Revealing Non-Covalent Interactions

Weitao Yang, Duke University

Theory
Biological
Nano
Material

Funding

NSF
NIH
ONR
DOE (EFRC)

LONI, Baton Rouge
July 2011

Revealing Non-covalent interactions

Erin Johnson (Duke, now UC-Merced)

Johnson, Contreras, Keinan, Mori-Sanchez, Cohen , and WY, *JACS, 2010.*

Contreras-García, Johnson, Keinan, Chaudret, Piquemal, Beratan, and Yang, J. Chem. Theory Comput. 2011

Julia Conteras-Garcia

Shahar Keinan

Paula Mori-Sanchez
(Duke, now Univ. Autonoma Madrid)

Aron J. Cohen
(Duke, now Cambridge)

DFT Calculations of Non-Covalent Interactions

- **Electrostatic Interaction – well described with electrostatic potential (OK)**
- **Hydrogen bond (OK)**
- **Van der Waals attraction (OK, beyond LDA, GGA, and hybrid functionals)**
- **Steric Repulsion (OK)**

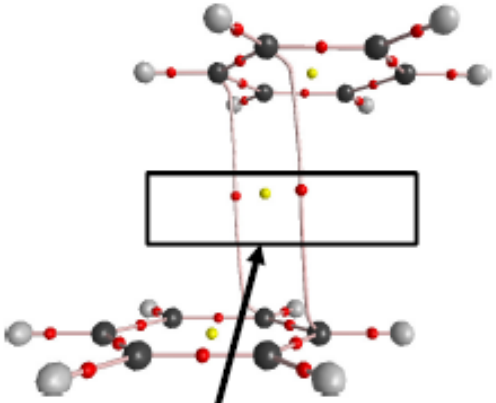
Visualizing Non-Covalent Interactions

- **Electrostatic Interaction – well described with electrostatic potential**
- **Hydrogen bond (?)**
- **Van der Waals attraction (?)**
- **Steric Repulsion (?)**

WEAK INTERACTIONS

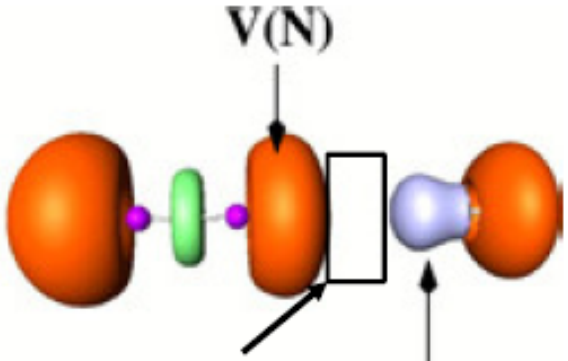
Topological approaches to weak interactions: AIM and ELF

AIM



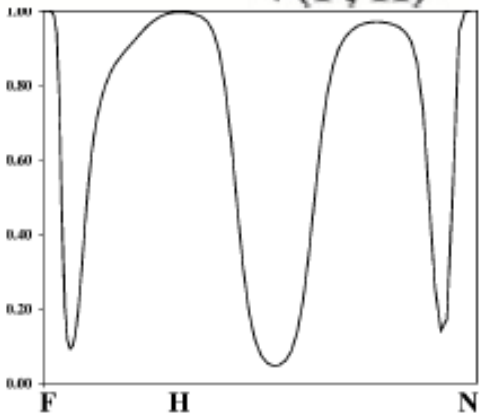
density critical points

ELF



ELF *bips* become higher

V(F, H)



But how can we actually see the weak interaction?

Revealing Non-Covalent Interactions

- Molecular structure does not identify the intricate non-covalent interactions that govern many areas of biology and chemistry.

- We develop an approach to detect non-covalent interactions in real space, based on the electron density and its gradient.

