

# Advanced Computation

EXPLORE THE CONFORMATIONAL PROPERTIES OF COMPOUNDS



Industrial-strength molecular design had its real start with the Advanced Computation tools from Tripos. Continuing customer success stories testify to an enduring competitive edge. This SYBYL<sup>®</sup> module 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.

## Features

- User control of viability criteria, softness of van der Waals contacts, energy cutoff, extent and resolution of conformational space
- Analysis based both on intramolecular contacts and energy
- Ability to constrain searches by known atomic distance ranges (e.g. NMR NOE data) or by results from previous searches on other molecules
- Applications include: determination of 3D structure using interatomic distances from experimental data such as 2D NMR or fluorescence measurements; and exploration of loop conformations in protein and peptide design
- Searching of ring conformations

## Systematic Conformational Searching

Systematic searching is at the heart of the active analog approach to molecular design. The method compares a series of molecules to find the active conformations. The shapes of the active conformations then guide the design of new active compounds. The basis is a fast, flexible rigid rotor search that is also a general conformational analysis tool.

## Random Conformational Searching

Random conformational searching<sup>1</sup> locates the important energy minima by randomly adjusting selected torsions and minimizing the structure. Because of the random adjustment, each minimization is likely to produce a somewhat different minimal

energy conformation. After minimization, the resulting conformation is checked against those conformations already found and is saved if it is unique.

This cycle is performed the desired number of times or until the search is complete. The SYBYL implementation allows ring bonds to be included in the search without special setup. One study has concluded that this random internal coordinate method is about one order of magnitude faster than molecular dynamics at locating energy minima<sup>2</sup>.

## Grid Search

Grid search differs from systematic search in that it holds the torsions being searched in fixed positions while the minimization is performed. This allows the rest of the molecule to relax around the current torsion angles. An unlimited number of bonds may be selected for searching, including bonds in rings. All conformations are then generated and minimized. During minimization of each structure, the torsion angles of the bonds being scanned are held fixed. This method is appropriate for research problems involving mapping rotational barriers and locating local energy minima.

## Enhanced by SYBYL's Molecular Spreadsheet

Analysis of conformational search results is carried out in the Molecular Spreadsheet<sup>™</sup>, with new distances and other geometric information added as columns in the Spreadsheet. Procedures are available for sorting, analyzing, grouping, and graphing the data so as to effectively summarize resulting information and data relationships. The analysis function uses SYBYL's 3D graphics to produce plots that can be

interactively queried about their data points and related both to each other and to the molecule whose data is being plotted. A point picked in one graph is associated with related points in other graphs by highlighting with the corresponding conformer(s) displayed. Graphical presentation of angle or distance data can be by scatter, contour, or mesh plots in 1, 2, or 3 dimensions with color a 4th dimension and hard copy also available.

Easy reading of externally-generated data files into spreadsheets with SYBYL allows these post-processing steps to be applied to conformational output obtained from other sources such as dynamics runs, user-based conformational searches or other SYBYL search options.

## Molecular Volume Comparison

Performing local operations on molecular volumes is an integral part of analyzing the shape of molecules for identification of the active site. This feature allows the scientist to compute differences, unions, and intersections of volumes for a series of molecules and to contour the results for display as a mesh surface.

## One Program with Many Possibilities

The Advanced Computation module builds on Tripos' tradition of providing industrial strength software for customer research success. It is a pivotal component of our complete program for strategic compound design.

## Hardware and Software Requirements

Advanced Computation requires a separate license, in addition to a SYBYL license. SYBYL and Advanced Computation run on workstations operating under IRIX<sup>®</sup> (SGI<sup>®</sup>) or Linux<sup>®</sup> (x86).

**Complementary Software**

- **Biopolymer** for predicting, building, and visualizing macromolecular 3D structure.
- **Composer™** for constructing 3D homology models of proteins.
- **DISCOtech™** for elucidating pharmacophore models from precalculated conformers.
- **GASP™** for developing pharmacophore hypotheses using full conformational flexibility.
- **MOLCAD™** for visualizing molecular surfaces and molecular properties.
- **ProTable™** for analyzing and assessing the quality of protein structures.
- **SiteID™** for finding and visualizing protein binding sites.
- **Tuplets™** for pharmacophore-based virtual screening.
- **UNITY®** for locating compounds in databases that match a pharmacophore or fit a receptor site.

**References**

1. Chang, G.; Guida, W.C.; Still, W.C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.
2. Saunders, M.; Houk, K.N.; Yung-Dong, W.; Still, W.C.; Lipton, M.; Chang, G.; Guida, W.C. *J. Am. Chem. Soc.* **1990**, *112*, 1419.



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