SYBYL®

EXPERT MOLECULAR MODELING ENVIRONMENT

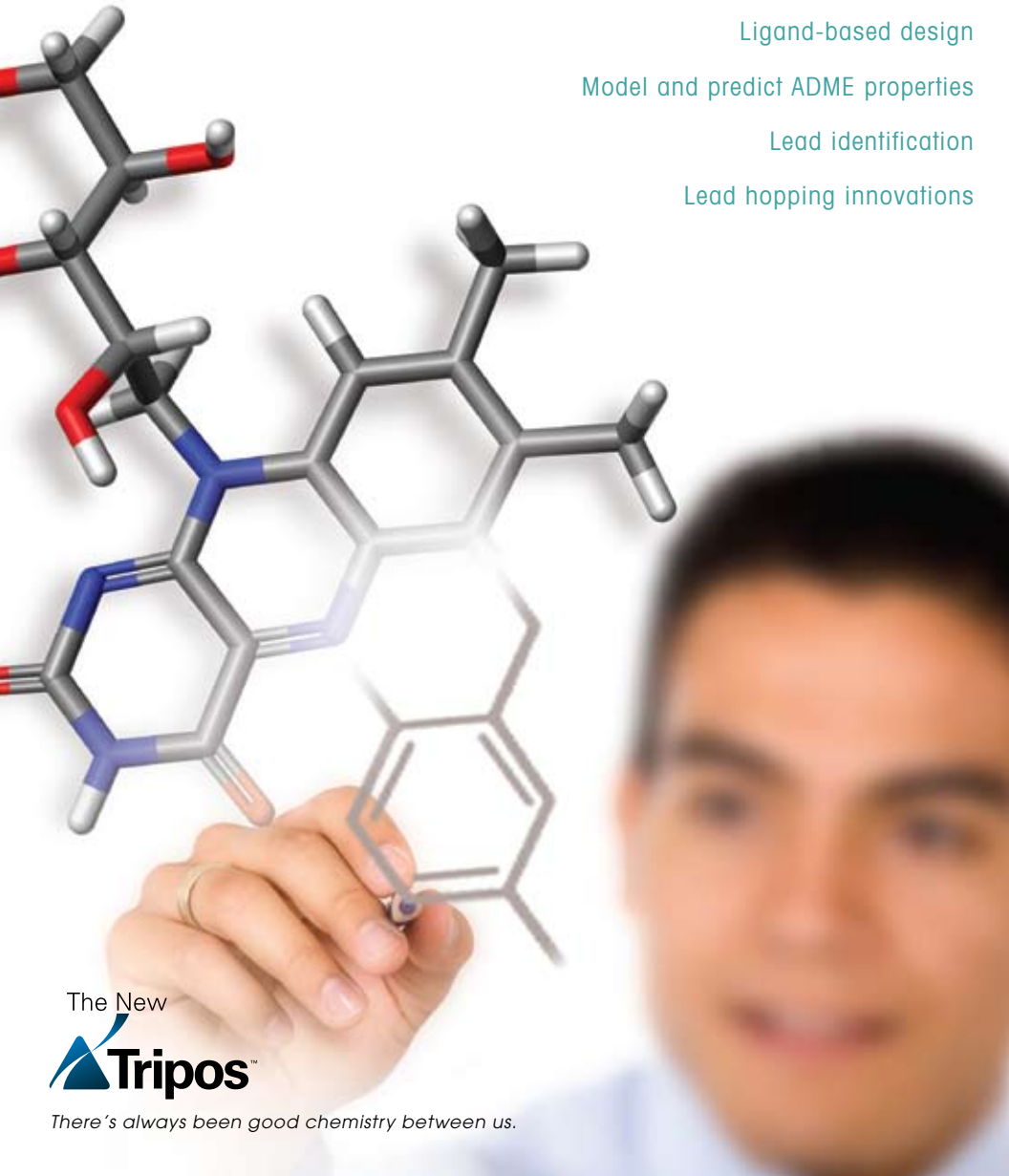
Structure-based design

Ligand-based design

Model and predict ADME properties

Lead identification

Lead hopping innovations



The New Tripos™

There's always been good chemistry between us.

