siteinterlock v0.1.0

Sebastian Raschka

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A novel approach to pose selection in protein-ligand docking based on graph theory.

{link to paper}

1 Installation

The `siteinterlock` package is compatible with both Python 2.7 and Python 3.x and does not require external dependencies or libraries. Below, you can find If you are using `pip`, you can download and install

1.1 Installing from Source

You can obtain the latest, stable release of `siteinterlock` from GitHub at https://github.com/rasbt/siteinterlock/releases.

1. After clicking on the `Source code (zip)` or `Source code (tar.gz)` download links, go to your download folder and unpack the source code archive using your preferred archive-tool.
2. Next, go into the unzipped `siteinterlock` directory, and install the siteinterlock package by executing `python setup.py install`.
3. You may verify your installation by executing the following command from your terminal: `python -c 'import siteinterlock; print(siteinterlock.__version__)'`, which should print `1.0.0`.
4. Now, you will be able to use the SiteInterlock scripts provided in the `scripts/` subdirectory from any location on your local drive.

1.2 Installing from PyPI via pip

If you are using `pip`, you can download and install SiteInterlock directly from PyPI, the Python Package Index, by executing

```
pip install siteinterlock
```

{!!add note about the scripts directory}

1.2.1 Upgrading via pip

To upgrade an existing version of `siteinterlock` from PyPI, execute

```
pip install siteinterlock --upgrade
```

2 user_guide.Overview

3 user_guide.Preparing_a_Protein_Structure_for_Docking

4 user_guide.Ligand_Docking

5 user_guide.Preparing_Docking_Poses_for_SiteInterlock

- After you successfully docked the ligand into the protein's binding site
- Prepare docking poses as PDB files containing protein and ligand for each docking pose
- Also, prepare the ligand-free structure of the protein
- Prior to ProFlex, make sure the proteins have protons
- You can use Reduce for instance
- We recommend you put each docking pose into a separate directory, for instance as in examples/proflex_input
  - for ? docking poses + ligand-free structure + crystal structure

6 Determining a Reasonable Energy Cut-Off for Hydrogen Bonds

```
cd 1com_nolig/

proflex -h 1com_nolig.pdb

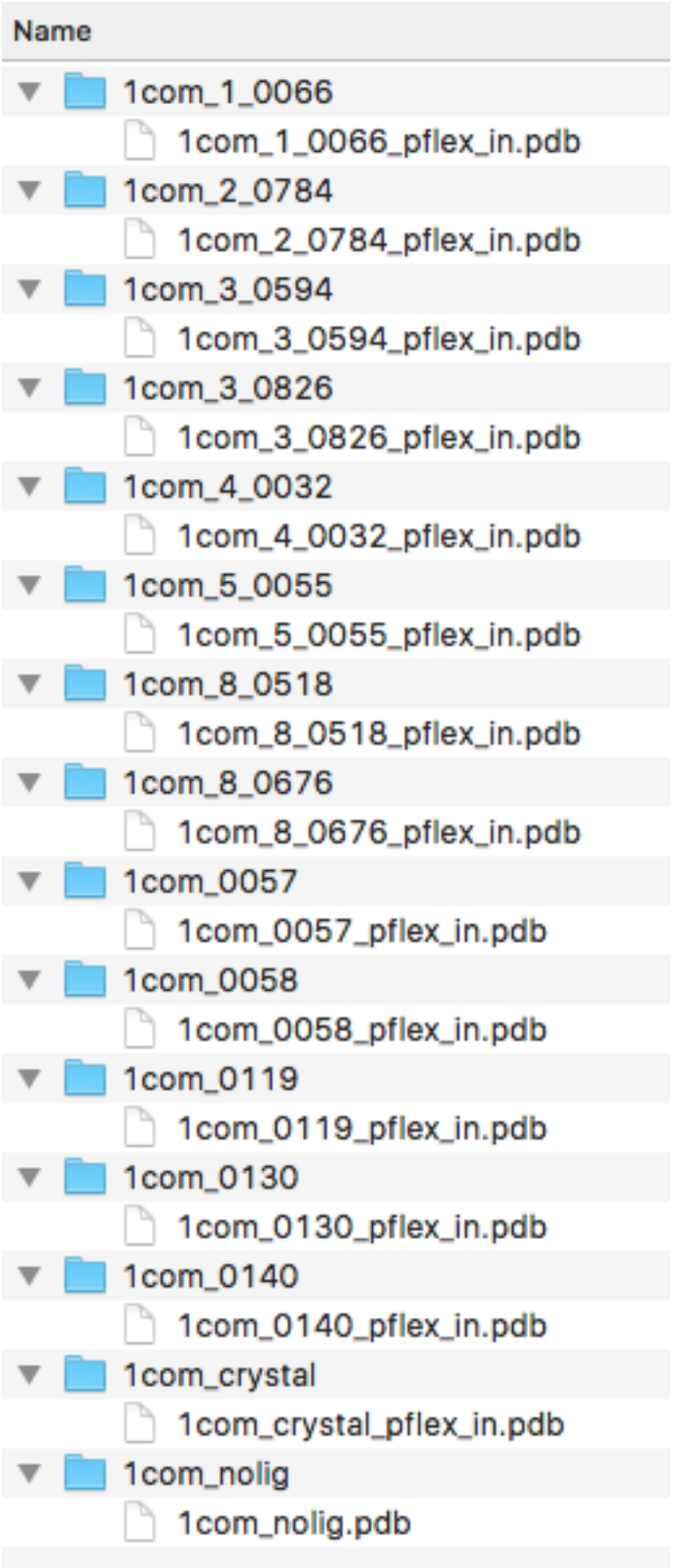
Number of H-bonds remaining: 202

Number of H-phobic tethers remaining: 166

         Filter on Hydrogen Bond Energy:
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    All current hydrogen bonds have energies between:
        -9.8419 Kcal/Mol  to  0.0226 Kcal/Mol

    Enter a maximum acceptable hydrogen bond energy (in Kcal/Mol)
    (-1.0 is a reasonable cutoff in general): 0
```


