Shape Signature, a New Approach to Computer-aided Ligand- and Receptor-Based Drug Design

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1 Introduction.

A unifying principle of rational drug design is the use of either shape similarity or complementarity to identify compounds expected to be active against a given target. Shape similarity is the underlying foundation of ligand-based methods, which seek compounds with structure similar to known active, while shape complementarity is the basis of most receptor-based design, where the goal is to identify compounds complementary in shape to a given receptor. These approaches can be extended to include molecular descriptors in addition to shape, such as lipophilicity or electrostatic potential.

We introduce a new technique, which we call Shape Signatures, for describing the shape of ligand molecules and of receptor site. *Shape Signatures* is an approach for compactly encoding the shapes of molecules and receptors [1]. This is achieved by a method much like ray tracing. We begin with either a ligand molecule or a receptor site in a protein. In either case, we enclose the molecule in its molecular surface [2,3]. A ray is initiated at a randomly chosen point on this surface, and is allowed to propagate by the rules of optical reflection. If we are considering a ligand molecule, then the ray is directed into the molecular interior, while for a receptor the ray is directed to the exterior of the molecule and propagates in the volume of the binding site. For further analysis we retain the positions of the reflection points, as well as the ray tracing *segments* (defined as the line segments that connect reflection points). In addition, we may associate the reflection points with various properties computed on the surface, such as the molecular electrostatic potential (MEP).

Given a completed ray tracing, we compute probability distributions based on the geometry of the ray, and perhaps also properties computed on the molecular surface. Our "Shape Signatures" are just these distributions, described as histograms. The simplest signature is the distribution of segment lengths observed in the ray tracing. This distribution has a one dimensional domain (namely segment length), and we refer to it as a "1D Signature". Signatures with higher dimensional domains can be defined as joint probability distributions that involve both ray tracing geometry and surface properties, such as the molecular electrostatic potential (MEP). A "2D-MEP" signature encodes information about both molecular shape and charge distribution.

Shape signatures can be generated from ray tracing of receptor sites in a manner identical to ligand ray tracing. Where a match between 1D signatures of two ligands indicates they may have similar shape, a match between a receptor-based query and a potential ligand indicates that they are *complementary* in shape.

2 Application.

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Searching Chemical Libraries for Lead Compounds. Shape Signatures can be used to scan libraries for compounds similar in shape to a query compound (presumably a known active). Matches can be found on the basis of shape alone (using 1D signatures), or shape combined with electrostatics (using 2D-MEP signatures). The first approach casts a wider net, while the 2D approach will locate compounds very similar to the query in both shape and electrostatic field.

Scanning Libraries for Compounds Complementary to a Protein Receptor. A special strength of the Shape Signatures approach is that the handling of receptors and ligands is completely symmetrical – to generate Shape Signatures for receptor sites or sub sites all that is required of the user is to select the atoms that define the site, save these as a file in the query structure database, and use an alternate script designed for receptor-based signature generation.

References

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