SYBYL

EXPERT MOLECULAR MODELING ENVIRONMENT

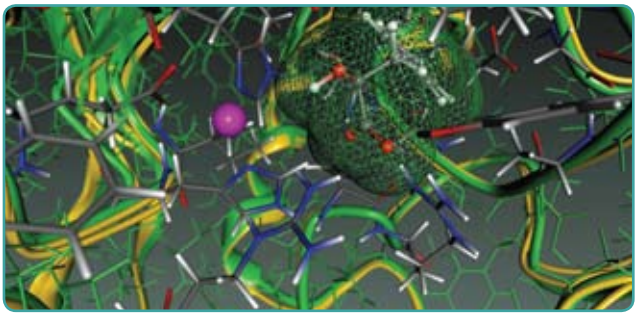


Table of Contents

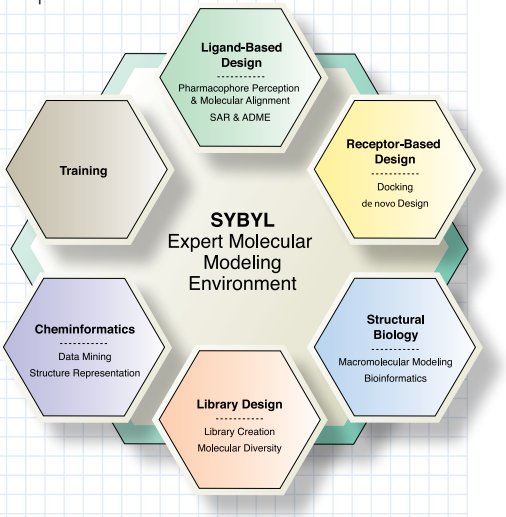
Table of Contents

SYBYL® – The Expert Molecular Modeling Environment

Straight Talk About Discovery Research

Whether you are looking for the next new breakthrough drug, the next generation in pesticides, the most exciting new flavor or fragrance, or any other molecular discovery project, we know what you're up against. You have enormous pressure to produce results, in a very short period of time.

Expectations are stratospheric, budgets more terrestrial, communication and data sharing is complex, time is constantly gnawing away on you, and oh, did we mention the competition? Discovery research is not for the faint hearted or the ill-prepared.



Understanding the Problem

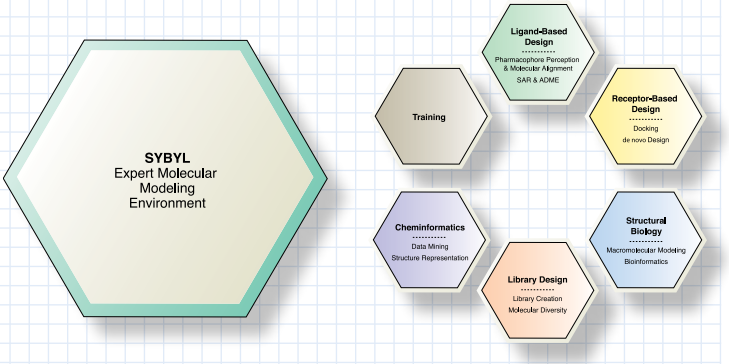
This brochure explains what you need to know about the tools available for molecular modeling and discovery projects. For the past two decades-plus, Tripos has helped the world's largest discovery organizations standardize on a molecular modeling environment that saves time, optimizes processes and workflow, and improves discovery results. It's called SYBYL and that's what this booklet is all about.

Your Workflow and Your Decisions

Tripos has spent more than 20 years working with computational chemists and molecular modelers, and we have identified one immutable concept – smart people approach tough problems in a variety of ways.

Sure, there are some common fundamental approaches, but we know that sophisticated research requires creative thinking and intuition, backed by the validation of solid science. That's what SYBYL enables – processes and decision-making that you control, not a one-size-fits-all confining approach. With SYBYL you look at molecular structures and properties in a manner that is designed to:

- produce and optimize lead candidates
- save time in your processes
- smooth and simplify workflows
- accelerate the pace of discovery



Functional Architecture

The key to SYBYL's widespread use and acceptance in the scientific community is its simple but highly functional architecture.

The SYBYL Standard Base contains a powerful core of tools and functions designed to optimize, visualize and compare the attributes of molecular models and structures. Two SYBYL Optional Base Modules, MOLCAD™ and Advanced Computation™, allow enhanced visualization capability, conformational searching and they facilitate unprecedented interoperability between and among other SYBYL application groups.

The SYBYL Applications are individually selected groups of computational chemistry and molecular modeling systems and tools tailored to accelerate and simplify the discovery process.

Best Practices, Best Solutions, Best Choice

Any endeavor can benefit from the lessons of the past. The thousands of customers who use SYBYL are receiving the benefit of more than 20 years of scientific experience, best practices, reliable technology solutions and access to people who helped build the industry. Savvy chemists understand they cannot afford to waste time and money on inventing infrastructure from scratch or bolting together a patchwork of non-integrated systems. SYBYL is the industry standard for computational informatics, computational chemistry and molecular modeling.

The Problems Are Complex, but SYBYL Helps Make Things Easier

Ask yourself these few key questions:

- Do I have a way to easily do molecular modeling that enables structure building, optimization and comparison?
- Can I quickly associate data with visualized structures?
- How do I produce hardcopy and screen captures for information validation, sharing and exchange?
- Do I have an efficient and proven technique for ligand-based design?
- What about receptor-based design?
- How will I handle building and manipulating protein structures?
- Can I keep pace with the constant changes in computational informatics requirements, and insure a secure, up-to-date approach to my workflow?

