NCIPLOT MANUAL

A PROGRAM FOR PLOTTING NON-COVALENT INTERACTION REGIONS

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1 Theoretical background

NCI (Non-Covalent Interactions) is a visualization index based on the density and its derivatives. It enables identification of non-covalent interactions. It is based on the peaks that appear in the reduced density gradient (RDG) at low densities. As highlighted in Figures 1a-b, there is a crucial change in the RDG at the critical points in between molecules due to the annihilation of the density gradient at these points.

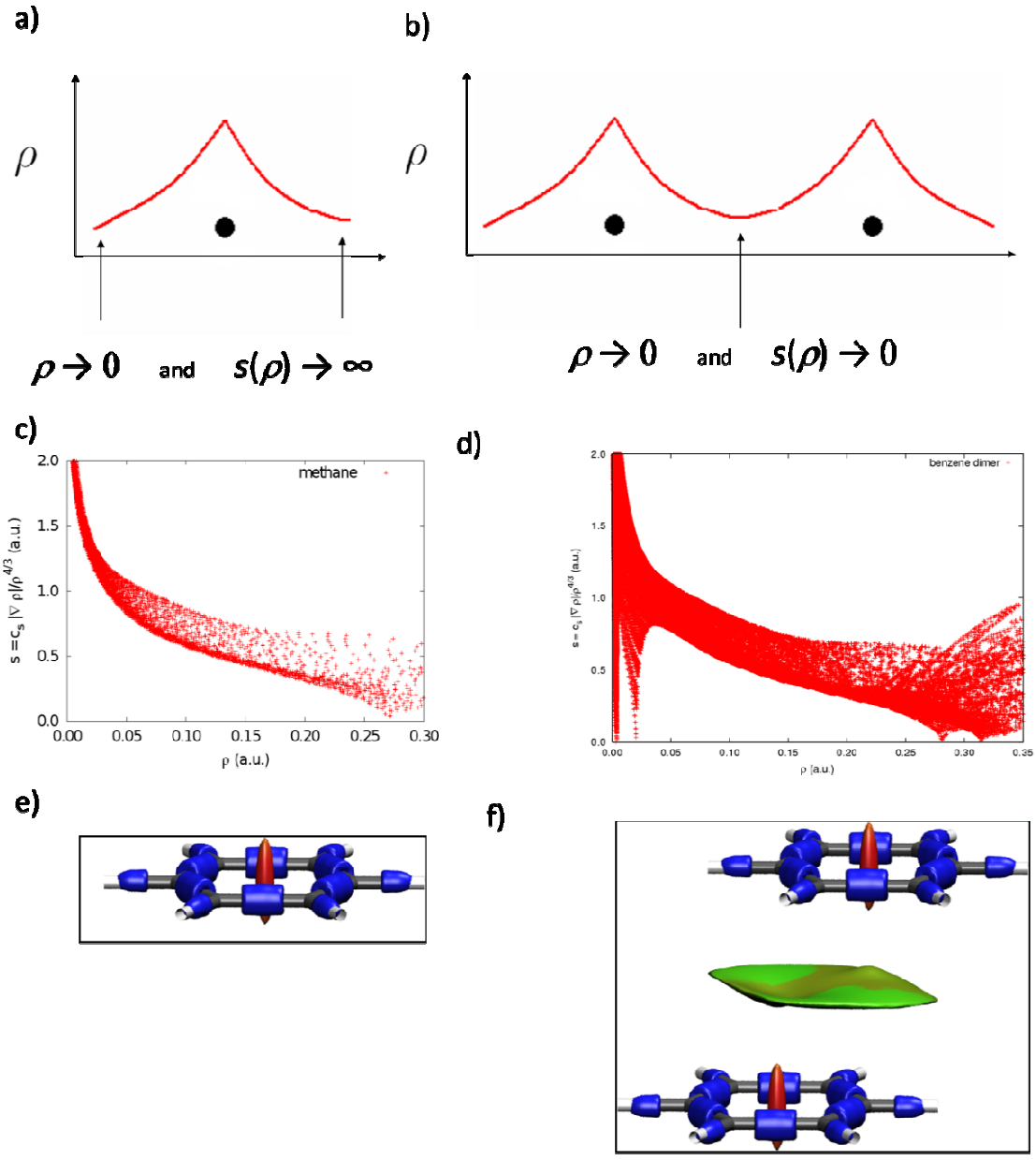


Figure 1. ρ(r), s(ρ) and NCI pieces in benzene monomer and benzene dimer

When we plot the RDG as a function of the density across a molecule, we see that the main difference between the monomer and dimer cases is the appearance of steep peaks at low density (Figure 1 c-d). When we search for the points in 3D space giving rise to these peaks, non covalent regions clearly appear in the (supra)molecular complex. These interactions correspond to both favorable and unfavorable interactions. In order to differentiate between them, the sign of the second density Hessian eigenvalue times the density is implemented. This value is able to characterize the strength of the interaction by means of the density, and its curvature thanks to the sign of the second eigenvalue (see Ref. [1] for a thorough explanation of the physics

behind it). Some examples are collected in Figure 2. It can be seen that the method is applicable to small molecules as well as inorganic complexes.