Name
1com_1_0066
1com_1_0066_pflex_in.pdb
1com_2_0784
1com_2_0784_pflex_in.pdb
1com_3_0594
1com_3_0594_pflex_in.pdb
1com_3_0826
1com_3_0826_pflex_in.pdb
1com_4_0032
1com_4_0032_pflex_in.pdb
1com_5_0055
1com_5_0055_pflex_in.pdb
1com_8_0518
1com_8_0518_pflex_in.pdb
1com_8_0676
1com_8_0676_pflex_in.pdb
1com_0057
1com_0057_pflex_in.pdb
1com_0058
1com_0058_pflex_in.pdb
1com_0119
1com_0119_pflex_in.pdb
1com_0130
1com_0130_pflex_in.pdb
1com_0140
1com_0140_pflex_in.pdb
1com_crystal
1com_crystal_pflex_in.pdb
1com_nolig
1com_nolig.pdb

```
    ANALYSIS MENU

  What would you like to perform:

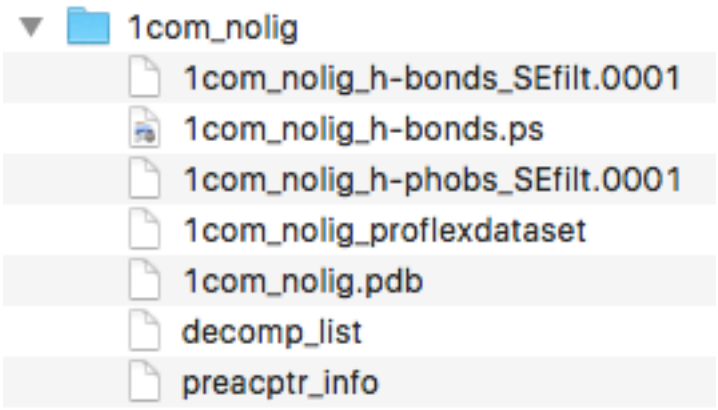
    (1) Flexibility and rigidity analysis
    (2) Hydrogen bond dilution
2


  Which hydrogen bond dilution analysis would you like?

  (1) Standard hydrogen bond dilution, removing weakestH-bonds, one at a time

   (2) Random dilution over all H-bonds.
       NOTE: This option is *not* recommended;
             It may be used to probe the influence of H-bond
             density, as opposed to strength, on rigidity

1
```




```
~/Desktop$ python siteinterlock-toolkit/scripts/hether.py\
--input1 examples/proflex_output/1com_nolig/1com_nolig_proflexdataset\
--input2 examples/proflex_output/1com_nolig/decomp_list
```

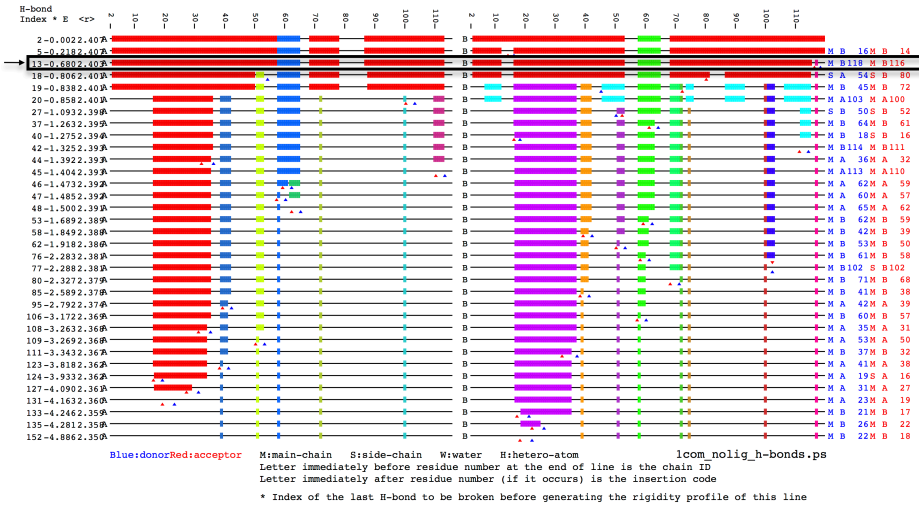
Output:

```
SiteInterlock version 1.0.0
Author: Sebastian Raschka
```

```
Timestamp: 2016-08-12T15:38:17

==============
HETHER results
==============
Suggested energy threshold: -0.806 kcal/mol
Number of rigid clusters: 4
Relative rigidity [0, 1]: 0.83
```

- suggest saving this to a logfile



7 Optional: Visualizing Rigid and Flexible Clusters in PyMOL

proflex -h 1com_nolig.pdb

```
Number of H-bonds remaining: 202

Number of H-phobic tethers remaining: 166

          Filter on Hydrogen Bond Energy:
          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

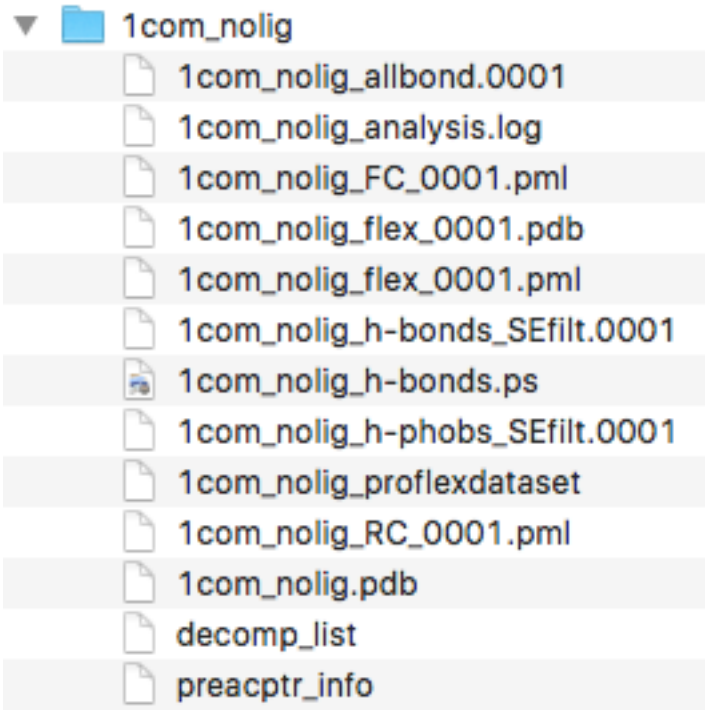
```
    All current hydrogen bonds have energies between:
        -9.8419 Kcal/Mol  to  0.0226 Kcal/Mol

    Enter a maximum acceptable hydrogen bond energy (in Kcal/Mol)
    (-1.0 is a reasonable cutoff in general): -0.806


