

GASP™

DEVELOP PHARMACOPHORE HYPOTHESES USING FULL CONFORMATIONAL FLEXIBILITY



GASP performs pharmacophore elucidation without requiring prior knowledge of pharmacophore elements or constraints. Using a genetic algorithm, GASP automatically allows conformational flexibility and maps features among molecules.

In the absence of a three-dimensional receptor structure, a model of the active site can be inferred from the ligands that bind to it. Key factors in developing such a model are the determination of functional groups essential for binding, their correspondence from one ligand to another, and the common spatial arrangement of these groups when bound to the receptor. GASP (Genetic Algorithm Similarity Program)¹ employs a genetic algorithm for determining the correspondence between functional groups in different molecules and the alignment of these groups in a common geometry for receptor binding.

Applications

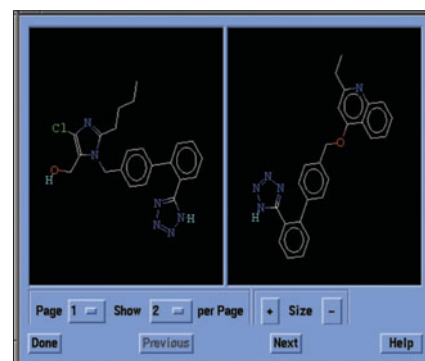
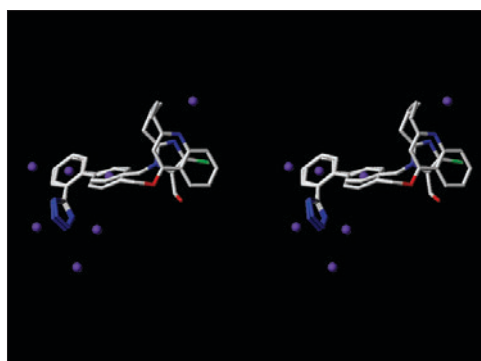
- Generate pharmacophore hypotheses from a set of receptor ligands
- Determine functional group correspondences for molecules bound to the same receptor
- Align molecules for 3D-QSAR studies
- Test the fit of ligands to a pharmacophore model

Using a mutation or crossover operator, child chromosomes are produced. Those with improved fitness scores replace the least fit members of the existing population. The calculation terminates when the fitness of the population fails to improve by a specified amount, or when the preset number of genetic operations is completed. GASP produces several sets of alignments and their associated pharmacophore elements.

Features

- Full ring flexibility
- Optional rigid template molecule
- Intramolecular distance and torsional constraints
- Full control of genetic algorithm parameters
- Optional torsional energy and dipole alignment terms in fitness score
- Adjustable weighting of fitness score terms

For a set of ligands, GASP automatically identifies rotatable bonds and pharmacophore elements such as rings and potential hydrogen-bonding sites. A population of chromosomes is randomly constructed, where each chromosome represents a possible alignment of all the molecules. Chromosomes encode the torsion settings for rotatable bonds as well as the intermolecular mapping of elements.² The fitness score of a particular alignment is the weighted sum of three terms: the number and similarity of overlaid elements, the common volume of all the molecules, and the internal van der Waals energy of each molecule.



Two angiotensin II receptor antagonists² (2D degree view at right) and one of their alignments determined by GASP (stereo view left). Pharmacophore elements are represented as purple spheres and include rings and receptor hydrogen bond sites.

Advantages

- Allows full conformational flexibility of ligands, unlike methods that are limited to a pre-computed set of rigid conformers.
- Requires no advance knowledge of key functional groups or predefined correspondences between functional groups in different ligands.
- Automatically identifies rotatable bonds and key pharmacophore features. The only input required is a set of molecules.
- Intermolecular constraints can force correspondence between specific functional groups.

Complementary Software

Integration of GASP in the SYBYL[®] expert molecular modeling environment allows users to access SYBYL's powerful molecular design and analysis tools.

- **Advanced Computation** for exploring the conformational properties of compounds.
- **AMPAC**[™] for calculating transition states and spectral properties using semiempirical quantum mechanical methods.
- **Concord**[®] for generating accurate 3D coordinates.
- **Confort**[™] for generating sets of diverse, low energy conformers.
- **DISCOtech**[™] for elucidating pharmacophore models from pre-calculated conformers.
- **Tuplets**[™] for pharmacophore-based virtual screening.

Validation

GASP reproduces alignments for 5-HT₃, angiotensin II, and dopamine antagonists derived by other methods.^{1,3,4}

Hardware and Software Requirements

GASP requires a separate license, and runs on workstations operating under IRIX[®] (SGI[®]) or Linux[®] (x86).

Acknowledgements

Software Partner: University of Sheffield, UK
Scientific Partners: Professor Peter Willett, Dr. Gareth Jones, Dr. Robert Glen

References

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