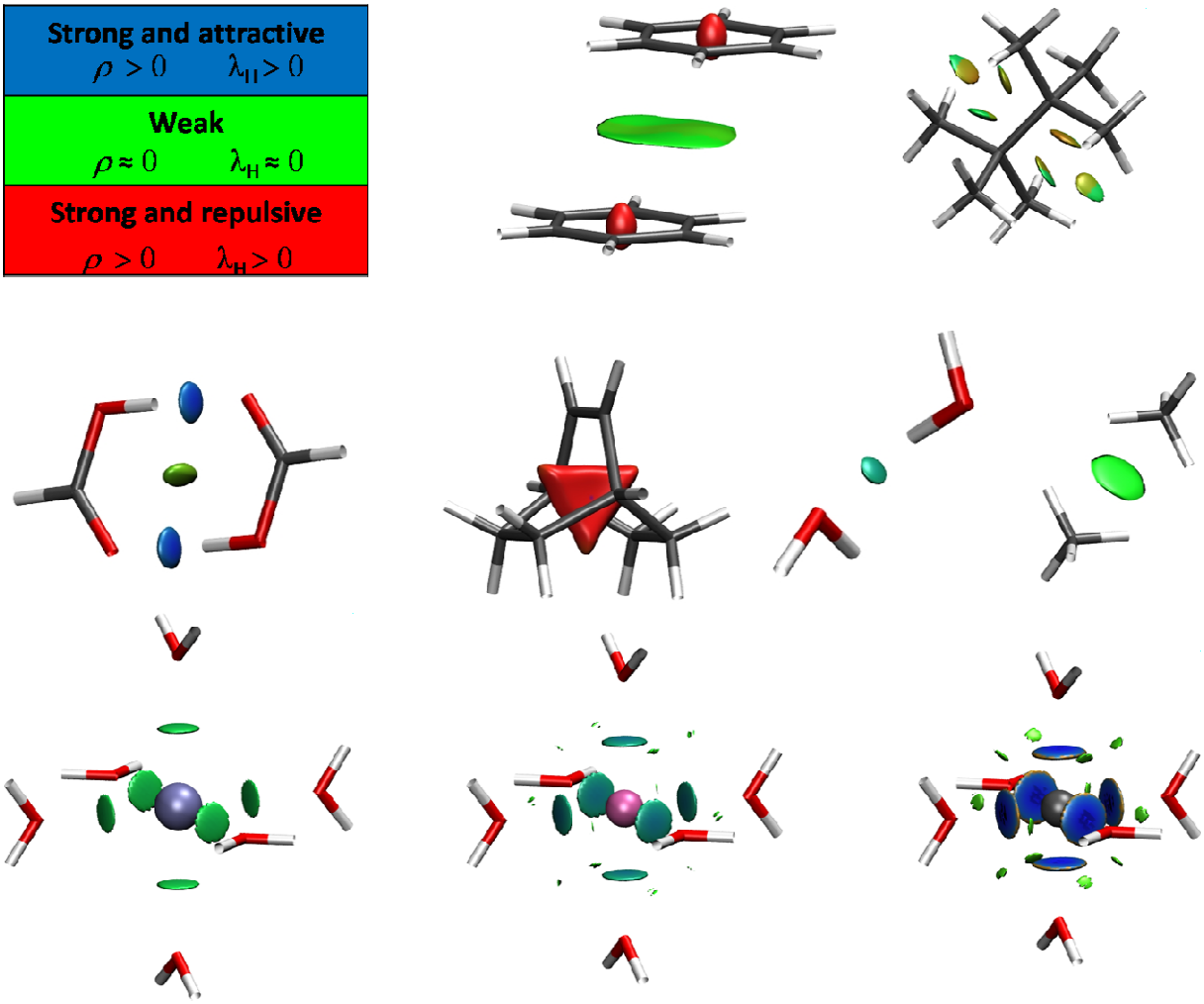


Figure 2. Some examples of applications of NCI to SCF calculations: benzene dimer, branched octane, formic acid dimer, bicyclo[2,2,2]octene, water dimer, methane dimer, $K(H_2O)_6^+$, $Ca(H_2O)_6^+$, $Zn(H_2O)_6^+$.

Furthermore, the method is also applicable to promolecular densities, enabling the analysis of biomolecules (Figure 3). In this case, only the atomic coordinates are required as input. Both options (SCF and promolecular are implemented in the code).