    ANALYSIS MENU

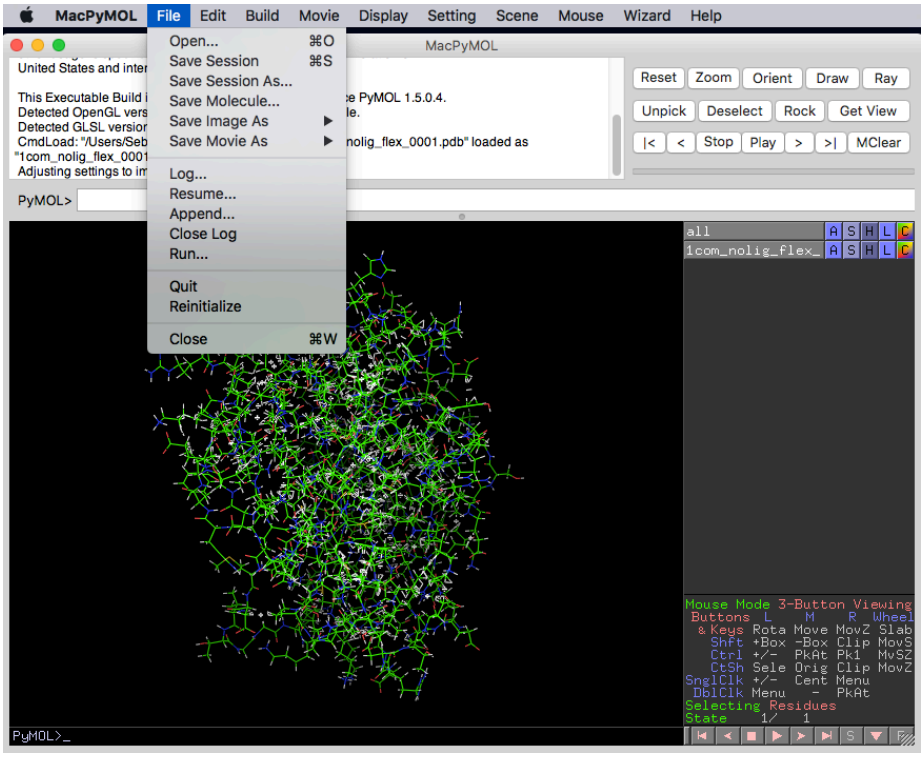
  What would you like to perform:

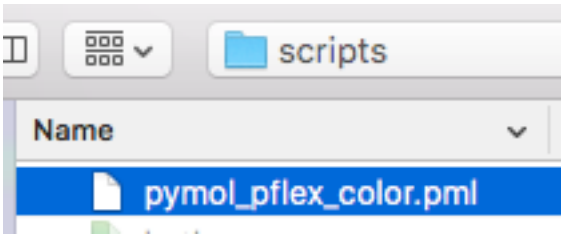
    (1) Flexibility and rigidity analysis
    (2) Hydrogen bond dilution
1
```

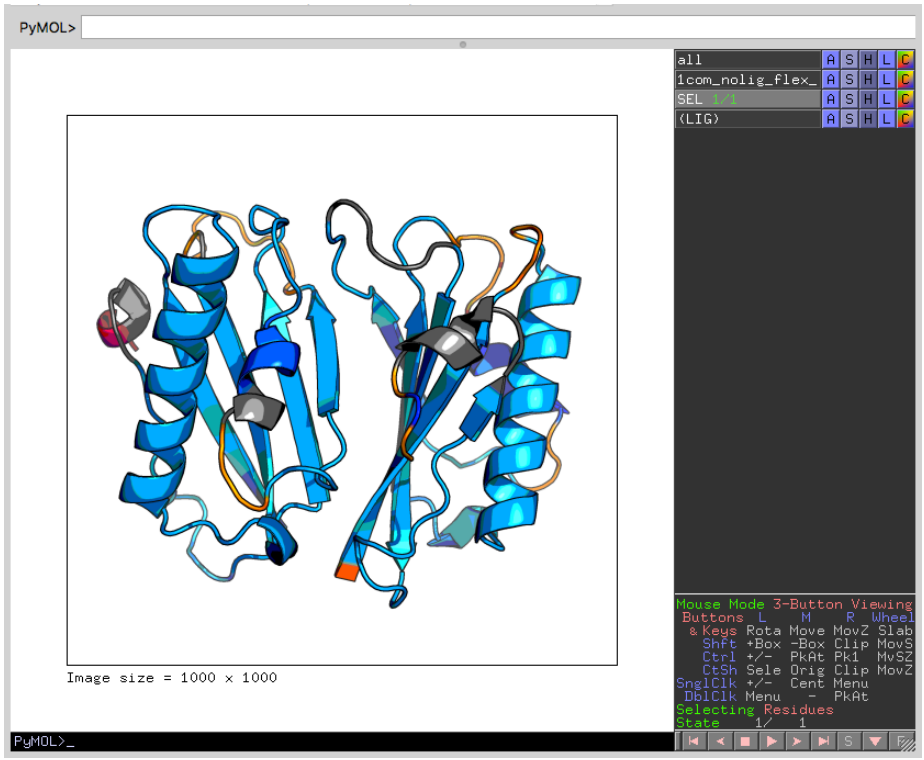


- open file 1com_nolig_flex_0001.pdb in pymol

- run scripts/pymol_pflex_color.pml


MacPyMOL
File
Edit
Build
Movie
Display
Setting
Scene
Mouse
Wizard
Help
Open... ⌘O
Save Session ⌘S
Save Session As...
Save Molecule...
Save Image As
Save Movie As
Log...
Resume...
Append...
Close Log
Run...
Quit
Reinitialize
Close ⌘W
MacPyMOL
Reset
Zoom
Orient
Draw
Ray
Unpick
Deselect
Rock
Get View
Stop
Play
MClear
PyMOL>
all
1com_nolig_flex_
Mouse Mode 3-Button Viewing
Selecting Residues
PyMOL>_


scripts
Name
pymol_pflex_color.pml


PyMOL>
all
1com_nolig_flex_
SEL 1/1
(LIG)
Image size = 1000 x 1000
Mouse Mode 3-Button Viewing
Buttons L M R Wheel
& Keys Rota Move MovZ Slab
Shft +Box -Box Clip MovS
Ctrl +/- PkAt Pk1 MvSZ
CtSh Sele Orig Clip MovZ
SnglClk +/- Cent Menu
DblClk Menu - PkAt
Selecting Residues
State 1/ 1
PyMOL>_

8 ProFlex Analysis on Docking Poses

- proflex -h .pdb
- for instance,
  - `proflex -h 1com_4_0032_pflex_in.pdb`
- example files in examples/slide-propmap
- run python scripts/slide-propmap.py –input1 ~/Desktop/1com_crystal.mol2 –input2 ~/Desktop/confs_1com_0.pts

