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COMPUTER SOFTWARE
REVIEWS

GALAHAD. Tripos, Inc., 1699 South Hanley Road, St. Louis, MO 63144-2319. www.tripos.com. Contact company for pricing information.

Pharmacophore modeling has been used extensively in drug discovery research to search for novel lead compounds in both academic and pharmaceutical industry environments. A pharmacophore is the spatial arrangement of essential structural features common to a set of active ligands. A new automated program for alignment of pharmacophores, GALAHAD, the acronym for *G*enetic *A*lgorithm with *L*inear *A*ssignment of *H*ypermolecular *A*lignment of *D*atasets, has been introduced by Tripos, Inc.

Over the years, several commercial programs have been developed for automatically identifying pharmacophore models from a set of active compounds. The primary difference between the different packages for pharmacophore modeling concerns the algorithm for the alignment of molecules and the methodology to treat conformational flexibility properly. GALAHAD uses Tripos' proprietary technology to align a set of ligand molecules and to generate pharmacophore hypotheses. The surprisingly efficient alignment of ligands in GALAHAD is the result of a two-stage alignment: first, a pair of ligands is aligned in internal coordinate space, which allows flexibility, and the resulting conformations are then aligned as rigid bodies in Cartesian space. This approach frees the user from having to select a template molecule. The flexibility of a molecular structure is treated through the initial alignment in torsional space by an advanced genetic algorithm. The resulting torsions are applied to the base structure of each ligand to generate the ligand conformation. The 3D similarity among the ligand conformations is estimated through the fast pharmacophoric and steric multiplets (Tuplet). The indicators of alignment and the total ligand energy are used to rank the fitness of the Tuplet pharmacophore. GALAHAD uses the HYPERMOL executable to generate structural similarity between a pair of ligands. A least-square alignment of the two ligands is carried out based on the structural similarity and consistency of geometry. A new single hypermolecule is generated from the least-square alignment. This new hypermolecule is then aligned with the third ligand and another hypermolecule is generated, and the whole process continues iteratively until all active ligands in the training set are aligned. The end result is a single master hypermolecule that incorporates information from every molecule in the training set. The master hypermolecule can then be used as a template for generating UNITY queries for database searching.

The interface of GALAHAD is very user-friendly. Users can open the GALAHAD interface through the SYBYL menu TOOLS/Pharmacophore Alignment, and the training set of molecules can be aligned using either features or atoms. The template alignment option allows users to align a database of ligands individually to a template, which can be a pharmacophore template generated from a set of active compounds. This option is extremely helpful for molecule alignment for CoMFA and CoMSIA studies. After the GALAHAD computation, a number of pharmacophore models are clustered in a database. Each pharmacophore model represents a different tradeoff between maximizing pharmacophore consensus, maximizing steric consensus, and minimizing energy. Users can examine each pharmacophore model by simply clicking forward or backward.

A very convenient design of the GALAHAD interface is that users can launch the UNITY Shortcuts dialog, which allows users to edit the UNITY queries immediately after reviewing the desirable pharmacophore model. A unique strength of GALAHAD is that it not only allows an individual ligand to be aligned according to a pharmacophore template but also simplifies the user's efforts in retrieving the best aligned conformation of the aligned ligands. Instead of creating a separate molecular spreadsheet for each molecule, GALAHAD creates a database to accommodate the best alignment for each molecule. In other words, the best alignment of a molecule becomes a row in the new output database. For example, if a user has a database of 100 ligands that need to be aligned with a common pharmacophore template, GALAHAD will create a new database that contains 100 rows, each of which contains the best alignment of the ligand molecule. This greatly enhances the time management for the users and makes the process less prone to errors that may occur during retrieving the best aligned structure in what would otherwise be 100 separate databases.

It is worth mentioning that the GALAHAD input database is compatible with other databases via the SD file (.sdf) format. It can also open and save the model molecules in a single multiMol2 (.mol2) file. This enables the database to be transferable to other software packages as well.

This pharmacophore modeling package should be useful to scientists and medicinal chemists involved in computer-assisted drug design. For first-time users, SYBYL provides the tutorials through the Tripos Bookshelf. Specific examples are given in the tutorials and are invaluable for learners new to these techniques. The reference provided in the tutorials is very helpful in understanding the underlying mechanism. GALAHAD, therefore, should greatly enhance the power of discovery in drug research through its user-friendly interface.

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