Tripos understands that these are just a few of the issues you may face daily. If you haven't investigated SYBYL you need to soon. The longer you put off consideration of Tripos' solutions, the more difficult it will be to resolve problems that inevitably lie ahead. When you consider the number of organizations that have chosen SYBYL, you have to ask yourself what you may be missing.

SYBYL®

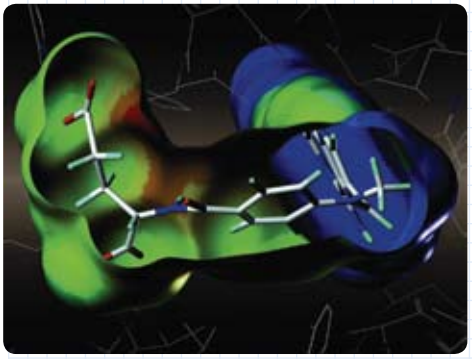
Complete Computational Chemistry and Molecular Modeling Environment

SYBYL, the heart of Tripos' expert molecular modeling environment, provides the fundamental components for understanding molecular structure and properties with a special focus on the creation of new chemical entities. SYBYL provides essential construction, editing, and visualization tools for both large and small molecules. Data organization and analysis rely on the Molecular Spreadsheet™, which integrates chemical information with standard data manipulation tools. SYBYL's programming language (SPL) and open architecture facilitate customized drug-design methods.

MOLCAD™

Advanced Visualization of Molecular Surfaces and Properties

MOLCAD[1] exploits the power of the human eye by creating graphical images that reveal the properties of molecules essential for molecular recognition. Van der Waals and solvent-accessible surfaces can be calculated, and a broad range of properties can be mapped onto these surfaces: lipophilic potential, electrostatic potential, hydrogen bonding ability, local curvature, and distance.



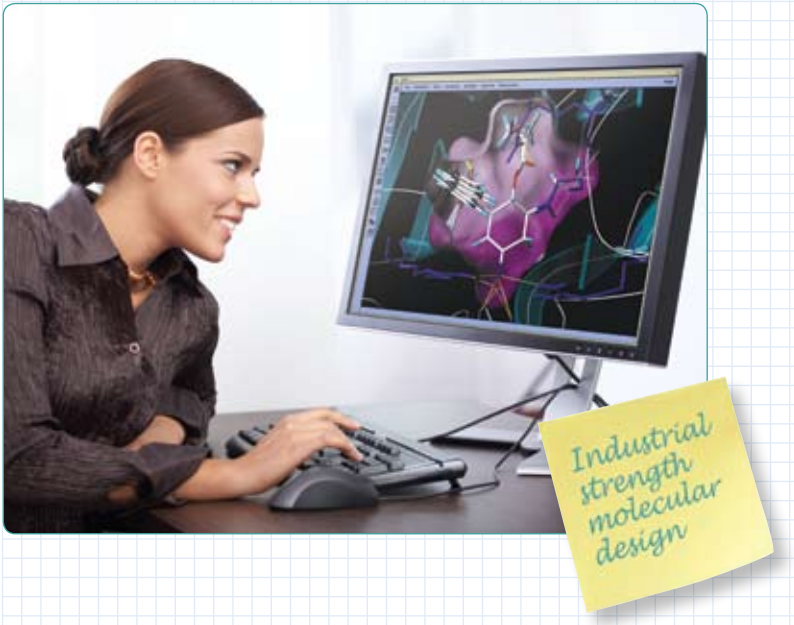
The inhibitor, methotrexate, bound to dihydrofolate reductase. A MOLCAD-generated surface has been created for methotrexate and is color-coded by electrostatic potential. Methotrexate is rendered as capped sticks, while the protein is shown as lines.

1. Software Partner: Darmstadt University of Technology, Germany
   Scientific Partner: Professor Dr. Jürgen Brickmann

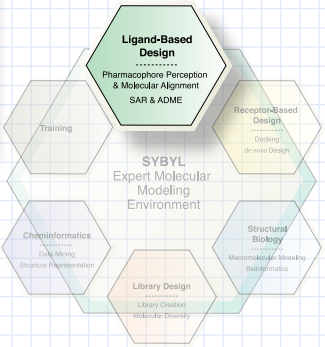
Advanced Computation™

Explore the Conformational Properties of Compounds

Industrial-strength molecular design had its real start with the Advanced Computation tools from Tripos. This SYBYL application delivers the industry's fastest and most flexible systematic conformational searching algorithm. Random and grid search techniques are also provided. The user selects the technique based on the goal of the conformational analysis.