```
SiteInterlock version 1.0.0
Author: Sebastian Raschka
Timestamp: 2016-08-12T18:22:46

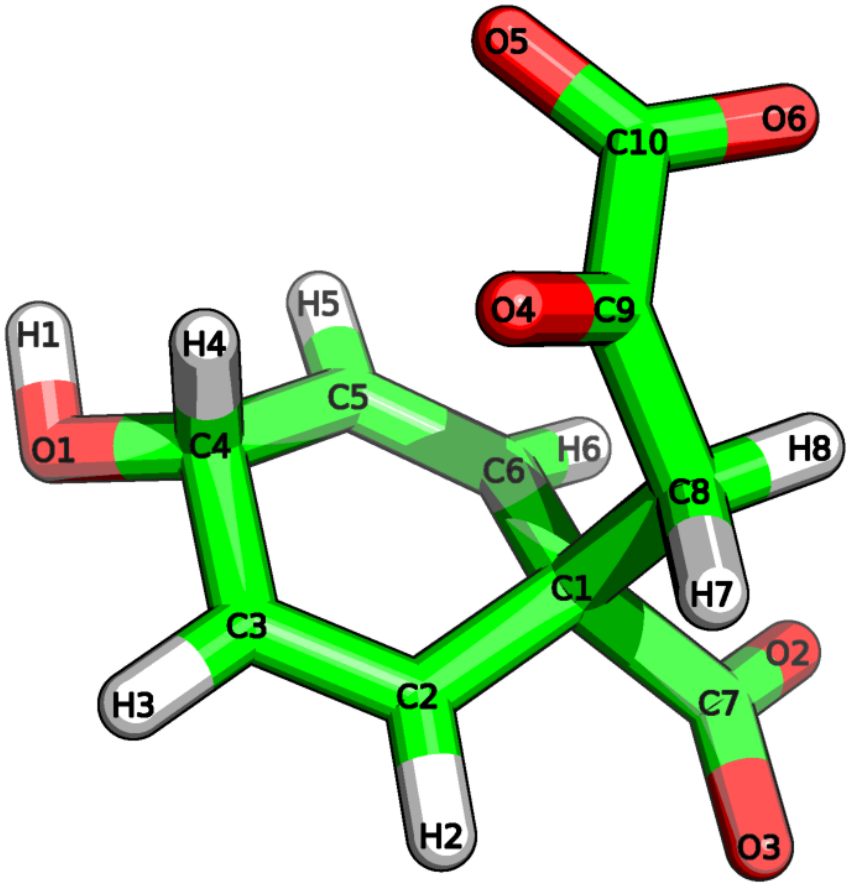
================
PROPMAP results
================
C1 --> hydrophobic contact
C3 --> hydrophobic contact
C5 --> hydrophobic contact
C8 --> hydrophobic contact
O1 --> b [H-bond Donor and/or Acceptor]
O2 --> a [H-bond Acceptor]
O3 --> a [H-bond Acceptor]
O4 --> a [H-bond Acceptor]
O5 --> a [H-bond Acceptor]
O6 --> a [H-bond Acceptor]



------------------------------------------------------------
    Identification of H-bond Donors, Acceptors etc.

    (d) H-bond Donor
    (a) H-bond Acceptor
    (b) Both H-bond Donor and H-bond Acceptor
    (c) Charged Donor
    (e) Charged Acceptor
    (n) None
------------------------------------------------------------
    Enter (a,b,c,d,e or n) for the following atoms.

     Atom#  Atom  Res    Res#    Chain
     3755    O1   <0>       1          Enter (a,b,c,d,e or n): b
```


O5
O6
C10
O4
C9
H5
H1
H4
C5
O1
C4
H6
C6
H8
C8
C1
H7
C3
O2
H3
C2
C7
H2
O3

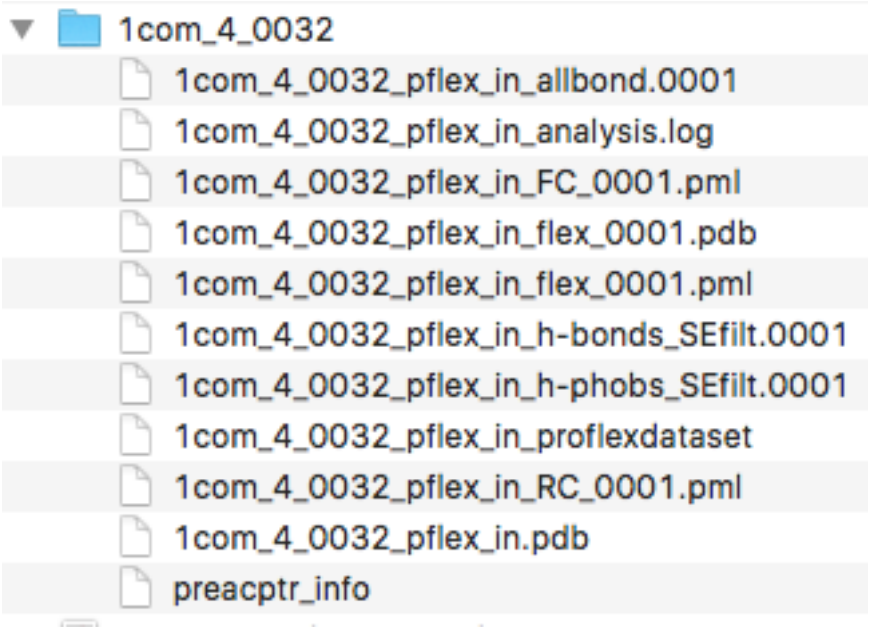
```
    3757    O2   <0>       1          Enter (a,b,c,d,e or n): a
    3759    O3   <0>       1          Enter (a,b,c,d,e or n): a
    3761    O4   <0>       1          Enter (a,b,c,d,e or n): a
    3763    O5   <0>       1          Enter (a,b,c,d,e or n): a
    3765    O6   <0>       1          Enter (a,b,c,d,e or n): a
```

blablabla

