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Review Article

Computational Strategies in Rational Drug Design: A Software-Centric Review

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ABSTRACT

The integration of advanced computational tools and software platforms has significantly transformed modern drug discovery and development processes. Traditional drug development is associated with high costs, extended timelines, and considerable uncertainty; however, the adoption of computer-aided drug design (CADD) and related in silico techniques has helped overcome many of these limitations. Methods such as molecular modeling, virtual screening, molecular docking, molecular dynamics simulations, and quantitative structure–activity relationship (QSAR) analysis enable efficient prediction of pharmacokinetic and pharmacodynamic properties, as well as detailed understanding of ligand–target interactions. A wide range of specialized software tools supports different stages of drug development. Programs such as DDDPlus and GastroPlus facilitate pharmacokinetic and biopharmaceutical modeling, while AutoDock and Schrödinger enable accurate analysis of ligand–protein interactions and structure-based drug design. Molecular modeling tools including Maestro, ArgusLab, GRAMM, and PASS assist in structural visualization and biological activity prediction. Additionally, imaging and visualization platforms such as AMIDE and Discovery Studio Visualizer enhance molecular interpretation, while data analysis tools like GeneSpring, QSARPro, and REST 2009 enable comprehensive analysis of complex biological datasets. Behavioral and in vivo analysis systems, including MARS and Ethowatcher, further extend computational approaches into preclinical research. Despite certain limitations, such as restricted receptor flexibility, reliance on approximate scoring functions, and high costs associated with proprietary software, these computational approaches continue to evolve. The integration of artificial intelligence, machine learning, and high-performance computing is expected

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to further enhance predictive accuracy and efficiency. Overall, software-driven methodologies play a critical role in accelerating drug discovery, reducing costs, and improving the development of safe and effective therapeutic agents.

INTRODUCTION

The discovery and optimization of novel drugs with bioactive properties across diverse therapeutic areas have been significantly supported by advances in software programs and version-based hardware systems. The extensive use of computer-aided approaches has accelerated the drug discovery process by removing many of the bottlenecks that previously limited progress. Computational medicinal chemistry techniques such as molecular modeling and virtual screening, ligand-based modeling, and molecular dynamics simulations are widely employed to elucidate the pharmacokinetic and pharmacodynamic properties of drug molecules, as well as to analyze the structure–activity relationships between ligands and their biological targets. Ligand-based computer-aided drug design (CADD) and simulation techniques offer a robust framework for advancing modern drug design and analytical processes. The adoption of these approaches helps minimize the reliance on animal models in preclinical and clinical studies while enabling efficient handling and analysis of large and complex datasets involved in drug discovery [1].

The successful discovery, development, and commercialization of a single new drug typically require an investment of approximately one billion dollars and nearly 12 years to complete. The drug development process is challenged by high financial costs, extended timelines, significant risks, uncertainty in outcomes, and highly complex regulatory and experimental procedures. To address these challenges, there is a need to adopt innovative and more cost-effective drug discovery and design approaches, such as software-based tools, computer-aided drug design (CADD), and molecular docking techniques. The present review focuses on commonly used software platforms involved in new drug development and highlights their potential applications in the drug discovery process [2].

SOFTWARE FOR DRUG DESIGNING, DISCOVERY AND DEVELOPMENT:

Software can be further classified based on the tasks they perform and their underlying working principles. These categories include software used for assessing pharmacokinetic parameters, analyzing ligand–receptor interactions and molecular dynamics, performing molecular modeling and structure–activity relationship studies, conducting image analysis and visualization, as well as data analysis and behavioral analysis [2].

Table 1 Software and computer-based programs used in drug discovery and development

Software name	Major use
1. Pharmacokinetic parameters	
DDDPlus	Dissolution and disintegration study
GastroPlus	In-vitro and in vivo correlation for various formulations
MapCheck	Compare dose or fluency measurements
2. Ligand interaction and molecular dynamics	
AutoDock	Evaluate the ligand-protein interactions
Schrodinger	Ligand-receptor docking
GOLD	Protein-ligand docking
BioSuite	Genome analyzing and sequence analyzing

3.Molecular modelling and structural activity relationship Maestro ArgusLab GRAMM SYBYL-X Suite Sanjeevini PASS	 Molecular modelling analysis Molecular docking calculations and molecular modelling package Protein-protein docking and protein-ligand docking Molecular modelling and ligand-based design Predict protein-ligand binding affinity Create and analysis of SAR models
4. Image analysis and Visualizers AMIDE (A Medical Image Data Examiner) Discovery Studio Visualizer Imaging Software Scge-Pro Xenogen Living Image Software	 Medical image analysis in molecular imaging Viewing and analyzing protein data Cytogenetic and DNA damage analysis In vivo imaging display and analysis
5. Data analysis GeneSpring QSARPro REST 2009 Software	 Assess sample to sample variation and define the correction procedure Protein-protein interaction study Analysis of gene expression data
6. Behavioural study Ethowatcher MARS (Multimodal Animal Rotation System)	 Behaviour analysis Animal activity tracking, enzyme activity, nanoparticle tracking and delivery study [2]