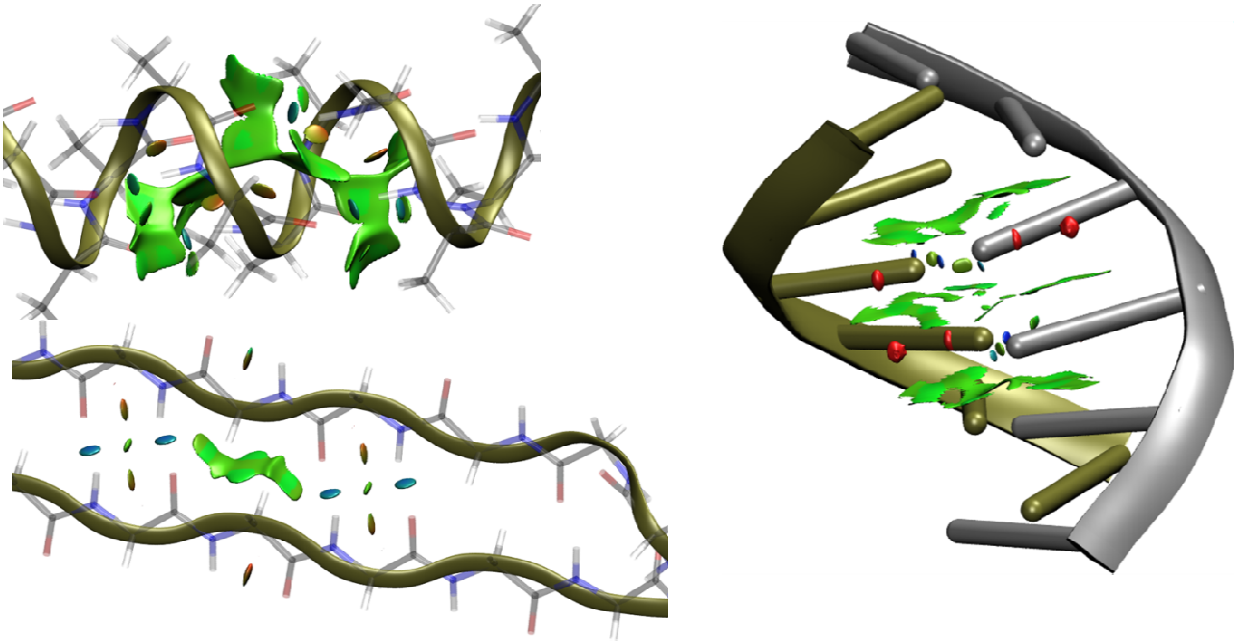


Figure 3. Promolecular applications: α-helix, β-sheet, DNA

2 Installing the program

The code has been assembled for an easy, user-friendly compilation. All subroutines are collected in the same code, so that no Makefile is required. For the moment, compilation with ifort is required under the following command:

```
ifort nciplot.f -o  nciplot.x
```

This will create the executable `nciplot.x`

3 Running the program

The code is invoked as follows:

```
nciplot.x input.file [output.file]
```

Alternatively, the repository is provided with an statically linked compilation which should work in most linux machines (`nciplot.x`)

4 The input

The input is keyword oriented, free-format, and the output is meant to be self-contained.

The following coding is used for variables:

- `r` stands for real.
- `x,y,z` stand for positions in space (real)
- `n` stands for integer

- `name` stands for any character string

Commentaries must be preceded by #

Obligatory input

THE FIRST LINE MUST CONTAIN THE NUMBER OF FILES TO BE ANALYZED. Currently, from 1 to 3 files are supported for xyz files, so that, if interactions between different molecules are to be analyzed, the molecules can be uploaded in different files.

Note that this version does not accept multiple wfn entries.

THE SECOND LINE MUST CONTAIN THE NAME OF THE MOLECULAR FILE. It accepts two different types of file format, depending on the level of approximation. They must have the following extensions depending on the desired calculation:

- `name`**`.xyz`** (Promolecular approximation) It requires an xyz file. Recommended for big systems [default]
- `name`**`.wfn`** wavefunction file in the AIMPAC WFN format (SCF calculation)

If several files are being read, they all must be in the same xyz format. Only one wfn file can be analyzed at one time. If more than one wfn file is given in the input, NCI calculations will be performed for the first wfn file only. Future versions of the code with implement options for treating multiple wfn files.

Optional keywords (by order):

- `LIGAND n r`

  n is the number of the file (in the order of introduction in the input)

  r is a distance in A

  This option will only plot interactions within a radius r of file #n. This option is especially designed for protein-ligand interactions and is only available for promolecular densities.

- `INTERMOLECULAR r`

  r should go from 0 to 1. For good results, r should be 0.8-0.9. This option will turn off all the interactions where at least a fraction r of the density comes from a single molecule. This enables only intermolecular interactions to be plotted, neglecting the intramolecular ones. The default is set so that an interaction is discarded if 0.95 of the density at the point comes from a single molecule. Note that this option is only available for promolecular densities.

- `RADIUS x y z r`

  x y z determine the position around which interactions are represented for a radius r (all in A)

- `ONAME name`

  `name` stands for the basic naming to be passed to the output file names (otherwise the default is taken from input file name). The `name` introduced will be always output in capital letters.

- `OUTPUT n`

  n is an integer running from 1 to 3.

  - 1 will only print the .dat file
  - 2 will only print the .cube files
  - 3 will print all three output files [default]

- `CUBE x0 y0 z0 x1 y1 z1`

  This option will set the cube within which NCI is analyzed as going from the Cartesian coordinate (x0,y0,z0) to (x1,y1,z1).

