

VolSurf™

CALCULATE ADME PROPERTIES AND CREATE PREDICTIVE ADME MODELS

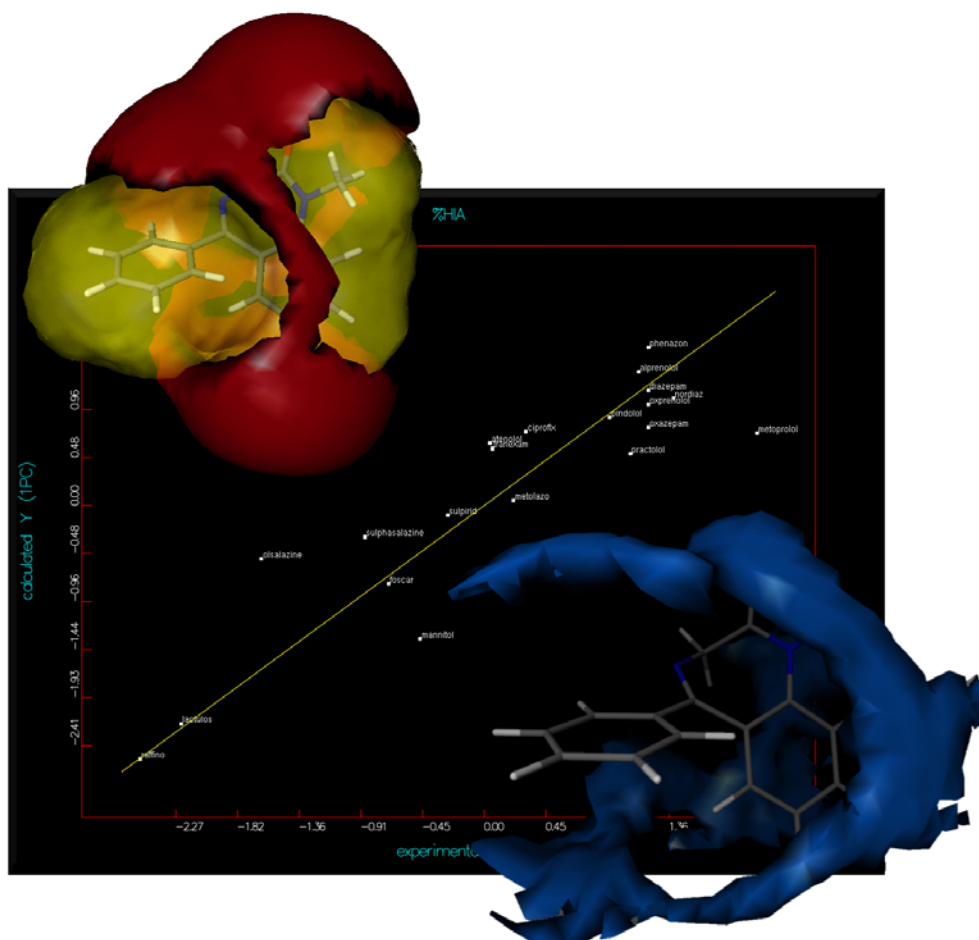


The significant failure rate of drug candidates in late stage development is driving the need for predictive tools that can eliminate inappropriate compounds before substantial time and money are invested in testing.¹ VolSurf^{2,3} predicts a variety of absorption, distribution, metabolism, and excretion (ADME) properties using pre-calculated models, computes unique ADME-relevant descriptors, and performs statistical analyses to generate predictive models of bioactivity or property.

VolSurf reads or computes 3D molecular interaction fields and uses image processing methods to convert these fields into simple molecular descriptors that are easy to understand and interpret. These descriptors quantitatively characterize size, shape, polarity, and hydrophobicity of molecules, and the balance between them.

VolSurf's descriptors have a clear chemical meaning, are not sensitive to alignment rules, and have proven to be useful in generating predictive ADME models. Descriptors can be calculated for small, medium, and large molecules, including DNA fragments, peptides, and proteins.