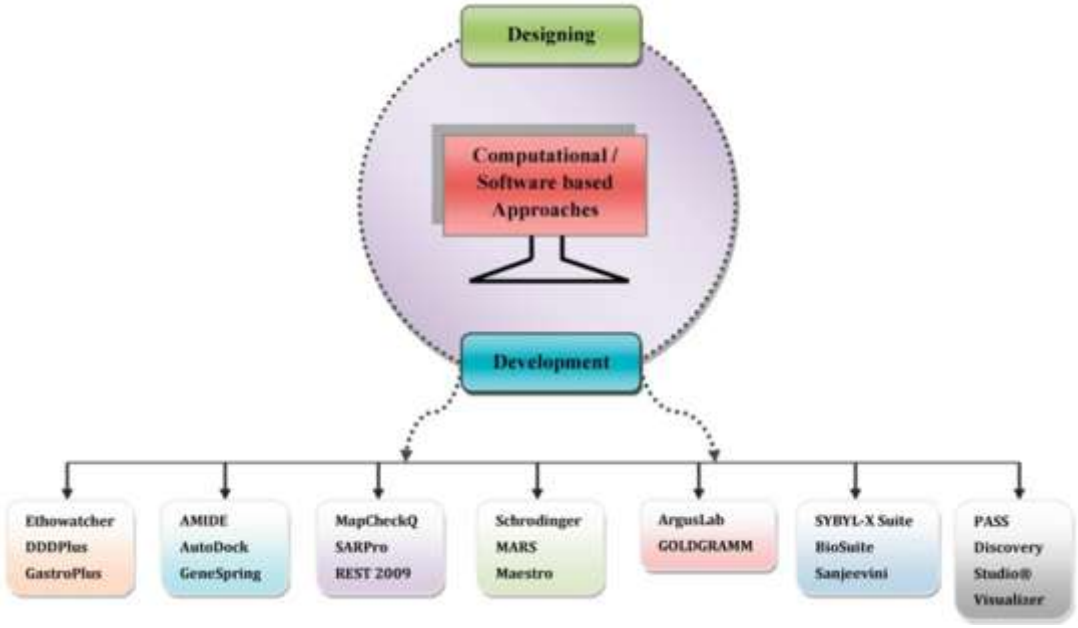

Fig. 1. Software based approaches for drug designing and development

1. PHARMACOKINETIC PARAMETERS:

1.1. DDDPlus:

DDDPlus (Dose Disintegration and Dissolution Plus) is a sophisticated computational tool used to simulate the in-vitro disintegration and dissolution behaviour of active pharmaceutical ingredients (APIs) and excipients in pharmaceutical formulations. Drug dissolution is a crucial step for drug absorption since the API must first dissolve before it can be absorbed into the systemic circulation. Therefore, in-vitro dissolution testing

is extensively employed during drug development to evaluate formulations and to maintain consistent batch-to-batch quality during pharmaceutical production. It also assists in assessing various factors such as gastrointestinal conditions, risk of dose dumping, food-related effects on bioavailability, and interactions between APIs and excipients [1].

During the development of new APIs, DDDPlus typically requires only a single calibration experiment, after which the program can estimate how modifications in formulation or experimental conditions influence the dissolution rate. The software offers reliable data on dissolution and disintegration behaviour, thereby minimizing the dependence on conventional trial-and-error approaches in formulation design. Furthermore, DDDPlus enables the use of five mathematical models and five dosage form options to simulate the dissolution characteristics of an individual ingredient and to analyse the effect of formulation and experimental variables on the dissolution process [2].

ADVANTAGES:

- The Optimization Module in DDDPlus allows rapid development of accurate models using experimental data.
- It helps evaluate formulations and predict dissolution behaviour under different formulation parameters such as particle size, API amount, excipient content, and compression force.
- The Parameter Sensitivity Analysis feature assesses the effect of key input variables on the predicted dissolution profile [1].

USES:

- ✓ DDDPlus can automatically determine the fluid velocity based on the type of dissolution apparatus and the instrument's rotational speed.
- ✓ DDDPlus includes an optimization module that can calibrate the drug dissolution rate using a single set of experimental data [2].

1.2. GASTRO PLUS:

GastroPlus is a mechanistic simulation software used to model drug absorption, biopharmaceutics, pharmacokinetics, and pharmacodynamics in both humans and animals [1]. The software can simulate drug absorption through several administration routes, including intravenous, oral, oral cavity, ocular, intranasal, pulmonary, inhalation, and dermal routes [2]. During each execution of the program, one or more model parameters are adjusted while simulations are carried out for each record [1]. Generally, hundreds of iterations are performed, each containing N simulations, where N represents the number of records used to compare predicted and observed results. Furthermore, objective or goal function weighting is defined by the user and includes commonly applied weighting methods [2].