```
    ANALYSIS MENU

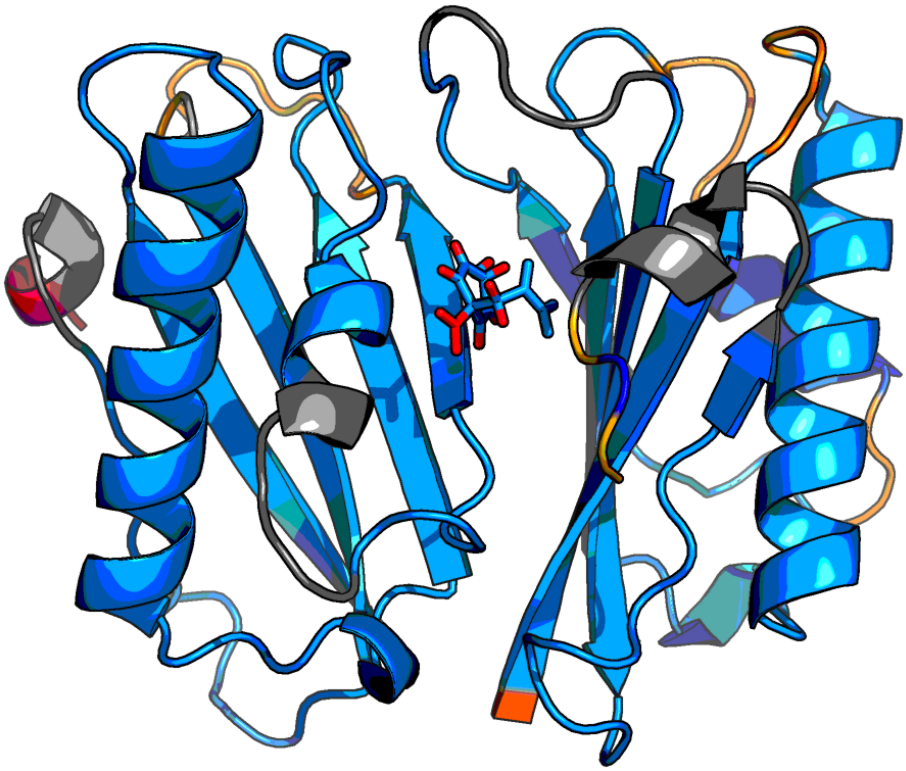
  What would you like to perform:

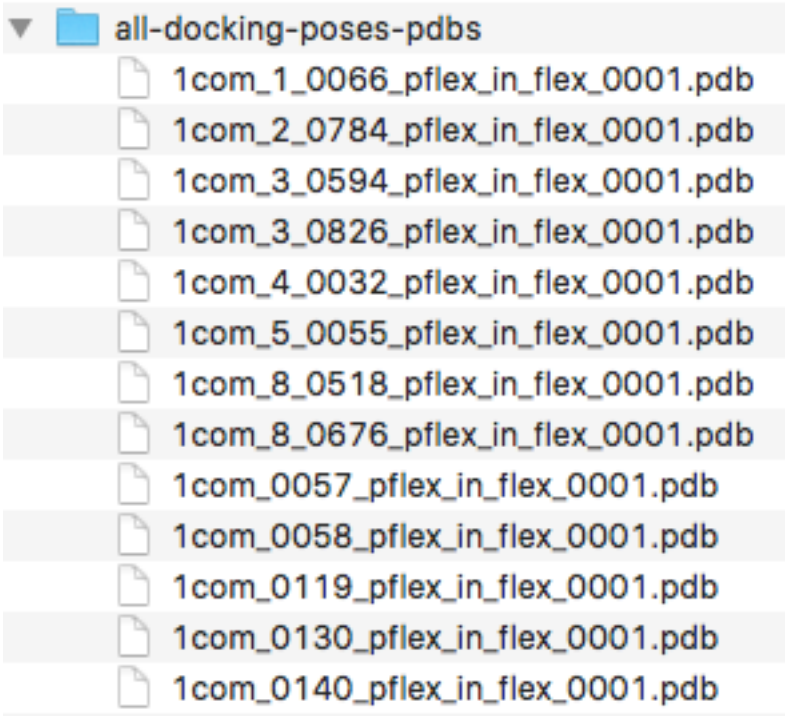
    (1) Flexibility and rigidity analysis
    (2) Hydrogen bond dilution
1
```



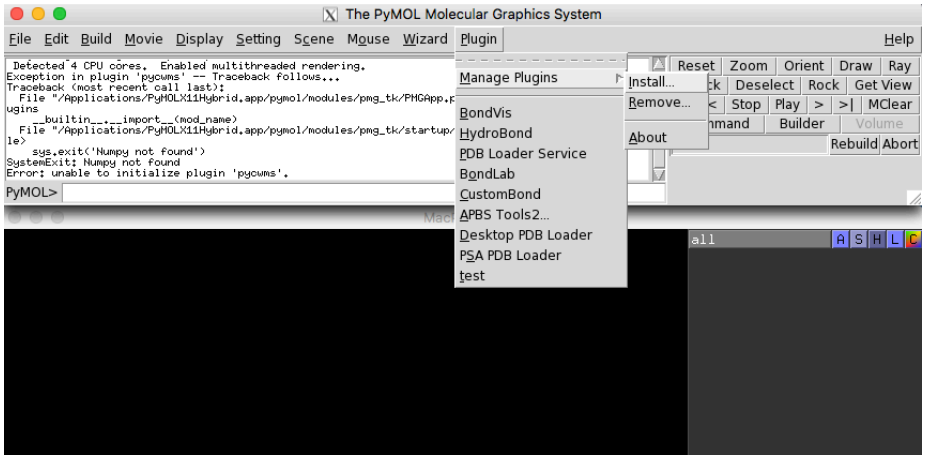
on 1com_0057_pflex_in_flex_0001.pdb:

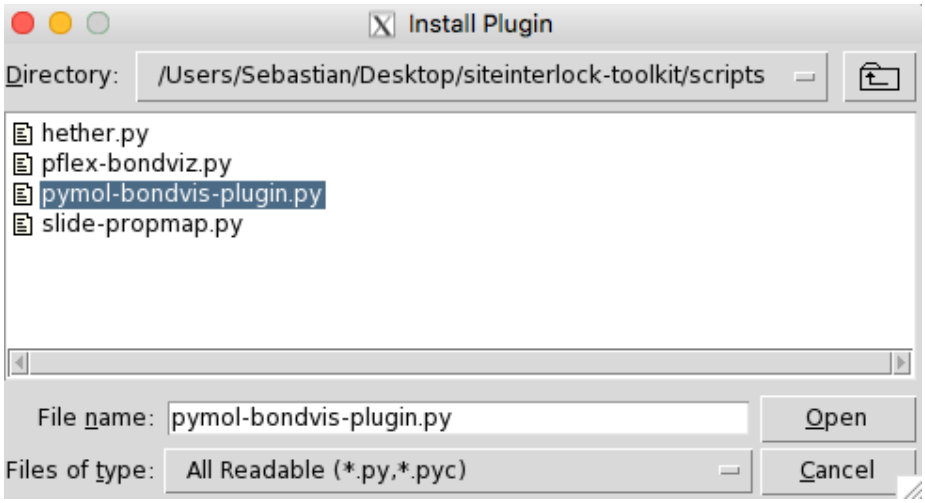
- repeat that for all docking poses
- collect them somewhere




all-docking-poses-pdbs
1com_1_0066_pflex_in_flex_0001.pdb
1com_2_0784_pflex_in_flex_0001.pdb
1com_3_0594_pflex_in_flex_0001.pdb
1com_3_0826_pflex_in_flex_0001.pdb
1com_4_0032_pflex_in_flex_0001.pdb
1com_5_0055_pflex_in_flex_0001.pdb
1com_8_0518_pflex_in_flex_0001.pdb
1com_8_0676_pflex_in_flex_0001.pdb
1com_0057_pflex_in_flex_0001.pdb
1com_0058_pflex_in_flex_0001.pdb
1com_0119_pflex_in_flex_0001.pdb
1com_0130_pflex_in_flex_0001.pdb
1com_0140_pflex_in_flex_0001.pdb

9 Optional: Visualizing H-bond Interactions between Proteins and Ligands





restart

To draw the intermolecular interactions (hydrogen bonds) as assessed by ProFlex, you need to

1. Run `python scripts/grab_bonds_proflexdataset.py -i my_proflexdataset`.

For instance