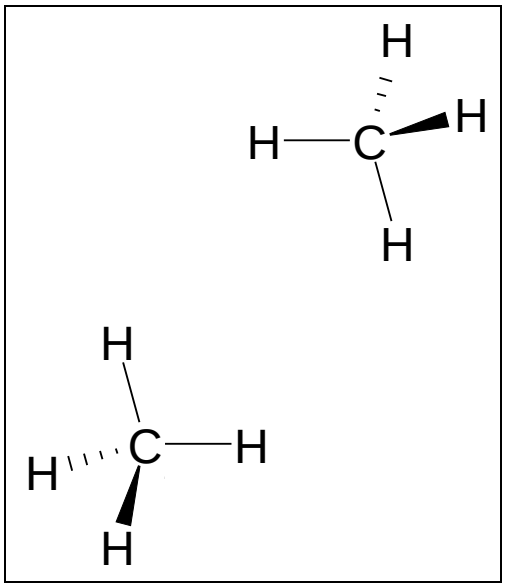
- Our approach reveals underlying chemistry that compliments the covalent structure

- The method, requiring only knowledge of the atomic coordinates, is efficient and applicable to large systems.

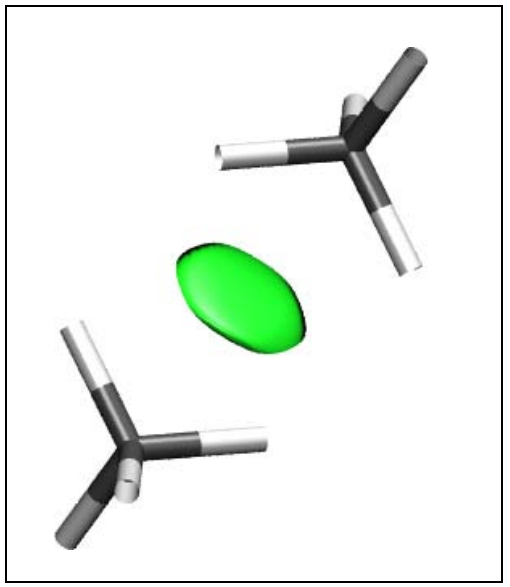
Johnson, Contreras, Keinan, Mori-Sanchez, Cohen , and WY , *JACS, 2010.*

Can we use the density to detect these interactions in ***real space***?