ADVANTAGES:

- Improves understanding and prediction of drug pharmacokinetics and tissue distribution.
- Integrates in-vitro and in-silico data to enhance PBPK model accuracy.
- Estimates drug solubility and absorption based on physiological parameters such as pH and pKa [1].

DISADVANTAGES:

- Requires a large amount of input data for accurate simulations.
- Needs multiple biopharmaceutical parameters for proper modelling.
- Some parameters are estimated from published population data, which may affect accuracy [1].

USES:

- ✓ GastroPlus can analyze transporter-mediated drug–drug interactions (DDIs) and metabolic or transporter induction, which are important in drug development [1,2].
- ✓ It is integrated with the Advanced Compartmental Absorption and Transit (ACAT) model, widely used to study drug dissolution and absorption [1].
- ✓ The software can simulate DDIs in different species using compartmental or physiologically based pharmacokinetic (PBPKPlus) models [2].

2. LIGAND INTERACTION AND MOLECULAR DYNAMICS:

2.1. AUTODOCK:

AutoDock is a widely recognized molecular docking software that has been developed as one of the early tools in the field of computational docking. It functions as an automated approach for predicting interactions between small molecules and biomacromolecular targets such as proteins and nucleic acids. The creation of AutoDock was driven by challenges encountered in the rational design of bioactive compounds, and it has since become an important component of computer-aided drug design. The program applies a Lamarckian genetic algorithm to perform global conformational searches and utilizes an empirical energy-based scoring function to estimate ligand binding affinities.

During docking, AutoDock allows flexibility of ligands while treating receptors as either rigid or partially flexible systems. The increasing availability of three-dimensional biomolecular structures obtained through X-ray crystallography has enabled the use of proteins and nucleic acids as reliable drug targets for therapeutic applications in plant and animal diseases. A thorough understanding of ligand–target interactions is essential for effective drug development, but achieving high accuracy while minimizing computational cost remains a major challenge. To address this, AutoDock simplifies the docking process by employing grid-based energy calculations and an efficient search of torsional degrees of freedom, allowing docking simulations to be completed within practical time limits on standard laboratory computers [2-5].

ADVANTAGES:

- **Open-source and freely available**

AutoDock, along with its graphical interface AutoDockTools, is distributed as free and open-source software, allowing both researchers and students to perform molecular docking studies without incurring licensing expenses.

- **Prediction of binding conformations and affinities**

The software enables the determination of preferred binding orientations of small-molecule ligands within the three-dimensional structure of biological targets and provides estimates of binding free energy, which are essential for assessing interaction strength and prioritizing candidate compounds [6].

- **Extensive use and validation**

AutoDock has been extensively employed and cited across a wide range of computational drug discovery studies, establishing its reliability and acceptance within the scientific community.

- **Applicability to virtual screening**

The program supports virtual screening of large chemical libraries, allowing rapid identification of potential lead compounds and significantly reducing the time and cost compared with traditional experimental screening methods [7].

DISADVANTAGES:

- **Restricted Receptor Flexibility**

In standard AutoDock workflows, the target protein is generally considered rigid, with flexibility allowed only for the ligand. This simplification overlooks the dynamic structural adjustments that proteins undergo during ligand binding, which can compromise the accuracy of docking predictions [8].

- **Simplified Scoring Function**

AutoDock employs empirical or semi-empirical scoring functions that approximate complex molecular interactions. Important contributions, such as explicit solvent effects, entropic factors, and electronic polarization, are often not fully accounted for, limiting the precision of binding evaluations [9].

- **Limited Reliability of Binding Affinity Estimates**

The predicted binding free energies from AutoDock may show only moderate correlation with experimentally determined ΔG or IC_{50} values. While suitable for ranking ligands in virtual screening, these predictions should not be relied upon for precise quantitative affinity measurements [10].

- **Neglect of Water-Mediated Interactions**

AutoDock typically does not explicitly consider water molecules within the binding site, despite their critical role in mediating hydrogen bonds and stabilizing protein–ligand complexes. This can reduce the biological relevance of docking results [11].

APPLICATIONS:

- **Based Drug Discovery and Lead Identification**

AutoDock is widely used to predict how ligands bind to protein targets, helping to screen and prioritize potential drug candidates. This computational approach reduces both the time and cost of experimental drug discovery [9].

- **High-Throughput Virtual Screening (HTVS)**

AutoDock and related tools like DOVIS perform automated docking of large compound libraries against protein targets, enabling rapid screening of millions of molecules in early- stage drug discovery [12].

