

FRESNO

Introduction

Fresno is a scoring function application. It calculates score terms such as hydrogen bonds, lipophilic contacts, and the penalty term due to frozen rotatable bonds. In addition, it calculates terms such as buried polar scores (a measure of the desolvation energy term), Lennard-Jones interactions, and a weighted H-bond term based on an estimate of the exposure of each ligand-protein H-bond to water.

Fresno is a C++ implementation based on scoring function algorithms¹ described in the literature. The software has been tested in studies on biologically active systems², including predictions before synthesis.

A free-energy estimate is calculated by the software based on internal parameters. Moreover, the user has full access to all calculated score terms for the purpose of re-fitting the energy score equation as needed, e.g. for specific classes of protein-ligand complexes.

Installation

Fresno is a self-contained application that can be installed at any convenient location on a workstation storage system. It runs on Mac OS X, Linux, and Windows.

Input

Fresno recognizes automatically three input file formats

- Trypos MOL2
- Macromodel (implementation © 1995 Columbia University)
- Accelrys CAR

The software is accessed through the command line as follows

```
fresno [options] < input
```

for a single file input containing both the ligand and protein coordinates.

Or as follows

```
fresno [options] -C <command-file>
```

¹ Eldridge M.D., Murray C.W., Auton T.R., Paolini G.V., Mee R.P. *J Comp -Aided Molec Des* **1997**, *11*, 425-445

² Rognan D., Lauemøller S. L., Holm A., Buus S., Tschinke V. *J Med Chem* **1999**, *42*, 4650–4658

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when using a file with the protein coordinates and several files with the (docked) ligand coordinates. Here, "command-file" is a text file containing the path of the file with the protein coordinates, followed by the paths of the files with the coordinates of the ligands. Because only one set of coordinates are used for the protein, this set-up is suitable to score the results of a rigid-docking calculation.

Options

The options for the applications are listed below

```
'h' this text
'a' <int> the number of an atom identifying the ligand
    [default=1]
'r' <int> the number of a residue identifying the ligand
'b' <float> "buried" polar threshold to define a non-exposed H-
    bond [default=20]
'd' <float> distance to add to the VdW radii sum to define a
    non-exposed H-Bond [default=3]
'C' <file> command file for a batch run
'e' output only the computed energy (batch only)
'c' <int> for "macromodel" input : starting connections on file
    [default=1]
'f' <file> read the coefficient to calculate the energy from a
    file
'H' do not calculate H-bond scores
'L' do not calculate lipophilic contact scores
'R' do not calculate rotatable bond scores
'm' <file> "mdf" file to match a "car" input file
's' "special" output with buried polar scores and LJ
    interactions
'v' verbose output
'x' "terse" output with all scores on a line
'X' same as 'x' preceded by a header line with the names of the
    scores
't' print the header for the "terse" format and exit
```

For the sake of consistency, the behavior of Fresno is the same on all operating systems. Each option keyword must be preceded by a "-" character, e.g.

```
fresno -t
```

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Score Terms

The score terms calculated by the program can be printed with the 'x' or 'X' options, as mentioned above. Table 1 lists these terms.

Header	Parameter
HB	Hydrogen Bonds (sum of)
LP	Lipophilic Score
RT	Rotational Score
Nr	Number of rotatable bonds (total)
FNr	Number of rotatable bonds (frozen)
BP	Buried Polar Score ("desolvation" score)
HBbp	Hydrogen Bonds (involving Buried Polar atoms)
LJt	Lennard-Jones (total)
LJr	Lennard-Jones (repulsive)
LJa	Lennard-Jones (attractive)

Table 1 Score terms calculated by the application

Output

Fresno writes its results to the standard output. If needed, the output can be redirected to a file:

```
fresno [options] < input > output  
fresno [options] -C command-file > output
```

Using Fresno

The simplest way to use Fresno is to read an input file from the command line with all options set to default

```
fresno < input
```

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here, it is assumed that the ligand is the first structure in the input file. The scoring parameters are given the values of the Proteus¹ scoring function, which are stored internally in the software. However, the score calculation is limited to the three terms Hydrogen bonds, lipophilic interactions, and frozen bond penalty. The output may look like

```
Ligand 1
 5241  atoms found
(  79  ligand atoms)
      Tot.      HB      Lipo      Rot.
Scores                3.1  286.1    3.7
Energy -39.8   -10.3  -33.5    9.5
P(Ki)    7.0
```

Where the H-bond, lipophilic, and frozen rotational bond penalty terms and contributions to the energy score are identified by the headers "HB", "Lipo", and "Rot.", respectively.

The standard coefficients can be replaced by others of choice using the 'f' option

```
fresno -f coeff_file < input
```

where the file "coeff_file" (or any other name) contains the following data

```
title
```

```
intercept
```

```
H-bond
```

```
metallic (not used)
```

```
lipophilic
```

```
aromatic (not used)
```

```
rotational
```

To access the full features of the program, all score terms can be computed, and the scoring coefficients calculated by suitable statistical methods. The energy scores can then be derived using spreadsheet calculations or a suitable script.

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The 'x' option is used to get a list of all computed score terms. The resulting output consists of a line of text for each complex, with all terms separated by *tabs*. The 'X' option produces the same output as 'x', only preceded by a header line with a brief identification of each term. The 't' option prints out this same header without any further input. The options 't' and 'x' can be used in the command line or in a script as follows

- set the working directory to the one containing the files to be processed
- run fresno with the 't' option to output the header into a file

```
fresno -t > output.txt
```

- run fresno several times, e.g. in a loop, to add a line of text for each file in a set to the same file, e.g. on Linux/Mac OS X

```
for f in *.mol2 ; do
    fresno -x < $f >> output.txt
done
```

or on Windows

```
for %f in (*.mol2) do ( fresno -x < %f >> output.txt )
```

The resulting output file may look as shown in Table 2.

Title	HB	LP	RT	Nr	FNr	BP	HBbp	LJt	LJr	LJa
Ligand 1	3.121	274.2	3.253	11	10	281.6	3.091	-207.2	94.3	301.5
Ligand 2	3.095	286.1	3.714	12	11	308.7	3.068	-218.9	95.3	314.3
Ligand 3	3.205	253.9	3.321	11	10	275.9	3.152	-196.6	83.7	280.3
Ligand 4	3.108	247.2	3.744	11	10	300.9	3.078	-203.5	93.1	296.6

Table 2 Sample output using the 't' options (first row), and the 'x' option (remaining rows). See Table 1 for the meaning of the symbols on the first row.