Generating Reaction criteria for simulating protein-ligand association with SDA

0.1 Introduction

A set of reaction criteria, that define the formation of an encounter complex between 2 solutes, need to be specified for performing docking and association rate calculations with SDA. Usually, donor-acceptor atom pairs in the bound protein-ligand complexes are considered as reaction criteria but other types of interacting atom pairs can also be included. These reaction criteria must be validated for the complex to be accepted and recorded in the *complexes* file. The list of reaction criteria must be provided in a separate file (named with a suffix **.rxna*), which consists of a set of definitions like:

```
#keyword                          criteria for solute 1  | distance|                          criteria for solute 2
CNONS ATOM    540  OE2 GLU A  60      26.527  32.135  -0.455 |    60.00| ATOM    332  N   LEU D  34      28.306  33.610   1.176
```

They consist of a 5 letter keyword for the type of reaction criterion (e.g. CNONS refers to non-specific criteria, CSPEC refers to a specific reaction criteria), the position of the reaction criteria of the solute 1 in PDB format, the distance criterion, and the position of the reaction criteria of the solute 2 in PDB format.

0.2 *ReactionCriteria.py*

The python script *ReactionCriteria.py* generates reaction criteria file (*.rxna* file) required by the SDA software for docking or calculation of association rates for protein-ligand association. It generates the reaction criteria by taking into account the hydrogen bonding interactions, halogen-π interactions, and the π-π interactions in the bound protein-ligand complex.

0.2.1 Input parameters:

It requires total 4 arguments where the 4th argument is optional:

1) Name of PDB file of the protein* (with .pdb extention)
2) Name of PDB file of the ligand* (with .pdb extension)
3) The reaction distance (in Å)
4) Name of MOL2 file of the ligand** (OPTIONAL ARGUMENT)

The script uses PyMOL function to add hydrogens (in case H atoms are missing in the input PDB files).

The MOL2 file for ligand can also be provided as an optional fourth argument, if π-π interactions between protein and ligand also need to be considered for generating reaction criteria.

0.2.2 Usage

```
python ReactionCriteria.py protein_pdb ligand_pdb distance ligand_mol2
```

protein_pdb is the name of PDB file of the protein with .pdb extension.

ligand_pdb is the name of the PDB file of the ligand with .pdb extension.

distance is the distance (integer value) for recording encounter complexes in docking simulations (although this distance value is ignored in association rate calculations, it should always be included as an argument due to the fixed format of the .rxna file).

ligand_mol2 is the name of the Tripos Mol2 file of the ligand with .mol2 extension (optional argument, used only when π-π interactions between protein and ligand also need to be considered).

0.2.3 Example Case

The reaction criteria for the diffusional association of Human Coagulation Factor Xa (*FXa.pdb*) and Rivaroxaban (*RIV.pdb*) can be generated using *ReactionCriteria.py* as:

```
python ReactionCriteria.py FXa.pdb RIV.pdb 6 RIV.mol2
```

(**** Output file is generated in the same directory with name : RIV.rxna ****)

```
cat RIV.rxna
```

```
CNONS ATOM   1285    N THR   98      10.829   0.686  12.834 |     6.00| ATOM     5   O5 RIV A1001      9.768   1.124  16.111
CNONS ATOM   1299    N TYR   99      12.420   2.291  14.218 |     6.00| ATOM     5   O5 RIV A1001      9.768   1.124  16.111
CNONS ATOM   1304   CG TYR   99      11.462   4.585  16.400 |     6.00| ATOM    10  C10 RIV A1001      7.918   4.619  19.048
CNONS ATOM   2538  CD2 PHE  174       7.510  -1.643  20.690 |     6.00| ATOM    11  C11 RIV A1001      6.837   2.690  20.070
CNONS ATOM   3174   CG TRP  215      11.647   4.092  20.850 |     6.00| ATOM    12  C12 RIV A1001      7.682   3.222  19.078
CNONS ATOM   3215    N GLY  219       4.929   4.193  26.175 |     6.00| ATOM    17  O17 RIV A1001      4.690   6.614  23.757
CNONS ATOM   3215    N GLY  219       4.929   4.193  26.175 |     6.00| ATOM    19  O19 RIV A1001      4.634   4.419  23.228
CNONS ATOM   3218    O GLY  219       6.537   5.971  27.315 |     6.00| ATOM    21  N21 RIV A1001      7.078   8.136  24.932
CNONS ATOM   3370  CD1 TYR  228      17.445   5.720  26.819 |     6.00| ATOM    29   CL RIV A1001     13.544   7.302  26.531
```