- **Mechanistic Studies of Protein–Ligand Interactions**

Docking models how small molecules bind to biomolecular targets, supporting mechanism interpretation, binding mode prediction, and identification of key interacting residues.

- **Lead Optimization and Binding Mode Refinement**

AutoDock refines binding poses and estimates relative affinities of lead compounds, guiding medicinal chemistry optimization and structure–activity relationship (SAR) studies [9].

2.2. SCHRODINGER:

Schrodinger software offers a comprehensive suite of computational packages designed to address the diverse challenges posed by biomolecular systems. Advances in molecular dynamics simulations, ligand–receptor docking, and biologics modeling have been specifically developed to overcome these complexities. The platform enables detailed analysis of structure-based molecular properties, including conformational changes and hydrophobic characteristics. A high-performance molecular dynamics engine is employed for the accurate and efficient validation of macrocycles, providing insights into atomic-level motions that contribute to molecular shape, stability, and energetics.

Schrodinger also provides powerful and user-friendly graphical interfaces for system preparation, simulation execution, and trajectory analysis. Furthermore, molecular dynamics simulations have been applied to investigate stabilized stapled peptides across varying temperatures, with predicted α-helical propensities showing strong agreement with experimental circular dichroism melting data. The binding affinity of stapled peptides toward MDM2 is influenced by the flexibility of key residues, and these simulations offer valuable strategies for the rational design and optimization of potent inhibitors targeting α-helical protein–protein interactions [1,2].

ADVANTAGES:

- **Unified Drug Discovery Platform**

Schrodinger integrates molecular modeling, dynamics, docking, QSAR, and biologics tools to support complete structure-based drug discovery within a single platform.

- **High-Fidelity Molecular Simulations**

Schrodinger employs advanced physics-based force fields from the OPLS family to achieve precise predictions of molecular structures, binding conformations, and energetic properties, thereby enhancing the reliability of computational simulation outcomes.

- **High-Performance Molecular Dynamics Engine**

The Desmond molecular dynamics engine supports rapid and scalable simulations of biomolecular systems, delivering both computational efficiency and accuracy for investigating protein–ligand stability and conformational dynamics.

- **Biologics and Protein–Protein Interaction Modeling**

Schrodinger enables detailed modeling of peptides, macrocycles, and protein–protein interactions, supporting the rational design of stapled peptides and inhibitors that target complex biomolecular interfaces [13].

DISADVANTAGES:

- **Expensive Licensing and Accessibility Constraints**

Schrodinger is a proprietary commercial software suite, and its high licensing fees limit access for academic institutions and smaller research groups compared to freely available open-source computational tools. Reviews on computational chemistry tools have highlighted cost and

accessibility as major barriers to widespread adoption.

- **Limited Transparency of Algorithms**

Schrodinger relies on proprietary algorithms and scoring functions, such as those used in Glide docking, which are not fully disclosed. This lack of transparency makes it challenging for researchers to independently validate or reproduce results, a limitation commonly noted in comparisons of docking tools [14].

- **Challenges in Integrating AI Methods**

With the rise of AI and machine learning in drug discovery, the rigid architecture of traditional physics-based platforms like Schrödinger can make it difficult to incorporate novel predictive approaches. Integrating data-driven and physics-based methods often requires significant adaptation and development. Reviews on AI in drug design highlight these integration challenges [15].

- **Competition from Open-Source Tools**

The growth of free, powerful tools like GROMACS, OpenMM, and AI-based prediction platforms reduces the distinct advantage of proprietary software. Reviews highlight that open-source resources increasingly match commercial tools for many routine computational tasks [16].

APPLICATIONS:

- **Structure-Based Drug Design and Virtual Screening**

Schrodinger is extensively applied in structure-based drug design to screen chemical libraries against biological targets.

The Glide docking module predicts ligand binding orientations and interaction patterns within protein active sites.

This approach enables efficient identification and prioritization of promising hit compounds for further drug development.

- **Peptide–Protein Interaction Modeling**

Schrodinger provides an integrated set of tools to analyze peptide binding and optimize peptide–protein interactions.

Docking, conformational analysis, molecular dynamics simulations, and structural refinement are combined to improve peptide ligand design and binding accuracy.

- **Lead Optimization Using Free Energy Calculations**

Schrodinger's FEP+ method is used to estimate relative binding free energies between structurally similar ligands.

These predictions support medicinal chemistry efforts by guiding lead optimization and ranking compounds based on predicted potency.

- **Molecular Dynamics–Based Complex Refinement**

The Desmond engine in the Schrödinger suite performs molecular dynamics simulations to evaluate the stability and conformational behavior of protein–ligand complexes.

These simulations refine docking results and provide insight into dynamic interactions under near-physiological conditions [17].