  The default is produced in terms of molecular coordinates. In order to ensure a correct cube in planar or linear cases, a minimum distance of +/- 2a.u. is added to the axes in all directions.

- `INCREMENTS r1 r2 r3`

  This option sets the increments along the x,y,z directions of the cube (atomic units). The default is set to 0.1,0.1,0.1

- `CUTOFFS r1 r2`

  Density (r1) and RDG (r2) cutoffs used in creating the dat file. The default density cutoff is set to 0.2. The RDG cutoff depends on the level of calculation:

  - In the promolecular case it is set to 1.0.
  - In the scf case it is set to 2.0.

- `CUTPLOT r1 r2`

  Density (r1) and RDG (r2) cutoffs used when creating the cube files. r1 will set the cutoff for both the density and the RDG to be registered in the cube files, whereas r2 will be used in the VMD script for the plotting of isosurfaces. The default values are:

  - In the promolecular case: r1=0.07, r2=0.3.
  - In the SCF case: r1=0.05, r2=0.5.

5 The output

The output (may) consist of 4 files:

- name.dat file collects rho vs RDG (OUTPUT= 1 or 3)

- name-grad.cube file with RDG (OUTPUT= 2 or 3)
- name-dens.cube file with sign(λ_2)xdensityx100 (OUTPUT= 2 or 3)
- name.vmd is a script for visualization of the results in VMD

The following information from the run will also be printed out, either to the screen or in the redirected output file:

```
# ----------------- NCIPLOT -----------------------
# --- PLOTTING NON COVALENT INTERACTION REGIONS ----
# ---              E.R. Johnson                  ----
# ---           J. Contreras-Garcia              ----
# ----------    Duke University         ------------
# -------------------------------------------------
# ---               Please cite                   ----
# --J. Am. Chem. Soc., 2010, 132 (18), pp 6498-6506-
# -------------------------------------------------


# -------------------------------------------------
# ---     Contributions for the wfn properties  ----
# ---      from H. L. Schmider are acknowledged  ---
# -------------------------------------------------
#
# Calculation starts at Wed May 26 16:56:26 EDT 2010 Calculation begins
#



-------------------------------------------------------
      TYPE OF CALCULATION:PROMOLECULAR               TYPE OF CALCULATION:
-------------------------------------------------------Promolecular or SCF

-------------------------------------------------------
      INPUT INFORMATION:
-------------------------------------------------------FILE INFORMATION,
      Reading XYZ input 1 from: benzene1.xyz          INTRAMOLECULAR and
      Reading XYZ input 2 from: benzene2.xyz          LIGAND options are
                                                      also shown here
-------------------------------------------------------
      Calculation details:
-------------------------------------------------------PLOTTING INFORMATION:
RHO  THRESHOLD   (au): 0.20                           applicable cutoffs
RDG  THRESHOLD   (au): 1.00                           in rho and RDG


-------------------------------------------------------
      Operating grid and increments:
-------------------------------------------------------CUBE INFORMATION:
 x0,y0,z0  = -3.7795 -9.3360 -8.4499                  cube begins here
 x1,y1,z1  =  7.1810  6.3124  8.4499                  cube ends here
 ix,iy,iz  =  0.10    0.10    0.10                    increments
 nx,ny,nz  =  109     156     168                     #points along x,y,z

-------------------------------------------------------
      Writting output in the following units:
-------------------------------------------------------OUTPUT INFORMATION:
 Reduced Density Gradient,RDG  = benzene1-grad.cube   name of files created
 Sign(lambda2)xDensity,LS      = benzene1-dens.cube
```

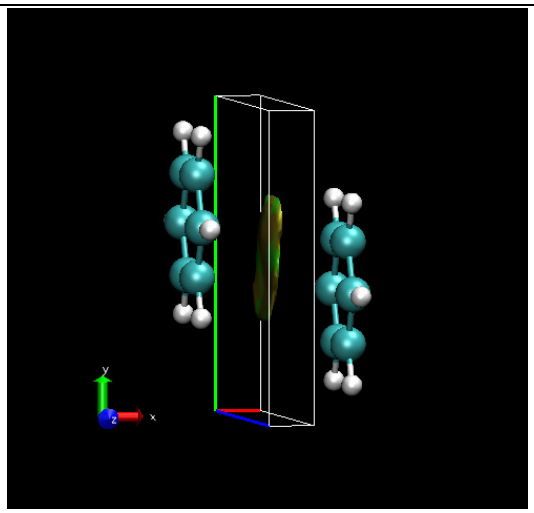
```
 LS x RDG                        = benzene1.dat
 VMD script                      = benzene1.vmd
-------------------------------------------------------


 #-----------------------------------------------     RUN INFORMATION:
 #*** timer:                                          calls and timing
 #***
 #*** -pid----name-----tottime-------pcalls--popen-
 #***  1     _main         76.720           1       F
 #***  2     _read          0.000           2       F
 #***  3     _prop          7.650     5713344       F
 #***  4     _eig           0.000     2856672       F
 #***  5     _dat          19.810     2856672       F
 #***  6     _cube         26.140     2856672       F
 #***

 #
 # Calculation ends at Wed May 26 16:57:44 EDT 2010  CALCULATION ENDS
 #
 #         Normal termination
 #
```

6 Examples

In all cases 3D pictures have been obtained by directly applying the VMD script from the calculation. The lines defining the cube edges have also been highlighted when appropriate. Geometries used are collected in the Appendix.