```
python scripts/grab_bonds_proflexdataset.py -i my_proflexdataset
```

```
~/Desktop/siteinterlock-toolkit$ python scripts/pflex-bondviz.py
-i examples/proflex_output/1com_0057/1com_0057_pflex_in_proflexdataset
-b hbonds


Atom#1 Atom#2
1951 3761
1949 3755
3269 3759
3566 3755
3266 3761
1185 3765
```

Copy and paste the results from the screen to a new text file or run the command again and pipe the output to a file

```
python grab_bonds_proflexdataset.py -i my_proflexdataset >
hbonds.txt
```

3. Open the renamed proflexdataset.pdb file in PyMOL and draw the bond lines (using my BondVis PyMOL plugin, which reads in this grab_bonds_proflexdataset.py result file; examples and instructions for BondVis plugin can be found on the PSA wiki: https://sol.bch.msu.edu/mediawiki/index.php/BondVis_Plugin_for_PyMOL.)

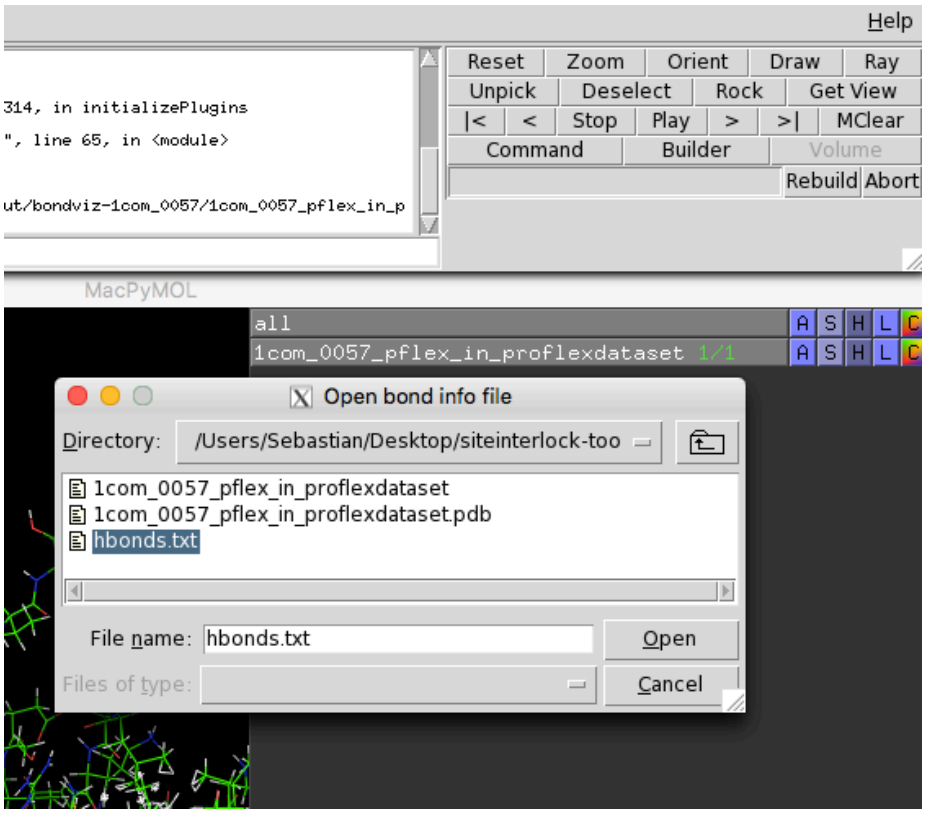
4. Hide all atoms in PyMol (you will have noticed that the secondary structure cannot be displayed properly).

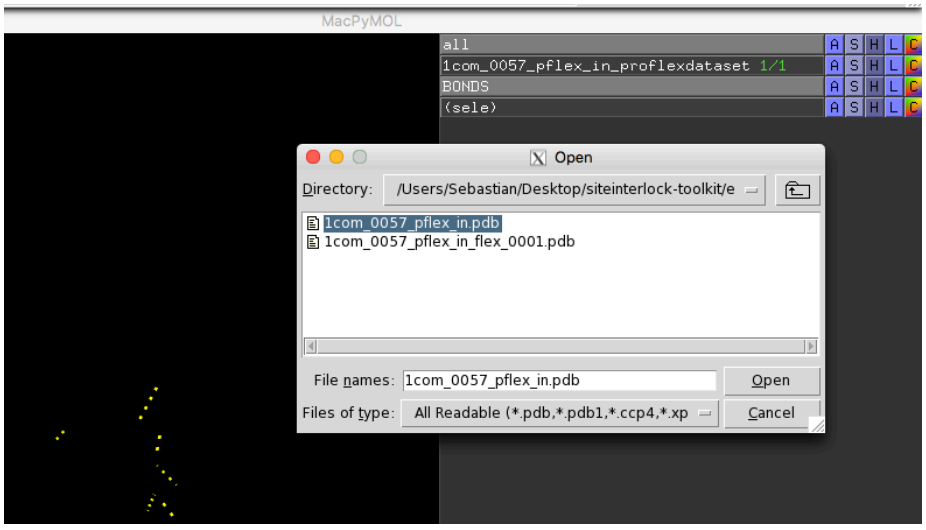
5. Now, open the Prolfex in- or output PDB file and overlay it with the bonds that where just drawn using the renamed proflexdataset.pdb file.

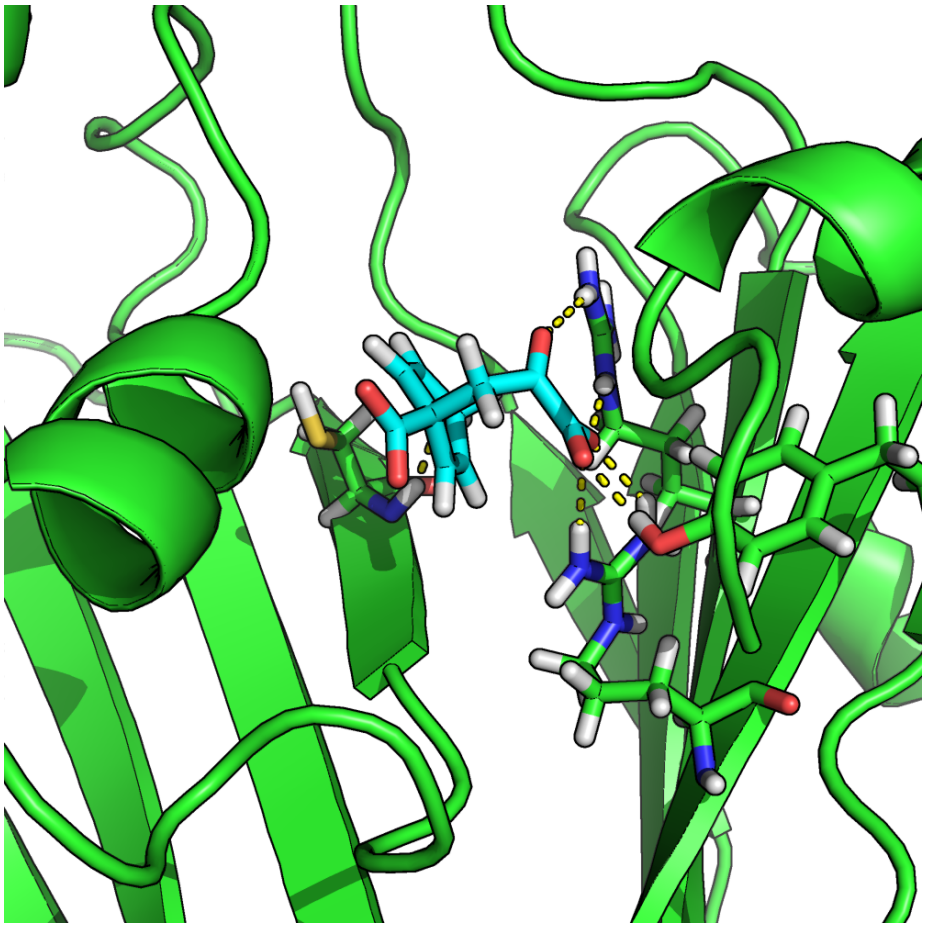