3. MOLECULAR MODELLING AND STRUCTURAL ACTIVITY RELATIONSHIP:

3.1. MAESTRO:

Maestro empowers users to visualize molecular structures and create/share 3D chemical models, making it ideal for analyzing and sharing computational experiment results. While not essential for Schrödinger's software suite, it stands out as a versatile powerhouse for molecular modeling in computational chemistry.

It excels at organizing and analyzing collected data through an intuitive interface that simplifies setup for automated calculations. Results integrate seamlessly into projects for easy viewing. With diverse visualization options, Maestro reveals key insights into molecular positions and targeted intermolecular interactions [1].

USES:

- ✓ Quantitative structural analysis
- ✓ Visualize vibrational modes, molecular orbitals, electron density, and key molecular properties [2].

3.2. ARGUSLAB:

ArgusLab is a molecular modeling, visualization, and drug design software developed for Windows operating systems. Conformational analysis, including geometry optimization studies, was carried out on a Windows-based computer using ArgusLab.

The software operates based on quantum mechanical principles and is capable of predicting potential energy, molecular structures, optimized geometries, vibrational frequencies of atomic coordinates, bond lengths, bond angles, and reaction pathways. ArgusLab determines the minimum potential energy of a molecule through a geometry convergence function.

USES:

- ✓ It is utilized to perform molecular docking calculations.
- ✓ The software is employed for constructing molecular structures.
- ✓ Molecules can be designed using a template-based structure approach.
- ✓ It serves as a comprehensive molecular modeling package [2].

3.3. GRAMM (global range molecular matching):

Protein docking is carried out using the GRAMM software program. The atomic coordinates of the two interacting molecules are utilized to predict the structure of their complex. The program produces a list of high-scoring (low-energy) ligand conformations, which can either be used directly or further refined using additional optimization techniques. Instead of relying on statistical sampling methods, this software performs a comprehensive search of all possible configurations to identify the best steric fit with a high scoring coefficient.

This software performs an exhaustive six-dimensional search of molecular configurations. The interacting pairs may include protein–protein, protein–small molecule, or transmembrane helix complexes. It is also used to detect incorrect molecular structures, particularly in cases involving large conformational changes.

It is an empirical approach that smooths the intermolecular energy function by modifying the number of atom–atom potentials. This method helps identify the region of minimum intermolecular energy at varying levels of accuracy. The reliability of the prediction mainly

depends on the accuracy of the molecular shape. Therefore, more precise predictions can be achieved when docking high-resolution systems with minimal conformational changes, whereas simpler predictions are sufficient for docking ultra-low-resolution structures [1].

USES:

- ✓ It is utilized for both protein–protein docking and protein–ligand docking studies [2].

3.4. PASS (prediction of activity spectra of substances):

The PASS program predicts new pharmaceutical compounds by comparing them with known molecular structures. It can estimate up to 4,366 types of biological activities with an average accuracy of approximately 95%.

In PASS, biological activity is predicted as "active/inactive." The compound is converted into a 2D structure and represented using MNA descriptors. The software applies Bayesian probability methods to estimate the biological activity spectrum from a MOL file input [1].

USES:

- ✓ Identify new effects and mechanisms of action for known compounds in corporate and personal databases.
- ✓ Discover new lead compounds with specific biological activity profiles from in-house and commercial databases.
- ✓ Select the most promising candidates from available samples for high-throughput screening [2].

4. IMAGE ANALYSIS AND VISUALIZERS:

4.1. AMIDE (A Medical Image Data Examiner):

AMIDE is designed to provide multimodal volumetric medical image analysis. It supports datasets such as PET, CT, and MRI, along with regions of interest (ROIs), which are systematically organized in a tree structure. This allows multiple datasets and ROIs to be displayed, edited, and analyzed simultaneously without limitation.

The internal data organization in AMIDE is based on a hierarchical tree model consisting of objects such as datasets and ROIs. Each object is assigned its own Euclidean coordinate space, and its local coordinate system is defined relative to a global reference frame.

In AMIDE, the following object types are implemented:

Study: This is the root object that groups related medical images and ROIs into a single logical unit and manages parameters that apply to the entire study.

Data Set: This object stores volumetric medical images along with essential metadata required for interpretation, such as voxel size, color tables, thresholds, patient weight, injected dose, and calibration factors.

ROI (Region of Interest): ROI objects define specific volumes where statistical analysis is performed. Available ROI shapes include ellipsoids, boxes, cylinders, and iso-contours (2D or 3D).

Fiducial Marker: These reference markers represent specific spatial locations and are primarily used for rigid body registration of datasets [2].

USES:

- ✓ Offers multimodal medical image analysis tools for the molecular imaging research community.
- ✓ Provides interactive "wizard"-based interfaces to implement advanced medical imaging algorithms, such as factor analysis and cardiac polar mapping [2].

4.2. DISCOVERY STUDIO VISUALIZER:

Discovery Studio Visualizer (DS Visualizer) is a free tool used to view, share, and analyze data related to proteins and small molecules. It supports both small-molecule and macromolecular applications.

