

MOLCAD™

ADVANCED VISUALIZATION OF MOLECULAR SURFACES AND PROPERTIES



Applications

- Visualize surface features and physical properties essential for molecular recognition
- Characterize the size, shape, and physical properties of intra-molecular cavities and channels
- Communicate key properties of complex structures using simplified displays
- View and analyze the results of AMPAC calculations
- Assess the effect of structural modifications on the properties and function of a molecule
- Examine the specificity of receptor-ligand or protein-protein interactions

MOLCAD exploits the power of the human eye by creating graphical images that reveal the properties of molecules essential for molecular recognition.¹

Van der Waals and solvent-accessible surfaces can be calculated, and a broad range of properties can be mapped onto these surfaces: lipophilic potential,² electrostatic potential, hydrogen bonding ability, local curvature, and distance.

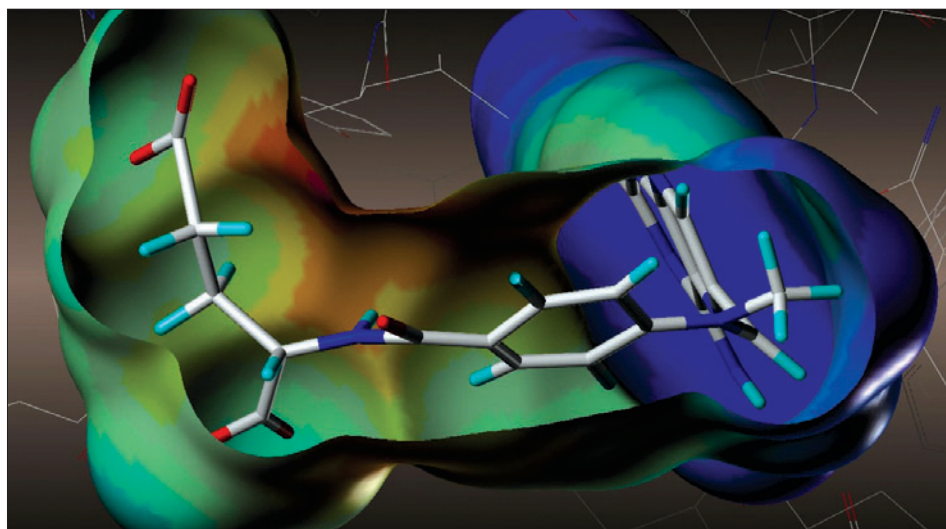
MOLCAD calculates and displays the surfaces of channels and cavities,³ as well as the separating surface between protein subunits, or between a receptor and ligand.⁴ For proteins, MOLCAD creates ribbon displays that reveal the underlying secondary and tertiary structure, and maps onto these displays physical properties such as residue lipophilicity, flexibility based on atomic temperature factors,⁵ and the packing density.

Three-dimensional vector fields associated with molecular structures can be represented by MOLCAD. Cones drawn in space represent both direction and magnitude of an electrostatic field. Three-dimensional

volume displays show all points of a three-dimensional property at once, with the density and color of the volume encoding the value of the property at any given point.

Both small and large molecules are within MOLCAD's capabilities. Surfaces generated by AMPAC™ can be imported, allowing the display of electron density, electrostatic potential, and molecular orbitals.

The "Plus" tools in MOLCAD allow surface or volume displays to change interactively when a molecule's position is changed. Slicing surfaces include planes, cylinders, or spheres onto which a molecule's property values are projected and color-coded. As the slicing object is moved through the molecule, the projection is updated to reflect the property at that point. Isocontour surfaces connect all points of a three-dimensional property grid that are equal to a selected value. Multiple isosurfaces can be displayed simultaneously and adjusted interactively. Distance surfaces, separating surfaces, and electrostatic cone surfaces are updated as a molecule is moved nearer to or farther from a second molecule.



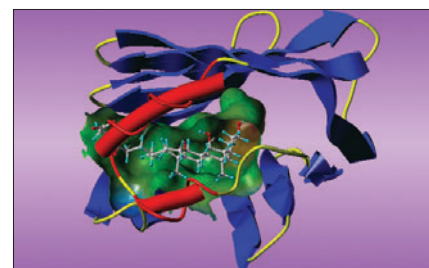
Methotrexate bound to dihydrofolate reductase. A MOLCAD-generated surface has been created for methotrexate and is color-coded by electrostatic potential. The inhibitor, methotrexate, is rendered as capped sticks, while the protein is shown as lines.