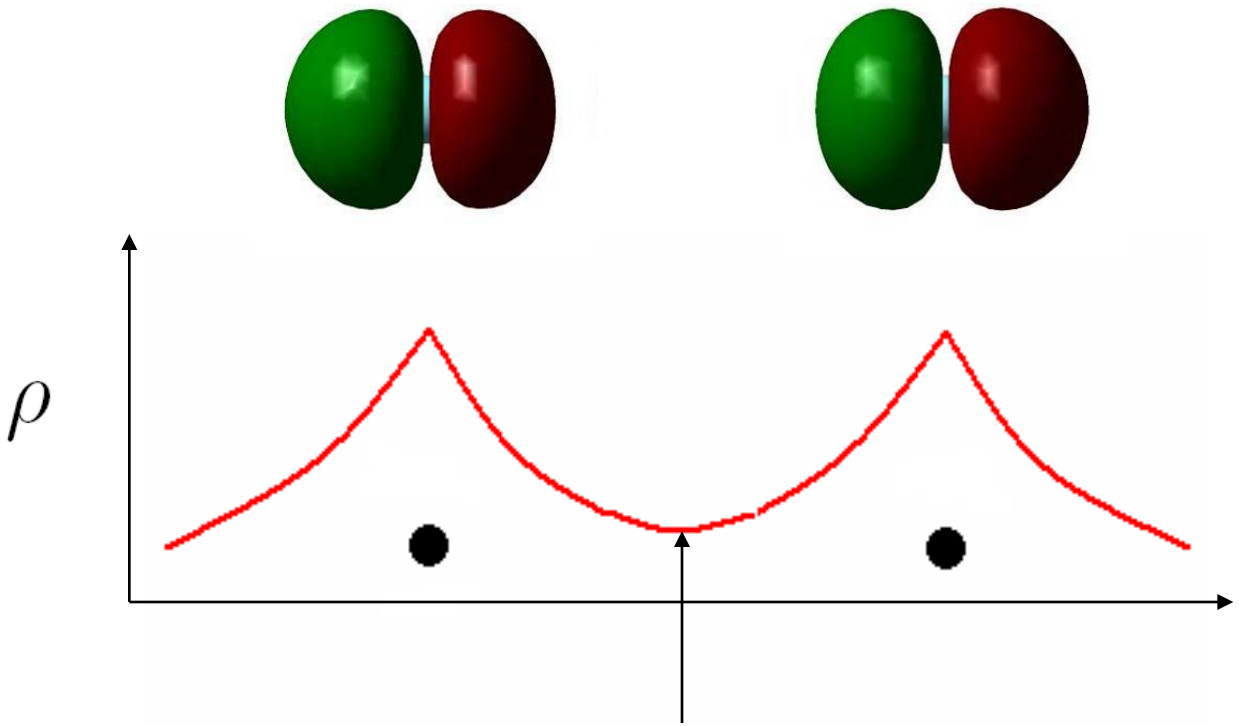
Covalent bonds: easy to represent



Dispersion?



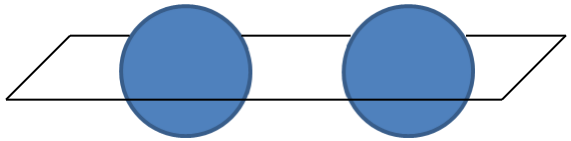
INTERACTIONS IN REAL SPACE



$$\rho > 0 \qquad \text{and} \qquad s = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla \rho|}{\rho^{4/3}} \longrightarrow 0$$