The software enables data import and analysis in multiple formats, including graphical representations, 3D structures, SMILES strings, and sequence data. Required structures and sequences can be obtained from databases such as Protein Data Bank and National Center for Biotechnology Information. Additionally, molecular properties can be examined by modifying structures and performing computational analyses [2].

USES:

- **Visualization**
- ✓ Provides advanced molecular visualization features.
- ✓ Generates high-quality graphics suitable for publication.
- **Macromolecule Design**
- ✓ Enables editing of multi-domain protein sequences, such as antibodies.
- ✓ Predicts secondary structural elements.
- ✓ Allows superimposition and modification of protein structures.
- **Ligand-Based Design**
- ✓ Offers tools for molecular sketching and fragment construction.
- ✓ Supports pharmacophore generation.
- ✓ Allows flexible alignment of ligands.
- **Structure-Based Design**
- ✓ Facilitates defining, viewing, and modifying ligand-binding sites.
- ✓ Creates 2D diagrams of ligand–receptor interactions.
- ✓ Analyzes non-bonded interactions, including favorable, unfavorable, and unsatisfied contacts [2].

4.3. XENOGEN LIVING IMAGE SOFTWARE:

Igor Pro developed by WaveMetrics is a powerful data analysis and programming platform used with Living Image software. It creates a customized environment for data acquisition and analysis and is compatible with both Macintosh® and Windows® operating systems.

The software interface includes an image acquisition control panel, image display and analysis window, system status and dialog window, and a lab notebook window. Tools for both Igor Pro and Living Image are available on the top menu bar. When Igor Pro is running, menu options specific to Living Image remain inactive to prevent interface clutter and user confusion.

Living Image displays a distinctive image window whenever a dataset is opened or newly acquired. The main section of the window presents a pseudo-colored image, representing either luminescent or fluorescent signals, superimposed on a photographic background. The software functions in a similar manner for both luminescent and fluorescent images unless specified otherwise.

Analysis tools are located at the top of the image window to manage display settings and perform measurements. A color scale bar on the right side illustrates the relationship between pseudo-colors and their corresponding numerical data values. At the bottom of the window, labeling information generated by the user and the imaging system provides guidance on the function of the various controls available within the interface [2].

USES:

- ✓ Designed for in vivo imaging applications.
- ✓ Supports low light-level imaging by managing sensitivity, binning, measurements, calibration procedures, background light interference, and dark charge control [2].

5. DATA ANALYSIS:

5.1. GENE SPRING:

GeneSpring's user interface offers explanations of key terms related to organizational elements, alongside a broad overview of the data types and analytical methods supported by the platform [1].

This software serves as a repository of samples processed through array experiments to address targeted scientific inquiries. It allows users to generate a fresh experiment by selecting a project, importing samples from a specific technology platform, and executing standard preprocessing operations—such as normalization, summarization, and baseline transformation—to transform raw data into an analysis-ready format. Each experiment encompasses the original samples, diverse interpretations that categorize them based on custom experimental variables, and additional outputs generated from subsequent analytical procedures [2].

The software comprises three core components: a user interface layer, a database, and a file system. The file system physically houses all objects within the app/data subdirectory of the installation directory. An SQL database manages annotations for these objects (such as searchable notes, names, and properties) to enable rapid querying; the UI layer then presents pertinent objects, structured into projects, experiments, and analyses [1].

USES:

- ✓ Batch effect correction.
- ✓ Binary segmentation within circular data structures.
- ✓ Filters for detecting loss of heterozygosity (LOH) events and regions of allelic imbalance unrelated to replication.
- ✓ Considers diverse standard deviation thresholds to reach definitive outcomes [2].

5.2. QSARPro:

This software discerns connections between molecular activities or properties and structural features, examines these correlations, and enables swift forecasts through dependable statistical models. It assesses over 1,000 molecular descriptors, encompassing physicochemical, topological, electro-topological, information-theoretic, quantum chemical, electrostatic, hydrophobic, alignment-independent, and MMFF atom type descriptors, among others [2].

In QSAR modeling, typical tasks include selecting and computing descriptors, statistically assessing those derived descriptors, training and validating model sets, performing regression analysis, and evaluating model performance. The software explores various descriptor categories and collections, alongside linear or nonlinear regression techniques and methods, to identify the optimal combination for a given project [1].

USES:

- ✓ Investigate and apply diverse combinations of variable selection techniques alongside regression approaches.
- ✓ Superimpose a specified group of molecules within the protein active site, using the co-crystallized ligand as a reference for accurate ligand positioning.
- ✓ Analyze interactions between proteins [2].