Advantages

- MOLCAD's rendering techniques allow the rapid calculation⁶ and display of property-coded surfaces for both small molecules and macromolecules.
- MOLCAD offers the most extensive set of surface displays available for understanding the physical properties of molecules and how they interact with other molecules.
- MOLCAD is unique in its ability to display the surface separating two molecules and the surface of intra-molecular channels.
- The "Plus" tools within MOLCAD enable dynamic assessment of the interactions between molecules.
- Multiple surface displays can be readily interpreted using interactive controls that restrict a surface area's display to regions within a specified property range.
- Displays can be normalized to enable comparison of surface properties on different molecules.
- MOLCAD allows real-time rotation and scaling of surfaces for molecules of any size, facilitating interactive examination of structures.

Features

- Electron density/Connolly surfaces and channels
- Surface maps color-coded by lipophilic potential, Coulombic or Poisson-Boltzman electrostatic potential, hydrogen bonding, local curvature, and distance
- Rotate, move, scale, save and reload molecular surfaces
- Color ramps that explain the range of colors for each mapped property
- Calculate surface area within any specified property range
- Display surfaces calculated by AMPAC (including molecular orbitals)
- Supports multiple processors
- Protein ribbon displays (tube, snake, cartoon, and secondary structure) color-coded by flexibility, lipophilicity, and packing density
- 3D property displays including electrostatic cones and 3D volume
- Display surfaces as dots, lines, translucent, or opaque styles
- Slicing surfaces, isosurfaces, and separating surfaces



The NMR structure of an ileal lipid binding protein complexed with glycocholate. The protein backbone is rendered as a tube. Blue arrows illustrate beta sheets, and red cylinders denote helices. The binding site was located using MOLCAD's channel finding capability and is color-coded by the lipophilic potential.

Validation

MOLCAD has been used to explain the substrate specificity of different P450 enzymes and to identify the active site in trypsin.⁵

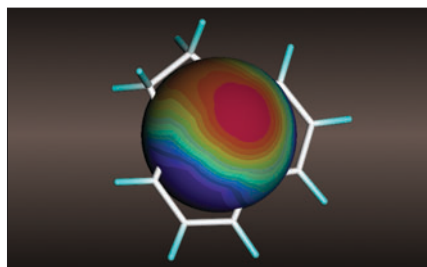
Acknowledgements

Software Partner: Darmstadt University of Technology; Germany

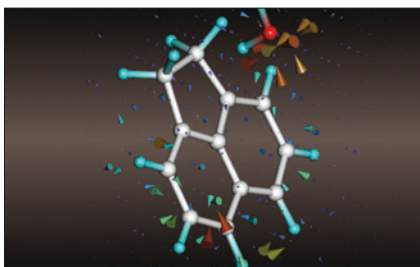
Scientific Partner: Professor Dr. Jürgen Brickman

Hardware and Software Requirements

MOLCAD requires a separate license in addition to a license for SYBYL[®]/Base. MOLCAD and SYBYL/Base run on workstations operating under IRIX[®] (SGI[®]) or Linux[®] (x86).



The Poisson-Boltzmann electrostatic potential of acenaphthene displayed as a spherical slicing surface. Blue/violet regions are negative and orange/red regions are positive.



The electrostatic cone surface during approach of a water molecule to acenaphthene. The cones are sized and color-coded according to their relative electric field strength. The base of the cones is positive; the tip is negative.

Complementary Software

- **AMPAC** for calculating transition states and spectral properties using semi-empirical quantum mechanical methods.
- **Biopolymer** for predicting, building, and visualizing macromolecular 3D structure.
- **CombiFlexX**® for rapidly docking combinatorial libraries into a receptor site.
- **Composer**™ for constructing 3D homology models of proteins.
- **CScore**™ for ranking the affinity of compounds bound to a target with consensus scoring.
- **FlexX**™ for flexibly docking ligands into a binding site.
- **FlexE**™ for considering protein flexibility during docking calculations.
- **FlexS**™ for performing shape-based screening of ligands in the absence of receptor structure.
- **FlexX-Pharm**™ for flexibly docking ligands under pharmacophore constraints.
- **FUGUE**™ for recognizing distant homologues by sequence-structure comparison.
- **GeneFold**® for identifying protein function from sequence.
- **LeapFrog**® for performing *de novo* ligand design.

- **MatchMaker**™ for building 3D models of proteins from sequence using inverse-folding techniques.
- **ProTable**™ for analyzing and assessing the quality of protein structures.
- **RACHEL**™ for optimizing lead compounds.
- **SiteID**™ for finding and visualizing protein binding sites.
- **UNITY**® for locating compounds in databases that match a pharmacophore or fit a receptor site.

References

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