This hack of using the proflexdataset file to draw the bonds and the PDB output file for actually overlaying the bonds with the protein structure was necessary because the atom numbers given in the `REMARK:HB` and `ATOM` section of the proflexdataset file differ from the numbers in the output PDB file.

10 user_guide.SiteInterlock_Scoring

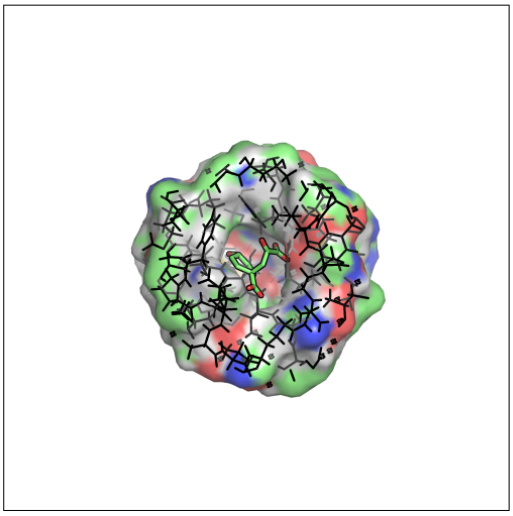
```
python scripts/get-substructures.py \
--input examples/proflex_output/all-docking-poses-pdbs/ \
```

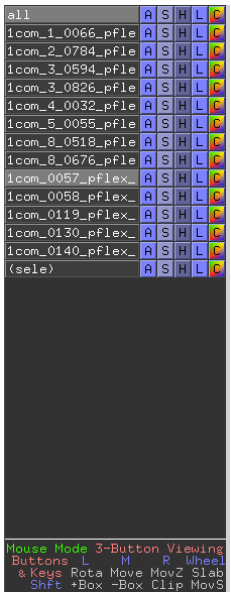

Help
Reset
Zoom
Orient
Draw
Ray
Unpick
Deselect
Rock
Get View
|<
<
Stop
Play
>
>|
MClear
Command
Builder
Volume
Rebuild
Abort
314, in initializePlugins
", line 65, in <module>
ut/bondviz-1com_0057/1com_0057_pflex_in_p
MacPyMOL
all
1com_0057_pflex_in_proflexdataset 1/1
Open bond info file
Directory:
/Users/Sebastian/Desktop/siteinterlock-too
1com_0057_pflex_in_proflexdataset
1com_0057_pflex_in_proflexdataset.pdb
hbonds.txt
File name:
hbonds.txt
Open
Files of type:
Cancel


MacPyMOL
all
1com_0057_pflex_in_proflexdataset 1/1
BONDS
(sele)
Open
Directory:
/Users/Sebastian/Desktop/siteinterlock-toolkit/e
1com_0057_pflex_in.pdb
1com_0057_pflex_in_flex_0001.pdb
File names:
1com_0057_pflex_in.pdb
Open
Files of type:
All Readable (*.pdb,*.pdb1,*.ccp4,*.xp
Cancel



```
--output examples/proflex_output/all-docking-poses-pdbs-9A/ \
--ligand "<0>" \
--apply_to_dir
```






```
~/Desktop/siteinterlock-toolkit$ python scripts/siteinterlock-score.py -i examples/proflex_o