5.3. REST 2009 SOFTWARE:

REST 2009 software serves as a unified platform for evaluating gene expression data obtained from quantitative and real-time PCR assays. Relative gene expression quantification relies on reference genes to standardize the levels of target genes (GOI) across various samples. This technique enables qPCR data normalization, such as accounting for discrepancies arising from uneven sample quantities.

This software employs a mathematical model that accounts for the varying PCR efficiencies between the target gene and reference genes. Result reliability improves by evaluating individual reference genes against combinations of multiple reference genes for normalization [2].

USES:

- ✓ Assess if a notable difference exists between the samples and control groups [2].

6. BEHAVIOURAL STUDY:

6.1. MARS (Multimodal Animal Rotation System):

MARS, or Multimodal Animal Rotation System, is a specialized imaging accessory designed for small in vivo animal studies, particularly in molecular imaging for drug discovery. It captures 360° movement of an experimental animal. This software is designed in such a way that it automatically rotates a mouse to the required angles or positions to track all the relevant molecular data and comprehensive anatomical information of experimental animal. It also detects optical signals generated due to orientation of the experimental animal [2].

This software enables co-registration and acquisition of multimodel and multispectral data sets across all imaging angles. The software amplifies the obtained signal sensitivity through precise image quantification, exporting complete rotation movements or complete motion capture. The system software comprises of an animal rotation apparatus, controlling software and integrated software for multimodel visualization and co-registration [2,18].

Table 2 Overview of Multimodel Imaging Uses in Tumor and Molecular Imaging

Context	Role	Example
Tumor Imaging	Monitors intra-peritoneal growth post-inoculation (7-21 days)	Detects ovarian cancer stem cells with NIR probes
Molecular Imaging	360° anatomical/molecular overlay	Screens CNS drugs for brain biodistribution in rodents [18].

ADVANTAGES:

- Improves physical examination and therapeutic skills through integrated modalities, outperforming traditional bedside teaching in efficiency and learner engagement [19].
- Maximizes exposure to varied drug distribution systems and sites, building confidence for multi-site practice and reducing onboarding time post-residency [20].
- Boosts evidence-based practice knowledge and performance, with significant pre-post improvements in students' self-perceived skills [21].

USES:

- ✓ Inflammatory disease
- ✓ Bone disease
- ✓ Cell tracking
- ✓ Enzyme activity
- ✓ Nanoparticle tracking and delivery [2]

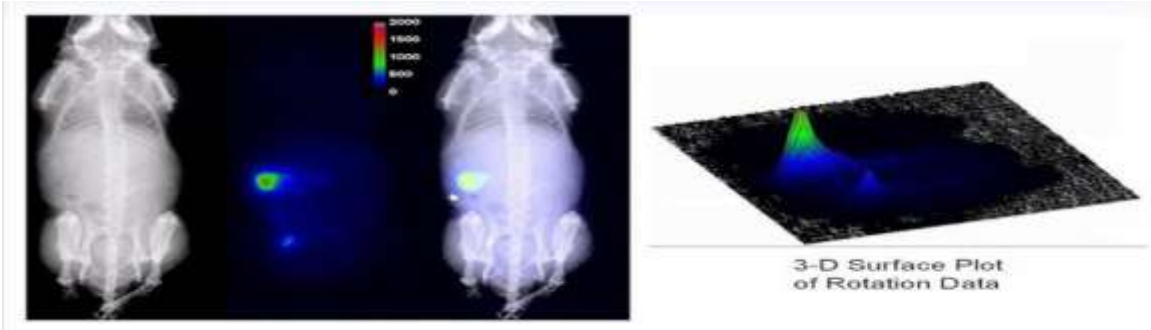

Fig. 2. In Vivo Imaging with 3D Surface Plot of Rotation Data

6.2. ETHOWATCHER:

Behavioural change is considered to be the most important parameter for diagnosing a wide variety of disorders. An experimental animal's complex behavioural patterns are closely linked to its morphological and physiological adaptations. Researchers often record these behavioural changes in both laboratory and free-ranging animals to support diverse biological and biomedical research areas, such as ecology, physiology, neurosciences, psychology, genetics, pharmacology and pathology.

Advanced automated systems selectively capture specific behaviours indirectly by detecting their consequences through the activation of pressure or infrared sensors or by image processing techniques derived from video-tracking analysis. Video tracking analysis readily yields a wide range of information which includes locomotor activity changes such as the frequency and duration in ambulation, velocity of movement and horizontal positioning [2].

Ethowatcher is developed in C++ and operates within C++ Builder 5.0 environments. This software serves as an integrated tool for constructing and storing behavioural changes, supporting both 'real-time' scoring (like directly from ongoing environmental activities or analog videos) or 'off-line' analysis (from digital video files). The obtained digital video files can be analyzed to automatically derive activity parameters (such as distance, angle, velocity, object area approximation and trajectory plots) alongside object (animal) tracking via digital image processing techniques.