Multivariate statistical methods within VolSurf enable the creation of models that relate these descriptors to biological properties. The ADME models included in VolSurf predict drug solubility, Caco-2 cell absorption, blood-brain barrier permeation, and drug distribution. These models have been developed from published experimental data collected from *in vitro* assays that emulate *in vivo* behavior of drugs.



The predicted versus actual percent Human Intestinal Absorption (%HIA) for a set of passively absorbed compounds determined by VolSurf. The r^2 and q^2 values for this model are 0.82 and 0.73, respectively. VolSurf's chemically intuitive descriptors are based on 3D molecular fields. Examples include the hydrophobic (bottom right, in blue) and hydrophilic surface area of diazepam (upper left, in red). In the latter, the solvent accessible surface is shown as a transparent yellow surface.

Applications

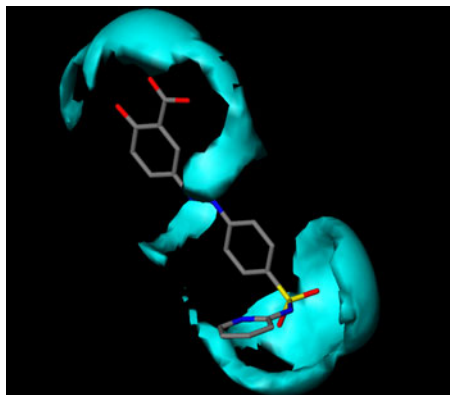
- Predict ADME properties of drug candidates
- Calculate relevant descriptors for generating ADME models
- Optimize pharmacokinetic properties of compounds
- Virtual screening of compound databases

Features

- Models for solubility, Caco2 permeation, Blood-Brain Barrier permeation, Biopharmaceutical classification, Protein binding, Volume of Distribution, hERG model, water/DMSO solubility, CYP3A4 Metabolic Stability
- Statistical methods (PLS and PCA) for creating QSAR models
- Reads mol2 or SD files; GRID, CoMFA®, or Gaussian fields
- Numerous probe atom options for generating GRID molecular fields: water, hydrophobe, amphipathic, charged
- Graphical displays of predicted vs. actual values, PLS scores and partial weights, and 3D molecular fields
- Descriptors include volume, surface, globularity, surface/volume ratio, hydrophobic and hydrophilic areas, probe interaction energy, critical packing, polarizability, amphiphilic moment, and hydrogen bonding capacity

Advantages

- Rapid predictions for use with virtual screening tools
- Models using Volsurf descriptors are significantly more predictive than those generated from other descriptors
- Supplement QSAR with CoMFA's built-in 2D and 3D descriptors
- Models do not require molecular alignment
- Translation of GRID or CoMFA fields into chemically intuitive descriptors
- Models are insensitive to conformational sampling



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

Hardware and Software Requirements

VolSurf requires a separate license and is accessible through the SYBYL[®] expert molecular modeling environment. SYBYL and VolSurf run on workstations operating under IRIX[®] (SGI[®]) or Linux[®] (x86).

Acknowledgements

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

Validation

VolSurf has been shown to generate structure-property models that accurately predict membrane partitioning of oligopeptides,⁴ blood-brain barrier permeation,⁵ the anti-HIV activity of quinolones,⁶ and oral availability.⁷

Complementary Software

- **Advanced CoMFA** for refining and enhancing 3D QSAR models.
- **Almond™** for calculating and utilizing alignment independent molecular descriptors.
- **AMPAC™** for calculating transition states and spectral properties.
- **ClogP/CMR** for including molar refractivity and logP in QSAR and ADME models.
- **Confort™** for generating sets of diverse, low energy conformers.
- **Distill™** for determining and visualizing SARs.
- **hint!™** for analyzing hydrophathy and hydrophobic interactions.
- **HQSAR™** for performing automated QSAR analyses.
- **Molconn-Z™** for computing a wide range of topological indices based on molecular structure.
- **QSAR with CoMFA** for building predictive structure-activity and structure-property models.
- **ZAP™** for calculating and displaying the electrostatic potential of molecules.

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