#
# SiteInterlock version 1.0.0
# Author: Sebastian Raschka
# Timestamp: 2016-08-17T14:37:12
#
# ==============================
# SiteInterlock Scoring Results
# ==============================
1com_0057_pflex_in_flex_0001.pdb,-1.393
1com_8_0676_pflex_in_flex_0001.pdb,-0.863
1com_0140_pflex_in_flex_0001.pdb,-0.776
1com_0058_pflex_in_flex_0001.pdb,-0.600
1com_crystal.pdb,-0.581
1com_4_0032_pflex_in_flex_0001.pdb,-0.562
1com_0119_pflex_in_flex_0001.pdb,-0.560
1com_5_0055_pflex_in_flex_0001.pdb,0.105
1com_1_0066_pflex_in_flex_0001.pdb,0.106
1com_3_0826_pflex_in_flex_0001.pdb,0.356
1com_3_0594_pflex_in_flex_0001.pdb,0.485
1com_0130_pflex_in_flex_0001.pdb,1.062
```

```
1com_2_0784_pflex_in_flex_0001.pdb,1.477
1com_8_0518_pflex_in_flex_0001.pdb,1.746
```

11 Optional

```
import pandas as pd

df1 = pd.read_csv('../../../examples/proflex_output/all-docking-poses-pdbs-9A.csv', comment=
df2 = pd.read_csv('../../../examples/1com_rmsds.csv')

df3 = df1.merge(right=df2, on='Filename')
df3.sort_values('RMSD', inplace=True)
df3
```

```
<tr style="text-align: right;">
  <th></th>
  <th>Filename</th>
  <th>SiteInterlock_Score</th>
  <th>RMSD</th>
</tr>
```

```
<tr>
  <th>0</th>
  <td>1com_0057_pflex_in_flex_0001.pdb</td>
  <td>-1.431</td>
  <td>0.3592</td>
</tr>
<tr>
  <th>2</th>
  <td>1com_0140_pflex_in_flex_0001.pdb</td>
  <td>-0.810</td>
  <td>1.0010</td>
</tr>
<tr>
  <th>3</th>
  <td>1com_0058_pflex_in_flex_0001.pdb</td>
  <td>-0.649</td>
  <td>1.2555</td>
</tr>
<tr>
  <th>6</th>
  <td>1com_1_0066_pflex_in_flex_0001.pdb</td>
  <td>0.055</td>
```

```
  <td>1.5126</td>
</tr>
<tr>
  <th>5</th>
  <td>1com_0119_pflex_in_flex_0001.pdb</td>
  <td>-0.601</td>
  <td>1.7488</td>
</tr>
<tr>
  <th>10</th>
  <td>1com_0130_pflex_in_flex_0001.pdb</td>
  <td>1.026</td>
  <td>1.9982</td>
</tr>
<tr>
  <th>4</th>
  <td>1com_4_0032_pflex_in_flex_0001.pdb</td>
  <td>-0.603</td>
  <td>2.2476</td>
</tr>
<tr>
  <th>8</th>
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  <td>2.4965</td>
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  <td>2.7501</td>
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  <td>1com_2_0784_pflex_in_flex_0001.pdb</td>
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  <td>2.9999</td>
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<tr>
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  <td>1com_8_0676_pflex_in_flex_0001.pdb</td>
  <td>-0.896</td>
  <td>3.5653</td>
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  <th>7</th>
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  <td>1com_5_0055_pflex_in_flex_0001.pdb</td>
  <td>0.067</td>
  <td>3.9528</td>
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<tr>
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  <td>1com_8_0518_pflex_in_flex_0001.pdb</td>
  <td>1.696</td>
  <td>4.8813</td>
</tr>
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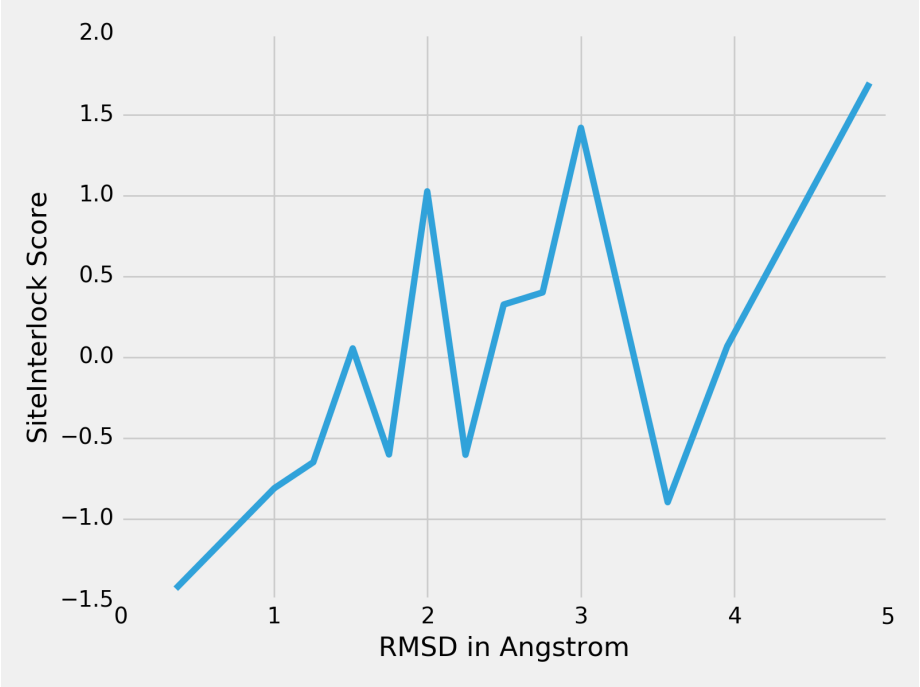
```
import matplotlib.pyplot as plt

with plt.style.context('fivethirtyeight'):
    plt.plot(df3['RMSD'].values, df3['SiteInterlock_Score'].values)
    plt.xlabel('RMSD in Angstrom')
    plt.ylabel('SiteInterlock Score')
    plt.tight_layout()
    plt.savefig('images/1com_scores.png', dpi=200)
```



12 Release Notes

12.0.1 Version 0.2.0dev

12.0.1.0.1 Downloads

~

12.0.1.0.2 New Features

- x

12.0.1.0.3 Changes

- x
- x

12.0.2 Version 0.1.0 (2016-09-01)

12.0.2.0.1 Downloads

- Source code (zip)
- Source code (tar.gz)
- PDF documentation

12.0.2.0.2 New Features

- x

12.0.2.0.3 Changes

- x

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