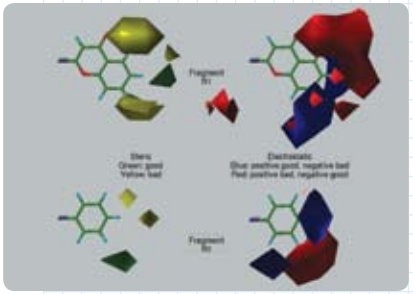


Ligand-Based Design



Ligand-based design techniques use information about one or several known actives (ligands) as a basis for the design of lead compounds. Tripos' core science and workflow-centric applications address critical ligand-based design tasks such as structure-activity relationship modeling, pharmacophore hypothesis generation, molecular alignment, and ADME prediction.

SAR and ADME



Topomer CoMFA contour plots explain how changes in the steric and electrostatic properties of your compounds can be modified to improve biological properties. These plots suggest regions where increasing steric bulk either enhances or diminishes activity, or regions where positive (or negative) electrostatic groups are predicted to improve activity.

Topomer CoMFA®

Effortless 3D QSAR

Topomer CoMFA is a novel 3D QSAR tool based on topomer technologies that automates the creation of models for predicting the biological activity or properties of compounds. Topomer CoMFA allows both expert and nonexpert users to create models in minutes, not days, and is seamlessly integrated with virtual screening for lead hopping, identification of novel scaffolds, and for optimization of R-groups (lead optimization).

Topomer Search

Exceptionally Fast 3D Ligand-Based Virtual Screening

Topomer Search is an exceptionally fast 3D ligand-based virtual screening tool that has been demonstrated to be effective for both lead hopping and scaffold hopping. Topomer Search can search millions of structures overnight on a single processor, allowing you to screen

very large collections of compounds and avoid the risk of missing important leads because of subsetting. Screen for whole molecules, side chains, or scaffolds using conformationally independent topomer similarity.

QSAR with CoMFA®

Build Predictive Structure-Activity and Structure-Property Models

QSAR with CoMFA builds statistical and graphical models that relate the properties of molecules (including biological activity) to their structures. These models are then used to predict the properties or activity of novel compounds. Tripos' patented Comparative Molecular Field Analysis (CoMFA) has been used as the method of choice in hundreds of published QSAR studies. A wide variety of structural descriptors can be calculated, including EVA and the molecular fields of CoMSIA.[2]

Advanced CoMFA®

Refine and Enhance 3D QSAR Models

Advanced CoMFA provides access to specialized types of CoMFA fields that assist in refinement of predictive models.

Surflex-Sim

Molecular Alignment and Virtual Screening

Surflex-Sim [3] generates molecular alignments and hypotheses of bioactive ligand conformations for 3D ligand-based design and virtual screening. Surflex-Sim rapidly and automatically optimizes the alignment of molecules, maximizing their three-dimensional similarity. Surflex-Sim uses a surface-based morphological similarity function while minimizing the overall molecular volume of the aligned structures. This approach has been demonstrated to outperform other techniques in comparisons of correlation to biological activity. The morphological similarity approach of Surflex-Sim effectively facilitates scaffold hopping, thus allowing the user

2. Software Partner: Philipps University of Marburg, Germany
   Scientific Partner: Professor Dr. Gerhard Klebe
3. Software Partner: BioPharmics, San Mateo, CA
   Scientific Partner: Professor Ajay N. Jain, Ph.D.

to find alternative chemical scaffolds without the same toxicity and potential intellectual property issues as the given lead. This leads to truly novel lead series with distinct properties while preserving those structural properties that are essential for biological activity.

HQSAR™

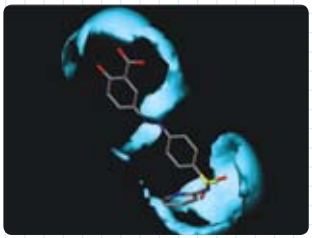
Perform Automated QSAR Analyses

Hologram QSAR (HQSAR) uses molecular holograms and PLS to generate fragment based structure-activity relationships. Unlike 3D QSAR methods, HQSAR does not require alignment of molecules, allowing automated analysis of very large data sets. Validation studies have shown that HQSAR has predictive capabilities comparable to those of much more complicated 3D QSAR techniques.

VolSurf™

Predict ADME Properties

VolSurf [4] predicts ADME properties using pre-calculated models; computes unique, ADME-relevant descriptors; and creates QSAR models of bioactivity or property. VolSurf's built-in ADME models have been developed from published experimental data and include Caco-2 cell absorption, human CYP3A4 metabolic stability, hERG inhibition, human serum albumin binding, thermodynamic solubility, blood-brain barrier permeation, and more.



The hydrophilic surface of an anti-inflammatory drug as determined by VolSurf.

