Generating NCI plots with ORCA, orca_2mkl, Multiwfn and Pymol

NCI (Non-covalent interaction) plots provide a useful tool to understand the types and distribution of non-covalent interactions present in chemical systems, based purely on the topology of the electron density.

It works on the principle that:

1. Near each nucleus, the electron density is very large and the gradient is small,
2. At the cusps the density is small but the gradient is large,
3. Covalent bonds have an intermediate to high density, and the gradient is small,
4. NCIs have a low density, but the gradient is small

This means that NCIs can be distinguished simply from a plot of the electron density ($\boldsymbol{\rho}$) against the gradient of the density (in the form of the reduced density gradient, $s = c_s(|\nabla\boldsymbol{\rho}|/\boldsymbol{\rho}^{4/3})$, a dimensionless quantity that indicates deviations from a homogenous density, see Figure 1).

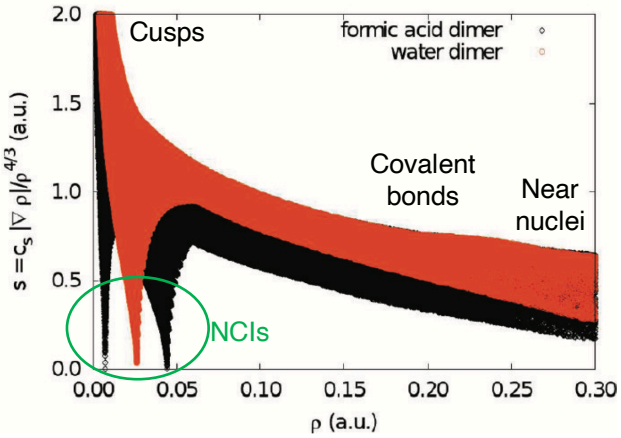

Figure 1. Plot of electron density ($\boldsymbol{\rho}$) against reduced density gradient (s), modified from ref. 3.

To further classify the types of NCIs present, the Laplacian of the electron density can be used to distinguish areas of accumulated or depleted density. To do this, $\nabla^2\boldsymbol{\rho}$ is decomposed into the sum of its three eigenvalues ($\nabla^2\boldsymbol{\rho} = \lambda_1 + \lambda_2 + \lambda_3$, where $\lambda_1 \leq \lambda_2 \leq \lambda_3$), from which the sign and magnitude of λ_2 is taken to represent the type of interaction (see Figure 2): $\lambda_2 > 0$ (red) indicates depletion of $\boldsymbol{\rho}$ (steric repulsion), $\lambda_2 \sim 0$ (green) indicates minimal changes in $\boldsymbol{\rho}$ (van der Waal's, π-stacking), and $\lambda_2 < 0$ (blue) indicates accumulation of density (ionic attraction, hydrogen and halogen bonding).

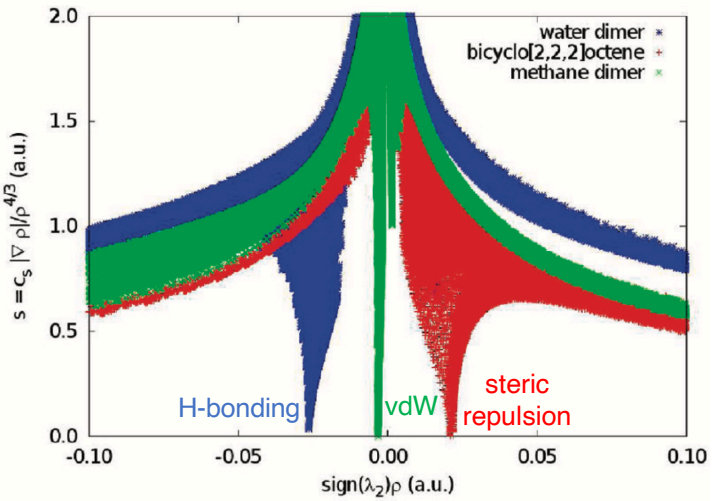

Figure 2. Plot of λ_2 against s, modified from ref. 3.

A 3D plot can be used to visualise the spatial distribution of each of these regions, and the following steps can be used to do this:

(NB text in `this font` should be run in the terminal, <filename> should be replaced by the name of your file, and comment lines start with #.)

1. Run electronic structure calculation calculation, making sure to keep the file containing the electron density information (e.g. .gbw file in ORCA)

2. Generate Multiwfn-friendly file format ,e.g. molden file from gbw with orca_2mkl:

    a. `orca_2mkl` <filename> `-molden` (do not give an extension to <filename>)
    b. `mv` <filename>`.molden.input` <filename>`.molden`

3. Run Multiwfn on the electron density file (e.g. .molden file):

    a. `Multiwfn` <filename>`.molden`
    b. Run "Visual study of weak interactions" (option `20`)
    c. Run NCI analysis (option `1`)
    d. Choose grid quality (High quality [option `3`] is suitable for publications but can be slow for large molecules)
    e. Output cube files to func1.cub and func2.cub in current folder (option `3`)
    f. Exit multiwfn (`ctrl+c`)

4. Rename func1.cub and func2.cub files:

    a. `mv func1.cub lamb.cube` (this is the λ_2 file)
    b. `mv func2.cub rdg.cube` (this is the reduced density gradient file)

5. Open lamb.cube, rdg.cube and <filename>.xyz (or <filename>.pdb) in Pymol, apply your favourite settings to the structure, then paste the following text into the Pymol terminal:

```
isosurface nci, rdg, 0.6
# the isovalue can be tweaked
ramp_new spectrum, lamb, [-0.01, 0, 0.01], [blue, green, red]
# in the order: attraction, vdW, repulsion
set surface_color, spectrum, nci
set transparency, 0.4
```

6. The resultant NCI isosurface can then be exported (ensure opaque background is turned on).

References:

1. F. Neese, *WIREs Comput Mol Sci*, **2018***, 8,* e1327.
2. T. Lu and F. Chen, *J. Comput. Chem.*, **2012**, *33*, 580–592.
3. E. R. Johnson, S. Keinan, P. Mori-Sánchez, J. Contreras-García, A. J. Cohen and W. Yang, *J. Am. Chem. Soc.*, **2010**, *132*, 6498–6506.