Generating Reaction criteria for protein-ligand complex

A set of reaction criteria are used to define the formation of a complex between 2 solutes for docking and association rate calculations. These reaction criteria must be validated for the complex to be accepted and recorded in the complex 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 keyword for the type of reaction criterion (e.g. CNONS refers to non-specific criteria, CSPEC refers to a specific reaction criteria), the type of position of the atom of the solute 1 in PDB format, the distance criterion, and the type of position of the atom of the solute 2 in PDB format.

Name of the Script: `ReactionCriteria.py`

Description:

This Python script generates reaction criteria file (.rxna file) required by the SDA software for calculation of association rates for Ligand and Protein association.

It defines reaction criteria on the basis of :

1) H-bonding contacts (donor-acceptor pairs) between protein and ligand molecules.
2) Chlorine-pi interactions .
3) pi-pi interactions between protein and ligand molecules.

Input parameters:

It takes total 4 parameters as input where 4th parameter is OPTIONAL (Name of Mol2 file of ligand):

1) Name of PDB file of protein (with .pdb extention)
2) Name of PDB file of ligand (with .pdb extension)
3) Distance to be considered for reaction criteria (integer number)
4) Name of Mol2 file of ligand (OPTIONAL ARGUMENT)

*** MOL2 file of the ligand must be provided as the 4th and the last argument to allow the pi-pi interactions between ligand and protein molecules to be considered for defining reaction criteria.***

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

Usage:

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

`protein_pdb` - Name of PDB file of the protein with .pdb extension

`ligand_pdb` - Name of the PDB file of the ligand with .pdb extension

`distance` - Distance criteria to include in reaction criteria file (integer number)

`ligand_mol2` - Name of the Mol2 file of the ligand with .mol2 extension

Example:

We have used crystal structure of protein-inhibitor complex (**PDB Id:2W26**) of Human Coagulation Factor Xa and its inhibitor: Rivaroxaban.

Coordinates of Factor Xa and Rivaroxaban were separated into two PDB files:

1) Xa.pdb (Chain A of PDB ID 2W26 corresponding to heavy chain of activated Human Coagulation Factor Xa).

2) RIV.pdb (HETATMs with residue name RIV corresponsing to rivaroxaban).

Both of the PDB structures were protonated at pH 7 and 300K using MOE software to add hydrogen atoms. Un-protonated PDB files can also be used as input files. In such case script adds hydrogen atoms to the respective files using PyMOL functionality and creates temporary files (with **_temp.pdb** extension) in the same directory which must be deleted later by the user.

Mol2 file of the Rivaroxaban (**RIV.mol2**) was generated using *antechamber* program of **AMBER 14** package. Distance of 6 Angstrom was used as distance criteria in our case.

Script was run as:

```
ganotrgv@arete:~/sda/auxi/Kon-rates-SmallMolecule/Generate-ReactionCriteria/TestRun$  python
ReactionCriteria.py  Xa.pdb   RIV.pdb   6   RIV.mol2
```

*** Output reaction criteria file is generated in the same directory with name: **RIV.rxna.**

```
ganotrgv@arete:~/sda/auxi/Kon-rates-SmallMolecule/Generate-ReactionCriteria/TestRun$ cat RIV.rxna

CNONS ATOM   1285    N THR A  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 A  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 A  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 A 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 A 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 A 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 A 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 A 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 A 228      17.445   5.720  26.819 |     6.00| ATOM     29   CL RIV A1001      13.544   7.302  26.531
```