Almond™

Calculate and Utilize Alignment-Independent Molecular Descriptors

Almond [5] generates and uses GRIND descriptors (GRid INdependent Descriptors). GRIND are alignment-independent 3D descriptors interpretable with the help of interactive graphic tools. This new generation of 3D molecular descriptors is useful in 3D QSAR, virtual screening, and design of combinatorial libraries.

4, 5. Software Partner: Molecular Discovery Ltd., UK
Scientific Partners: Professor Gabriele Cruciani, Professor Manuel Pastor

Distill™

Determine and Visualize SARs

Distill clusters compounds according to their common substructures and displays the results to reveal structure-activity relationships. The interactive dendrogram produced by Distill allows visual comparison of compounds in the same cluster or between compounds in different clusters. Statistical tools assess the impact of substructure on property or activity.

ClogP/CMR™

Include Molar Refractivity and logP in QSAR and ADME Models

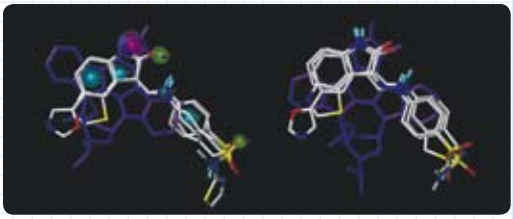
The ClogP/CMR[6] application provides highly accurate calculated logP and molar refractivity values. Octanol/water partition coefficients (logP) are often a critical piece of information in the compound discovery process. Molar refractivity (MR) serves as a convenient estimate of molecular polarizability. Both properties are useful descriptors in establishing QSAR relationships.

Pharmacophore Perception and Molecular Alignment

GALAHAD™

Generate Rapid, High Quality Pharmacophoric Perception and Molecular Alignments

GALAHAD[7] allows researchers to automatically develop pharmacophore hypotheses and structural alignments from a set of molecules that bind at a common site. No prior knowledge of pharmacophore elements, constraints, or molecular alignment is required, making it ideal for exploring new targets and new modes of action.



GALAHAD model derived from four cyclin-dependent kinase (CDK2) inhibitors (left) vs. the overlay based on the corresponding X-ray crystal structures (right).

6. Software Partner: BioByte Corporation, Claremont, CA
   Scientific Partners: Dr. Albert Leo, Dr. Corwin Hansch, Mr. David Hoekman
7. Software Partner: University of Sheffield, UK
   Scientific Partners: Professor Peter Willett, Dr. Nicola Richmond

GALAHAD uses a sophisticated genetic algorithm (GA) that defines each molecule as a core structure plus a set of torsions. To overcome limitations in existing pharmacophore tools, GALAHAD's genetic algorithm was developed on real-world data sets.

Tuplets™

Pharmacophore-Based Virtual Screening

Tuplets facilitates the retrieval of compounds from molecular structure databases that are likely to exhibit biological activity. Additionally, Tuplets can be used to prioritize virtual combinatorial libraries for pharmaceutical research and can provide a biasing descriptor to allow the design of focused combinatorial libraries.

GASP™

Use Full Conformational Flexibility to Develop Pharmacophore Hypotheses

GASP[8] performs pharmacophore elucidation without requiring prior knowledge of pharmacophore elements or constraints. Using a genetic algorithm, GASP automatically allows conformational flexibility and maps features among molecules.

DISCOtech™

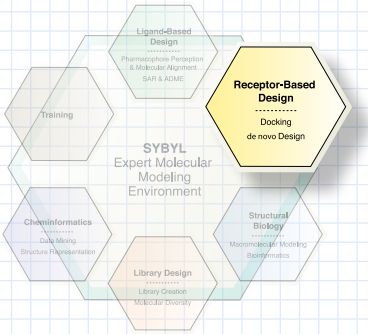
Elucidate Pharmacophore Models from Precalculated Conformers

DISCOtech[9] performs pharmacophore elucidation from a set of active compounds. Starting from a set of representative conformers for each molecule, DISCOtech considers all possible mappings of features to create a set of alignments, each of which is a hypothesis for the pharmacophore and its geometry.

8. Software Partner: University of Sheffield, UK
   Scientific Partners: Professor Peter Willett, Dr. Gareth Jones, Professor Robert Glen
9. Software Partner: Abbott Laboratories, Inc., Abbott Park, IL
   Scientific Partner: Dr. Yvonne C. Martin

Receptor-Based Design

Receptor-based design techniques use information about the structure of a drug target (receptor) as a basis for the design of lead compounds. Tripos' core science and workflow-centric applications address critical receptor-based design tasks such as ligand docking, virtual screening, *de novo* design, and lead optimization.

