

LASSO Similarity Searching Tool

A Ligand Based Screening tool designed for Scaffold Hopping

LASSO is a similarity searching tool that uses LASSO descriptors to find molecules with diverse chemical scaffolds but similar surface properties. Based on the idea that ligands must have surface properties compatible with the target site in order to bind, LASSO uses a descriptor of Interacting Surface Point Types (ISPT). This descriptor contains no 2D skeletal information about the molecule, no 3D geometrical relationships (shape) and very little volume information. However it is this “fuzziness” that allows LASSO to perform well as a scaffold hopping tool. LASSO will retrieve molecules, from a screened database, that have similar surface properties to those of a query set of known actives, regardless of the underlying scaffolds.

What is a LASSO descriptor?

LASSO descriptors contain a count of the different Interacting Surface Point Types (ISPT) found on a molecule. LASSO descriptors use 23 different surface point types, ranging from hydrogen bond donors/acceptor, to hydrophobic sites, to pi stacking interactions. Figure 1 shows a “histidine-like” fragment of a molecule. The triangles are the surface point types of this fragment, colored by type. LASSO descriptors for this molecule would simply be a count of the different types, each type is one bit in the descriptor. For instance there are 5 surface points above and below the face of the ring (shown in yellow) they would count as 10 aromatic pi surface points in the LASSO descriptor.

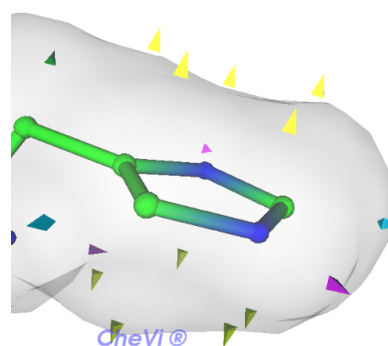


Figure 1: Histidine-like fragment of a molecule showing the surface point types as different colored triangles.

Conformation Independent Similarity Search

The bioactive conformation is NOT needed for LASSO to perform a query search. Actually only one 3D conformation is necessary, eliminating the need to generate multiple conformations. While LASSO does use a 3D representation of molecules to create the LASSO descriptor, the descriptor is independent of the conformation. Each surface point is placed based on the hybridization and local connectivity of each heavy atom, which does not change by conformation. Figure 2 illustrates the conformational independence of LASSO descriptors, each conformation of the ligand from the 1FJS complex generates the same LASSO descriptor.

LASSO Descriptor for 1FJS Ligand

0	4	0	0	1	0	4	6	1	0	0	0	8	8	0	0	23	5	2	2	0	6	0
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	----	---	---	---	---	---	---

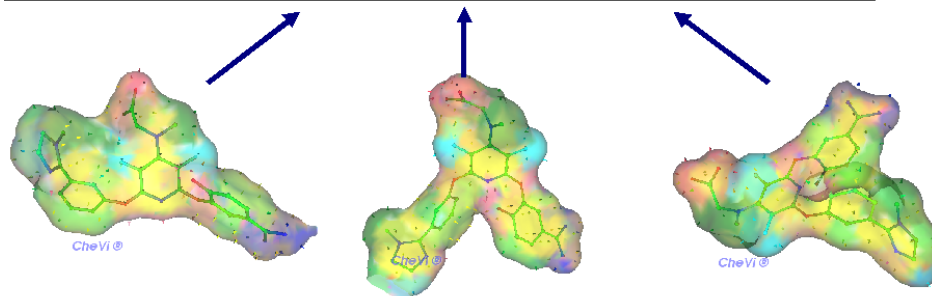


Figure 2: The LASSO descriptor for all three conformations of the 1FJS ligand are identical, illustrating the conformation independence of the LASSO descriptor.