'off-line' behavioural recordings. Validation of a tool for behaviour analysis in laboratory animal and Video-tracking analysis in laboratory animals. Are its uses.

MARS

MARS (Multimodal Animal Rotation System) is a Multimodal Animal Rotation System which captures 360° movement of an experimental animal, it automatically rotates a mouse to the required positions or angels to track all the relevant molecular and anatomical information of experimental animal and also captures optical signals generated due to orientation of experimental. Applications are Cell tracking, Enzyme activity, Bone disease, Inflammatory disease and Nanoparticle tracking and delivery.

CONCLUSION

Software and model based tools have become a critical factor for the drug discovery and development in pharmaceutical industry, playing a key role in expanding new bio-active drugs across a range of therapeutic field. Implementation of software based techniques cater an opportunity for the in vitro identification of biologically active agents, without bias towards known hits or leads. Methods such as docking also help to undo diverse mechanisms high lighting complex target ligands interaction. It made a milestone in the field of pharmacokinetic and pharmacodynamic resulting in proving benefits in the process of drug discovery. The drug designing software's such as Insight II, Discovery Studio, Materials Studio, Accord, Prime and Jaguar are for structure based drug designing and drug designing software's such as Glide, Macro Model, Autodock and Argus lab are for ligand based drug designing and structural based drug designing software's for molecular modelling, protein modelling and gene sequence analysis.

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