6.1 Plotting options

```
1
benzene.xyz
OUTPUT 2
CUBE -0.7 -9. -9. 0.7 9. 9.
INCREMENTS 0.2 0.2 0.2
CUTOFFS 0.05 0.27
```



6.2 Number of files

In this case, different options are possible. If we want to obtain all the interactions in the complex, we can either introduce the molecules in a unique file (Option A) or separately (Option B):

Option A

```
1
BenzeneDimer.xyz
```

Option B

```
2
benzene1.xyz
benzene2.xyz
```

In both cases we will obtain the same results:

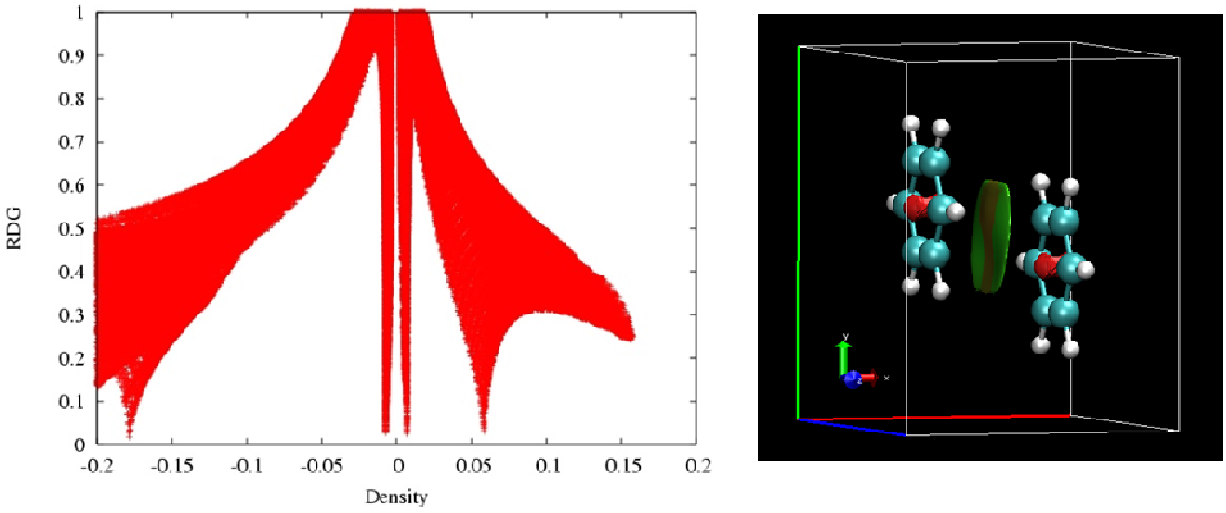


Figure 4.

6.3 SCF or promolecular?

The type of run (SCF or promolecular) is chosen from the extension of the input files: xyz for promolecular and wfn for scf. In both cases the visualization results are very similar. The main changes occur in the cutoffs values. Figure 5 shows the results for different intramolecular and intermolecular interactions. It can be seen that RDG moves to higher values, and peaks shift toward more negative values, if the scf density is used.

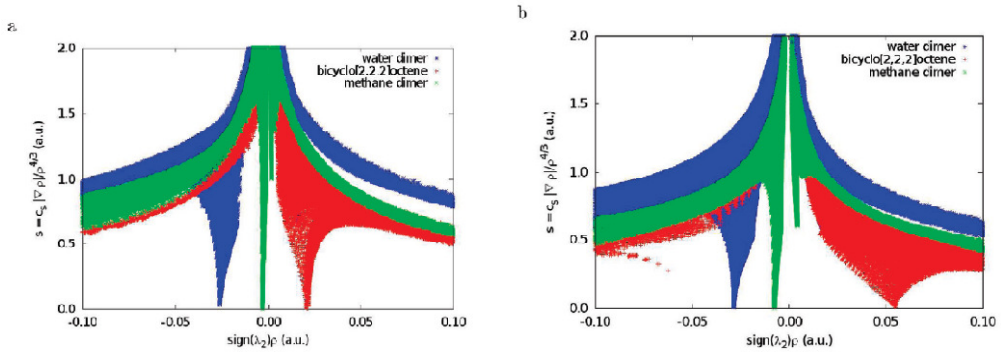


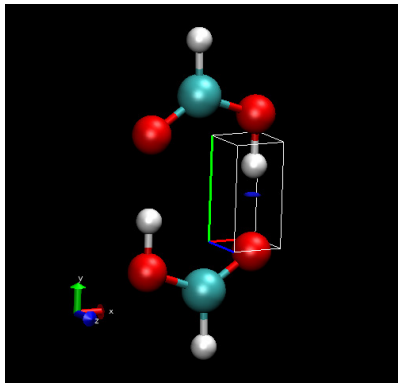
Figure 5.