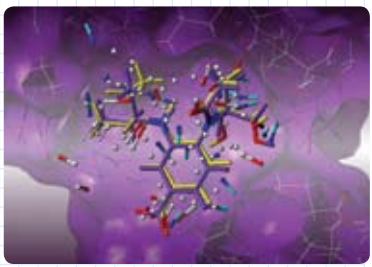


Docking

Surflex-Dock™

Ligand-Receptor Docking and Virtual Screening

Surflex-Dock[10] offers unparalleled enrichments in virtual high-throughput screening combined with state-of-the-art speed, accuracy, and usability. It uses an empirical scoring function (based on the Hammerhead docking system) that has been updated and re-parameterized with additional negative training data, along with a search engine that relies on a surface-based molecular similarity method.



Influenza virus neuraminidase (1B9V) in complex with an inhibitor (purple-capped sticks). The minimized inhibitor has been redocked by Surflex-Dock into the protein (yellow-capped sticks) with an rms deviation of 0.645 Angstroms.

CScore™

Rank the Affinity of Compounds Bound to a Target with Consensus Scoring

CScore uses multiple types of scoring functions to rank the affinity of ligands bound to the active site of a receptor. The strengths of individual scoring functions combine to produce a consensus that is more robust and accurate than any single function for evaluating ligand-receptor interactions.

10. Software Partner: BioPharmics, San Mateo, CA
Scientific Partner: Professor Ajay N. Jain, Ph.D.

de novo Design

EA-Inventor™

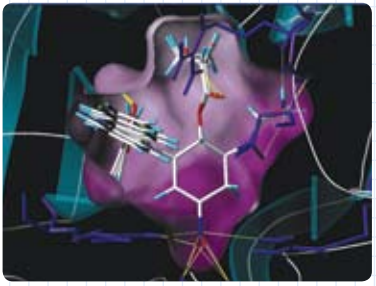
Invent New Compound Ideas and Lead Hop Using Novel *de novo* Design Engine

EA-Inventor[11] is a new and different approach to *de novo* design. It enables researchers to invent new compounds, new R-groups around a fixed scaffold, or new scaffolds. Unlike typical *de novo* design programs, EA-Inventor gives the user control over how the new structures are generated and scored, and is useful for *in silico* lead discovery, lead exploration, and lead- or scaffold-hopping.

RACHEL™

Sophisticated Tools for Optimization of Lead Compounds

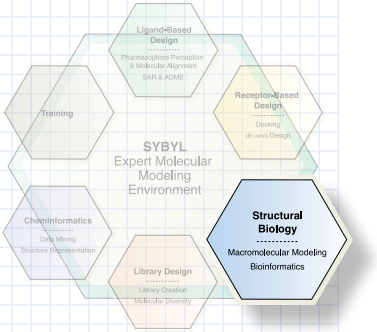
Starting from a ligand/receptor complex, RACHEL[12] performs automated combinatorial optimization of lead compounds by systemically derivatizing user-defined sites on the ligand. These compounds are conformationally searched within the active site, evaluated, and only those that bind tightly with the receptor are retained. This new population of compounds is then processed to form the next generation of derivatives. Over time, a lead compound is iteratively refined into a set of high-affinity structures.



The X-ray structure of wild type tern N9 influenza virus neuraminidase (2QWK) shown with five ligands generated using RACHEL that are predicted to be active.

11. Scientific Partner: Professor Robert S. Pearlman
12. Software Partner: Drug Design Methodologies, LLC, St. Louis, MO
    Scientific Partner: Chris Ho, M.D., Ph.D.

Structural Biology and Bioinformatics

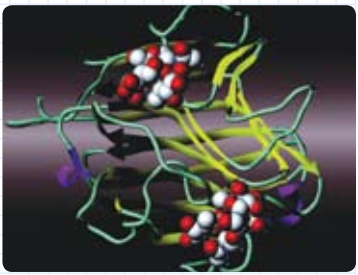


Structural biology techniques aid discovery researchers in the study of protein structure and function. Predicting, constructing, and assessing 3D protein models are critical components to a better understanding of receptor-ligand interactions. Tripos applies homolog recognition, structure and function prediction from sequence, ligand binding site analysis, and 3D modeling techniques in workflow-centric applications that address critical structural biology design tasks such as macromolecular modeling and bioinformatic analysis.

Biopolymer™

Predict, Build, Visualize, and Analyze Macromolecular 3D Structure

Biopolymer provides the tools needed for building and manipulating peptide, protein, DNA/RNA, and carbohydrate structures. Biopolymer is fully integrated with SYBYL for structure building, refinement, visualization, and analysis. Protein structures can be analyzed in detail using the SYBYL Molecular Spreadsheet. Structures, spreadsheets, and graphs are linked to help identify and explore correlations between physical and geometric attributes. Interesting or unusual residues can be colored-coded in a structure. Any value computed can be visually mapped onto 3D tube or ribbon drawings by varying either the tube color or thickness.