The software generates time-segmented reports detailing sequences, durations, frequencies, and latencies of scored behaviors, along with activity-related indices, all synchronized via a unified time source [1].

ADVANTAGES:

- Provides precise tracking of animal movement, including distance traveled, orientation, length, area, and path graphs from video files.
- Enables detailed ethography by allowing users to create behavioral catalogs for recording events in real-time or from videos, generating reports on duration, frequency, latency, and sequences.
- Detects angles at animal poles (head/tail movements) relative to the body axis, offering superior kinematic analysis compared to some alternatives [22].

USES:

✓ Validation of behavioural analysis software in laboratory animals.

✓ Video-tracking analysis in laboratory animals [1].

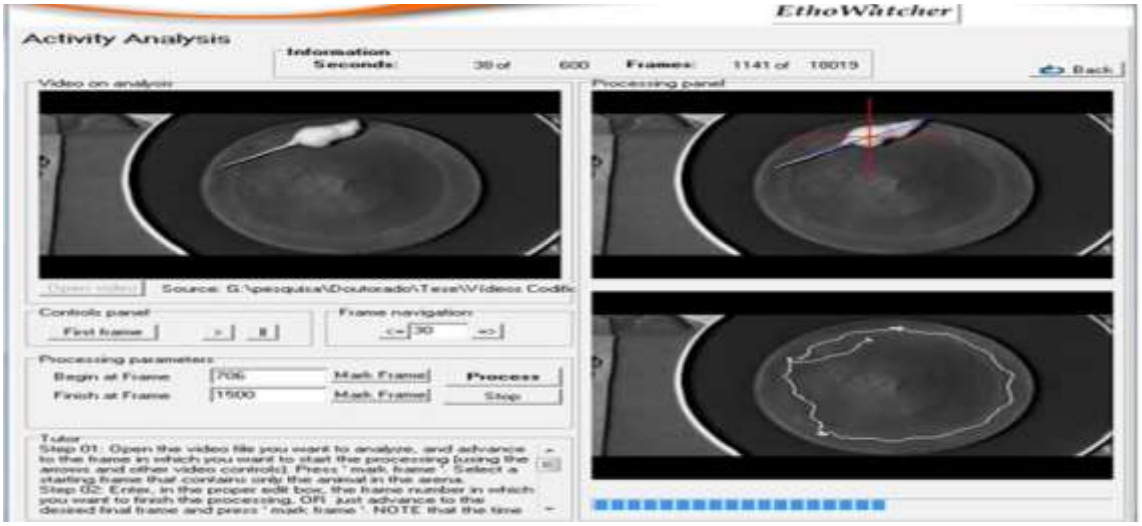

Fig. 3. Ethological Activity Analysis and Movement Tracking Using EthoVision

CONCLUSION:

The incorporation of advanced computational methodologies and specialized software platforms has significantly reshaped contemporary drug discovery and development. Approaches such as computer-aided drug design (CADD), molecular docking, molecular dynamics simulations, quantitative structure–activity relationship (QSAR) analysis, bioinformatics tools, and imaging technologies provide a structured, efficient, and data-driven framework for pharmaceutical research. Collectively, these technologies help minimize the time, financial investment, and experimental complexity traditionally required for the identification, optimization, and validation of new therapeutic agents.

Software platforms such as AutoDock and Schrödinger have significantly advanced structure-based drug design by enabling precise prediction of ligand–receptor binding modes and affinity estimations. Molecular modeling applications like Maestro and ArgusLab improve three-dimensional visualization, geometry

refinement, and detailed structural evaluation, while predictive systems such as PASS enhance the early estimation of biological activity profiles before experimental confirmation.

In parallel, imaging and visualization tools including AMIDE and Discovery Studio Visualizer facilitate molecular imaging analysis and structural interpretation. Data-driven platforms such as GeneSpring and QSARPro contribute to robust statistical evaluation and comprehensive biomolecular data analysis. Furthermore, behavioral and multimodal systems like Ethowatcher and MARS extend computational approaches into preclinical research by supporting in vivo imaging and behavioral assessment studies.

Although these computational tools face limitations—including constrained receptor flexibility, approximate scoring functions, expensive licensing fees for proprietary platforms, and difficulties in merging artificial intelligence with traditional physics-based models—they continue to advance at a rapid pace. The growing adoption of machine learning techniques, high-performance computing infrastructures, cloud-based technologies, and multi-omics data integration is anticipated to significantly improve predictive precision and accelerate translational outcomes in drug discovery.

In summary, computational and software-driven strategies have emerged as essential elements of the modern drug development process. By supporting systematic target identification, lead refinement, pharmacokinetic evaluation, molecular imaging, and behavioral analysis, these technologies effectively connect laboratory research with clinical application. Ongoing advancements and deeper integration of computational approaches will play a crucial role in expediting the development of safe, efficacious, and cost-effective therapeutic agents in the years ahead.

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