6.4 Choosing the interactions

i. Appropriate choice of the cube boundaries enables the user to choose individual interactions (Input Option C).
ii. It is also possible to select the interactions in terms of their strength by an appropriate choice of cutoff parameters (Input Option D)
iii. To analyze only intermolecular interactions, the `INTERMOLECULAR` keyword should be used (Input Option E).
iv. To analyze only interactions close to a given molecule, the `LIGAND` or `RADIUS` keywords can be used (Input Options A and F).

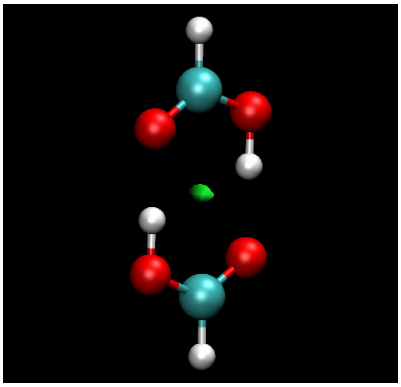
Option C

```
1
formicaciddimmer.xyz
CUBE 1. -2. -1. 3. 2. 1.
```



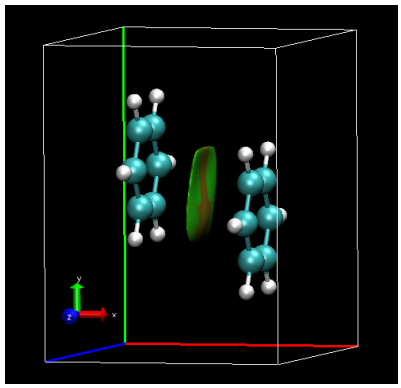
Option D

```
1
formicaciddimmer.xyz
CUTOFFS 0.01 1.
```



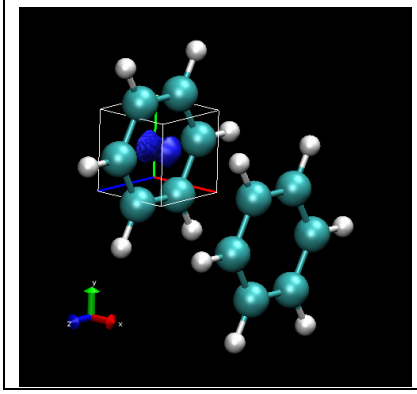
Option E

```
2
benzene1.xyz
benzene2.xyz
INTERMOLECULAR
```



Option F

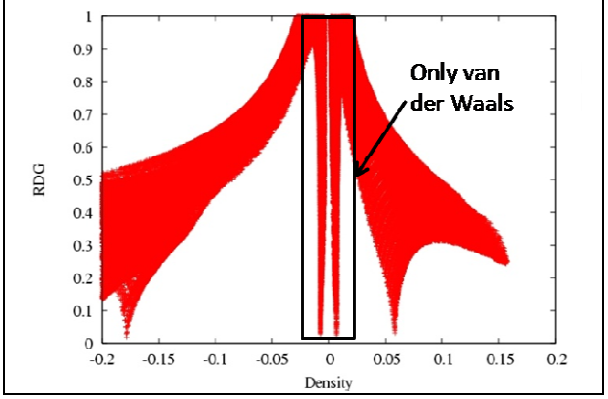
```
2
benzene1.xyz
benzene2.xyz
RADIUS -1.8 0.8 0.0 1.0
```



In order to choose appropriate cutoffs, it is possible to first make a run with OUTPUT=1, so that only the .dat file is printed out. Plotting the results, with a program such as gnuplot, will help in choosing the cutoff values. A second run can then be made with OUTPUT=2 and using the PLOTCUT keyword, in order to obtain the cube files:

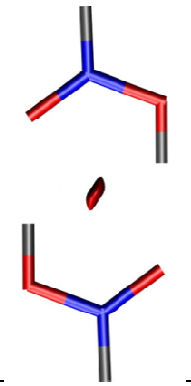
Run #1

```
1
formicaciddimmer.xyz
OUTPUT 1
```