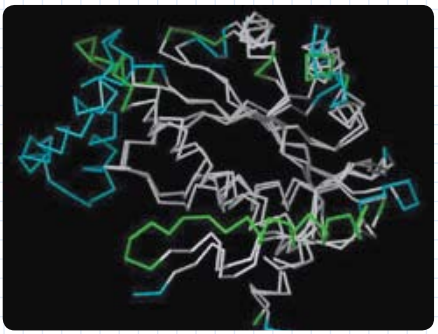
Biopolymer's rendering of the methyl glycoside of the Lewis b human blood group determinant complexed with Lectin IV of Griffonia simplicifolia.

Identification of potential binding sites within or at the surface of biological targets can also be determined using a cavity detection algorithm. Protein pockets are rapidly identified by solvating the structure to locate regions where solvent-spheres tend to cluster.

Advanced Protein Modeling

Find Homologs by Sequence-Structure Comparison and Construct 3D Models from Protein Sequences

Advanced Protein Modeling enables the user to perform both homolog finding and comparative modeling through a streamlined interface. The recognition of homology between protein sequences and known structures provides invaluable information toward understanding the biological behavior and biochemical function of uncharacterized sequences.



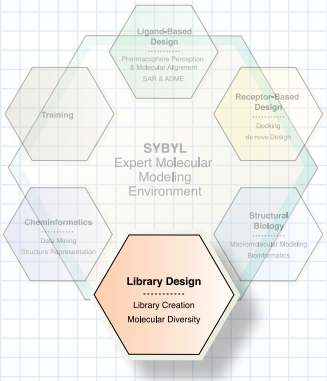
A set of structurally aligned oxidoreductase structures of 8% sequence identity, with the structurally conserved regions highlighted in gray.

This recognition also enables prediction of three-dimensional structures through comparative modeling. Using the FUGUE™[13] technology, structural homologs of a target sequence can be identified by sequence-structure comparison using a database of detailed structural profiles of all known protein families. Using the ORCHESTRAR™[14] technology, comparative models can be built from a target sequence using single or multiple structural homologs found by FUGUE or provided by the user.

13. Software Partner: University of Cambridge, UK
Scientific Partners: Professor Sir Thomas Blundell, Dr. Kenji Mizuguchi, Dr. Jiye Shi

14. Software Partners: University of Cambridge, UK
Scientific Partners: Professor Sir Thomas Blundell

Chemical library design techniques allow researchers to develop combinatorial or focused compound collections useful in lead identification and optimization. Truly diverse, representative, and synthetically feasible compound sets speed the identification of active small molecules. Tripos' core science and workflow-centric applications address critical library design tasks such as library creation and molecular diversity enhancement.

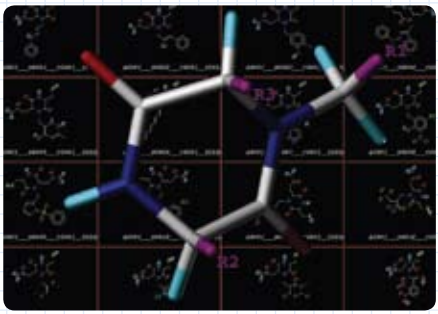


Library Creation

Legion™/CombiLibMaker™

Construct Virtual Compound Libraries

Legion and CombiLibMaker[15] provide the capability for building and storing combinatorial libraries of compounds. Libraries of compounds can be defined and enumerated with full control of stereochemistry. Library structures can be output singly (as SLNs) or in a searchable combinatorial format (as cSLN). The libraries can be stored in a variety of formats.



A virtual library of potential matrix metalloproteinase inhibitors built using CombiLibMaker. The core common to all products is shown in the foreground. R1, R2, and R3 are the sites of variation.

15. Scientific Partner: Professor Robert S. Pearlman

Selector™

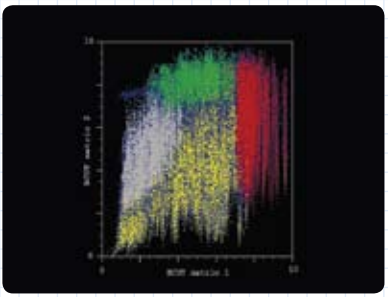
Characterize and Sample Compound Libraries

Selector characterizes, compares, and samples sets of compounds. Clustering tools identify relationships between compounds based on their similarity. Selector can create diverse or representative subsets, filter compound lists based on properties, find compounds similar to a lead compound, and compare the diversity of sets of compounds.

