pharmACOphore

user manual

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The ligand alignment mode allows for the superimposition of a given set of ligand molecules: *PLANTS --mode align yourconfigfile*

A given alignment can be rescored with: *PLANTS --mode rescorealign yourconfigfile*

1 Configuration File Settings

pharmACOphore needs (in the same way as PLANTS) a configuration file that contains all data needed for the ligand alignment. The following sections describe the settings that can be adjusted by the user. For the case that no parameters are specified, recommended standard settings are used.

1.1 General Input

- **ligand_file** *string* [**fixed**]: ligand file to be aligned; can be set fixed by adding keyword *fixed*. Multiple ligand files can be specified.
- **score** *class*1 *class*2 w_{ij} $r_{\mathbf{opt}_{ij}}$: activate scoring of pairwise interactions between atoms of types *class*1 and *class*2. For a description of the other parameters see the next sections.
- **ringscore** w r: activate scoring of ring systems (ring center distance plus ring normal direction); the score w for optimally aligning the ring centers for rings of the same type is scaled by the deviation of the ring ring normals (for a detailed description see below).

1.2 Search Algorithm

pharmACOphore offers predefined search speed settings.

- **search_speed** *value*: search speed setting, *value* can be set to *speed1* (highest reliability, slowest setting), *speed2* (good reliability, twice as fast as speed1) or *speed4* (modest reliability, four times as fast as speed1) (standard: speed1)

The parameters can be altered by adding one or more of the following keywords to the configuration file:

- **aco_ants** *value*: number of ants (standard: 20)
- **aco_evap** *value*: evaporation factor $\rho \in [0; 1]$
- **aco_sigma** *value*: iteration scaling factor σ
- **flip_amide_bonds** *value*: activate (1) or deactivate flipping of amide bonds (standard: 0)
- **flip_planar_n** *value*: activate (1) or deactivate flipping of bonds next to planar nitrogens (standard: 1)
- **force_flipped_bonds_planarity** *value*: activate (1) or deactivate (0) automatic planarity correction for flippable bonds (standard: 0)
- **force_planar_bond_rotation** *value*: activate (1) or deactivate (0) free rotation of planar bonds (standard: 1)
- **rescore_mode** *value*: perform simplex optimization during rescoring (*value*=simplex) or only direct input conformation scoring (*value*=no_simplex) (standard: simplex)
- **flip_ring_corners** *value*: activate (1) or deactivate flipping of free ring corners (standard: 0)

Pairwise scoring

Pairwise interactions are scored according to equation 1:

$$s_p(r_{ij}) = w_{ij} \cdot \begin{cases} 1 & \text{if } r_{ij} \leq r_{\text{opt}_{ij}} \\ \left(1 + s \cdot \frac{r_{ij}^2 - r_{\text{opt}_{ij}}^2}{c^2 - r_{\text{opt}_{ij}}^2}\right)^{-1} & \text{otherwise,} \end{cases} \tag{1}$$

r_{ij}: distance between point i and point j

c: cutoff-radius for pairwise score calculations (standard: 10Å)

s: sharpness parameter (standard: 50.0)

w_{ij}: score weight for pair ij

$r_{\text{opt}_{ij}}$: distance for pair ij inside which the full score w_{ij} is rewarded

Predefined fragment classes:

- DONOR_H: hydrogen atom attached to heavy donor atom
- DONOR: hydrogen bond donor

- DONOR_RING: hydrogen bond donor, only ring atoms
- DONOR_NORING: hydrogen bond donor, except ring atoms
- ACCEPTOR: hydrogen bond acceptor
- ACCEPTOR_RING: hydrogen bond acceptor, only ring atoms
- ACCEPTOR_NORING: hydrogen bond acceptor, except ring atoms
- DONACC: hydrogen bond donor/acceptor
- DONACC_RING: hydrogen bond donor/acceptor, only ring atoms
- DONACC_NORING: hydrogen bond donor/acceptor, except ring atoms
- NONPOLAR: nonpolar atoms, no hydrogens
- NONPOLAR_RING: nonpolar atoms, no hydrogens, only ring atoms
- NONPOLAR_NORING: like NONPOLAR, except ring atoms
- LIPOPHILIC: lipophilic atoms (carbons not attached to polar atoms, Cl, Br, I, nonpolar sulphur atoms)
- LIPOPHILIC_NORING: like LIPOPHILIC, except ring atoms
- LIPOPHILIC_RING: like LIPOPHILIC, only ring atoms
- CHARGED_N: positively charged nitrogens
- COO: carboxylate groups (matched fragment: C-COO)
- CO: carbonyl groups

User-defined fragment classes:
See section **??** for a description how to add user-defined fragment definitions to a ligand file. The name specified in the field FRAGMENT_NAME can be used in the scoring definition for $class1/class2$.

Vector scoring

Ring system interactions are scored according to equation 2:

$$s_v(p_{i0}, p_{i1}, p_{j0}, p_{j1}) = s_p(\sqrt{\overrightarrow{p_{i0}p_{j0}} \bullet \overrightarrow{p_{i0}p_{j0}}}) \cdot |\overrightarrow{p_{i0}p_{i1}} \bullet \overrightarrow{p_{j0}p_{j1}}|^3 \quad (2)$$

p_{i0},p_{i1}: points defining vector $\overrightarrow{p_{i0}p_{i1}}$ with origin p_{i0}

p_{j0},p_{j1}: points defining vector $\overrightarrow{p_{j0}p_{j1}}$ with origin p_{j0}