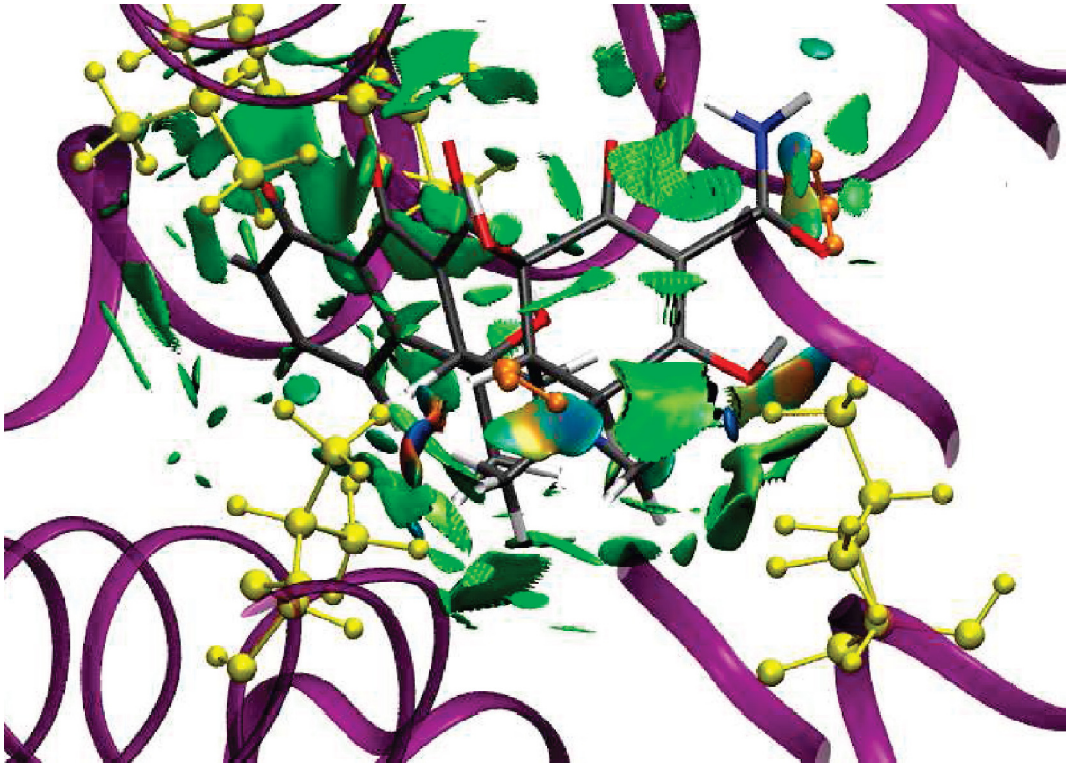
Run #2

```
1
formicaciddimmer.xyz
CUTOFFS 0.01 1.
```



6.5 Protein-ligand interactions

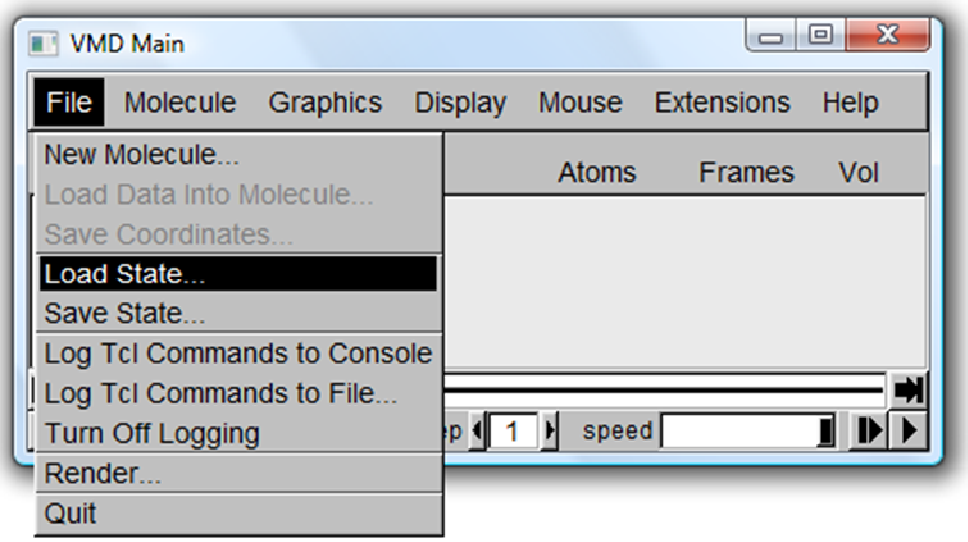
Option D is especially designed for studying inclusion complexes and protein-ligand interactions, where a small molecule fits into a cavity, and we want to understand the interactions with the active site. Here we have an example:



```
2
protein.xyz
ligand.xyz
LIGAND 2 4.0  ligand is file #2=ligand.xyz and we take
                intermolecular interactions around it at <4A
```

7 Using the VMD script

The program generates a script for visualization of the results under the `name.vmd`. This script can be loaded in VMD. After entering the working directory, the script will automatically generate an NCI picture with a RDG cutoff as specified by the keyword `PLOTCUT` (otherwise, a default is used).



The script is as follows:

```
#!/usr/local/bin/vmd
# VMD script written by save_state $Revision: 1.41 $
# VMD version: 1.8.6
set viewplist
set fixedlist
# Display settings
display projection   Orthographic
display nearclip set 0.000000
# load new molecule
mol new name-dens.cube type cube first 0 last -1 step 1 filebonds 1
autobonds 1 waitfor all
mol addfile name-grad.cube type cube first 0 last -1 step 1 filebonds 1
autobonds 1 waitfor all
#
# representation of the atoms
```

```
mol delrep 0 top
mol representation CPK 1.000000 0.300000  118.000000 131.000000
mol color Name
mol selection {all}
mol material Opaque
mol addrep top
#
# add representation of the surface
mol representation Isosurface 0.30000 1 0 0 1 1
mol color Volume 0
mol selection {all}
mol material Opaque
mol addrep top
mol selupdate 1 top 0
mol colupdate 1 top 0
mol scaleminmax top 1 -4.000000 4.000000
mol smoothrep top 1 0
mol drawframes top 1 {now}
color scale method BGR
set colorcmds {{color Name {C} gray}}
#some more
```