DiverseSolutions®

Design, Compare, and Select Compound Libraries

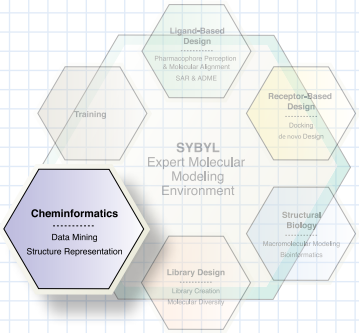
DiverseSolutions[16] assesses the chemical diversity of a population of molecules, selects diverse or representative subsets, and compares the diversity of two or more different populations of molecules. DiverseSolutions generates metrics relevant to inter-molecular interactions, and then identifies those metrics that best distinguish structural differences between compounds. A novel, reactant-biased, product-based, library design algorithm generates full synthetic arrays that preserve diversity and satisfy user-specified constraints. These constraints may include the number of reactants, their cost and availability, and the plate format of a robotic synthesizer.



A 9,600-compound library (yellow) filling diversity missing from three 12,800-compound libraries (gray, green, and red) using DiverseSolutions.

16. Scientific Partner: Professor Robert S. Pearlman

Cheminformatics



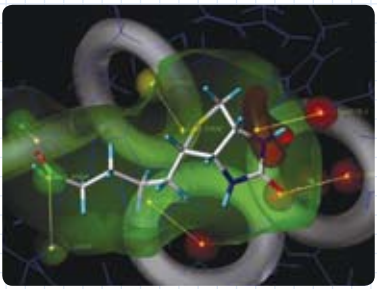
Cheminformatics tools help researchers extract usable information from the volumes of data generated by high-throughput and combinatorial technologies that characterize modern research methods. These tools address the need to facilitate, store, and explore the chemical and biological data that is key to the success of molecular discovery programs. Tripos' core science and integrated applications address critical cheminformatic tasks such as data mining and analysis, as well as structure representation and optimization.

Data Mining

UNITY®

Locate Compounds in Databases that Match a Pharmacophore or Fit a Receptor Site

UNITY is a search and analysis system for exploring chemical and biological databases. UNITY's 2D searching capabilities offer exact, substructure, and similarity searching. Conformationally flexible 3D searching rapidly finds molecules that can satisfy queries regardless of the conformation stored in a database. Structural queries may be based on molecules, molecular fragments, pharmacophore models, or receptor sites. The tight integration between UNITY and SYBYL facilitates analysis by other methods, such as QSAR with CoMFA.



A UNITY query constructed at the active site of the streptavidin/biotin complex (1STP).

Structure Representation

Concord®

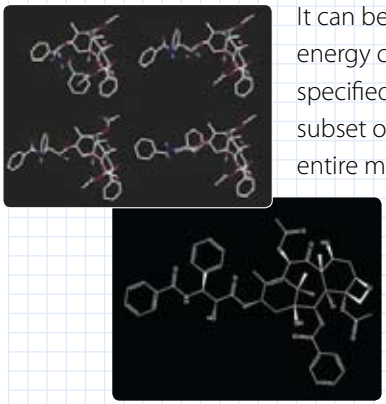
Generate Accurate 3D Coordinates

Concord[17] sets the industry standard for extremely rapid conversion of 2D (or crude 3D) input to accurate, geometry-optimized 3D structures. Although most often used for the conversion of large corporate and commercially distributed databases, Concord is also a productivity tool useful for molecular modeling and QSAR/QSPR research.

Confort™

Generate Sets of Diverse, Low-Energy Conformers

Confort[18] is a powerful conformational analysis tool that performs exhaustive, yet rapid, analysis of drug-sized molecules. It can be used to identify the global minimum energy conformer, all local minima within a user specified energy range, or a maximally diverse subset of conformers. Confort can be applied to entire molecular structures or to user-specified substructures and is equally adept at searching rings or acyclic rotatable bonds.



A sampling (left) from a larger Confort-generated set of diverse conformers of taxol and a 2D view of the molecule (right). This analysis identified conformers within 10 kcal of taxol's global minimum and included all 23 acyclic rotatable bonds.

StereoPlex®

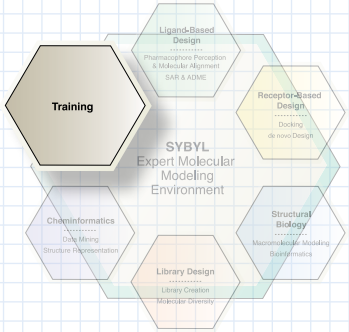
Expand the Stereochemical Diversity of a Database

StereoPlex[19] generates multiple stereoisomers of each input compound structure according to a user-specified limit on the number of stereoisomers and a user-specified priority rule which tells the program which stereoisomers to generate if the complete set would exceed the user's limit. StereoPlex multiplexes both atom-centered and bond-centered chirality, while employing a novel and unique algorithm to exclude topologically impossible stereoisomers.

17, 18, 19. Scientific Partner: Professor Robert S. Pearlman

Tripos Training

Increase your knowledge and decrease your time to getting started on the process of discovery



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