In case the user wants to change it, the main options have been highlighted in red:

- `name-dens.cube`: name of the density cube file
- `name-dens.cube`: name of the gradient cube file
- `0.30000`: value of RDG isosurface
- `-4.000000 4.000000` where this is 100 times the value of rhoplot

8 Advanced users

Here is a list of variables and parameters that can be internally tuned if desired:

PARAMETER	DEFAULT	MEANING
NNUCM2	10000	Maximum # of atoms (PROMOL)
NNUCM	500	Maximum # of atoms (SCF)
NPRIM	10000	Maximum # of primitives (SCF)
NMOM	1000	Maximum # of orbitals (SCF)
MFILE	3	Maximum # of input files

9 What went wrong?

9.1 Error messages

- `REQUESTED FILE DOES NOT EXIST`

One of the input files does not exist in the directory

- `TOO MANY ATOMS IN THE LIST, TRY DELETING NON INTERACTING ATOMS`

The number of atoms is greater than allowed (Check NNUCM or NNUCM2)

- `POWER L=X NOT SUPPORTED or TYPE X NOT ALLOWED`

Orbital types supported are: s,sp and p

- `PROBLEM READING ATOM TYPES`

The format of the input file is not correct and the program is not reading all of the atoms

9.2 Other sources of problems

- Of course, units: the program deals with units automatically, but beware of input transformation. xyz files are in A and wfn files are in au!!!
- Atomic densities for PROMOLECULAR calculations are only implemented for the atoms in the first three row of the periodic table, H-Ar.
- Where is my data? Check the cutoffs, you might be discarding all your points.
- The VMD script is not working:
    - The working directory should be the same that contains the script and the files
    - The name of the files should be less than 40 characters long

10 Cite us

Erin R. Johnson, Shahar Keinan, Paula Mori-Sánchez, Julia Contreras-García, Aron J. Cohen, and Weitao Yang, *J. Am. Chem. Soc*., **2010**, *132* , pp 6498–6506

11 Appendix: Geometry data

```
benzene1:

     C           -1.800000    0.800000    1.391500
     C           -1.800000   -0.405074    0.695750
     C           -1.800000   -0.405074   -0.695750
     C           -1.800000    0.800000   -1.391500
     C           -1.800000    2.005074   -0.695750
     C           -1.800000    2.005074    0.695750
     H           -1.800000    0.800000    2.471500
     H           -1.800000   -1.340382    1.235750
     H           -1.800000   -1.340382   -1.235750
     H           -1.800000    0.800000   -2.471500
     H           -1.800000    2.940382   -1.235750
     H           -1.800000    2.940382    1.235750
benzene 2:

     C            1.800000   -0.800000    1.391500
     C            1.800000    0.405074    0.695750
     C            1.800000    0.405074   -0.695750
     C            1.800000   -0.800000   -1.391500
     C            1.800000   -2.005074   -0.695750
     C            1.800000   -2.005074    0.695750
     H            1.800000   -0.800000    2.471500
     H            1.800000    1.340382    1.235750
     H            1.800000    1.340382   -1.235750
     H            1.800000   -0.800000   -2.471500
     H            1.800000   -2.940382   -1.235750
     H            1.800000   -2.940382    1.235750

Benzene Dimer:
```

C	-1.800000	0.800000	1.391500
C	-1.800000	-0.405074	0.695750
C	-1.800000	-0.405074	-0.695750
C	-1.800000	0.800000	-1.391500
C	-1.800000	2.005074	-0.695750
C	-1.800000	2.005074	0.695750
H	-1.800000	0.800000	2.471500
H	-1.800000	-1.340382	1.235750
H	-1.800000	-1.340382	-1.235750
H	-1.800000	0.800000	-2.471500
H	-1.800000	2.940382	-1.235750
H	-1.800000	2.940382	1.235750
C	1.800000	-0.800000	1.391500
C	1.800000	0.405074	0.695750
C	1.800000	0.405074	-0.695750
C	1.800000	-0.800000	-1.391500
C	1.800000	-2.005074	-0.695750
C	1.800000	-2.005074	0.695750
H	1.800000	-0.800000	2.471500
H	1.800000	1.340382	1.235750
H	1.800000	1.340382	-1.235750
H	1.800000	-0.800000	-2.471500
H	1.800000	-2.940382	-1.235750
H	1.800000	-2.940382	1.235750

Formic acid dimer:

C	-.120234	1.914070	.000000
H	-.167295	3.007018	.000000
O	-1.121857	1.220982	.000000
O	1.121857	1.480489	.000000
H	1.127582	.489024	.000000
O	1.121857	-1.220982	.000000
C	.120234	-1.914070	.000000
O	-1.121857	-1.480489	.000000
H	-1.127582	-.489024	.000000
H	.167295	-3.007018	.000000