INTERACTIONS IN REAL SPACE

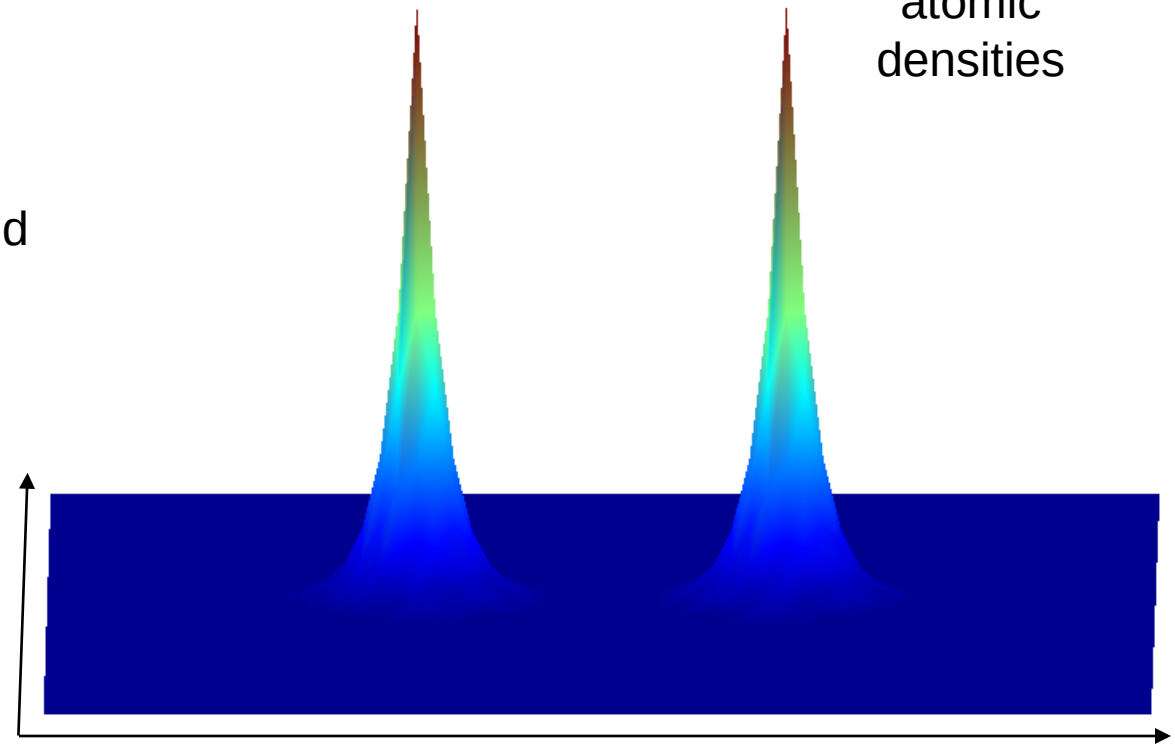
At all grid points, evaluate and plot



$$s(\rho(r))$$

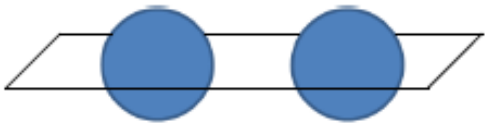
Simple DFT or atomic densities

$\nabla\rho(r), s(r) \to 0$ at nuclei, bonds (large ρ) and between atoms (small ρ).

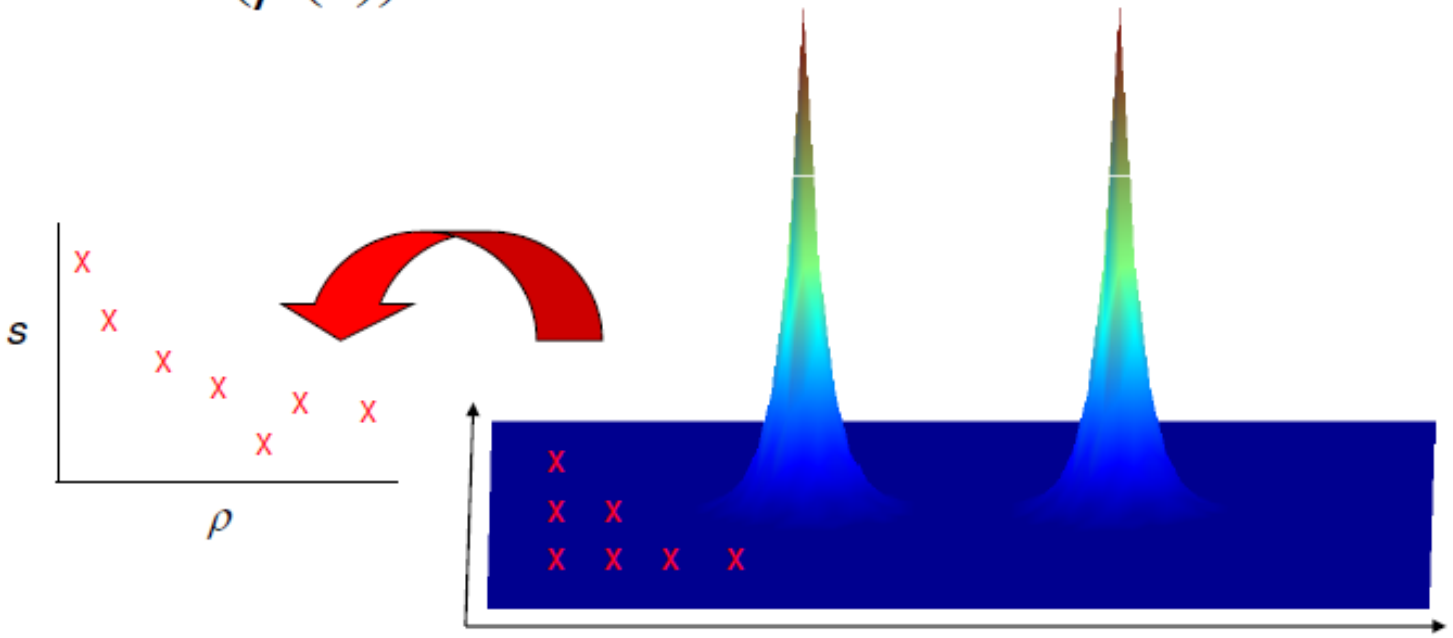


NCI

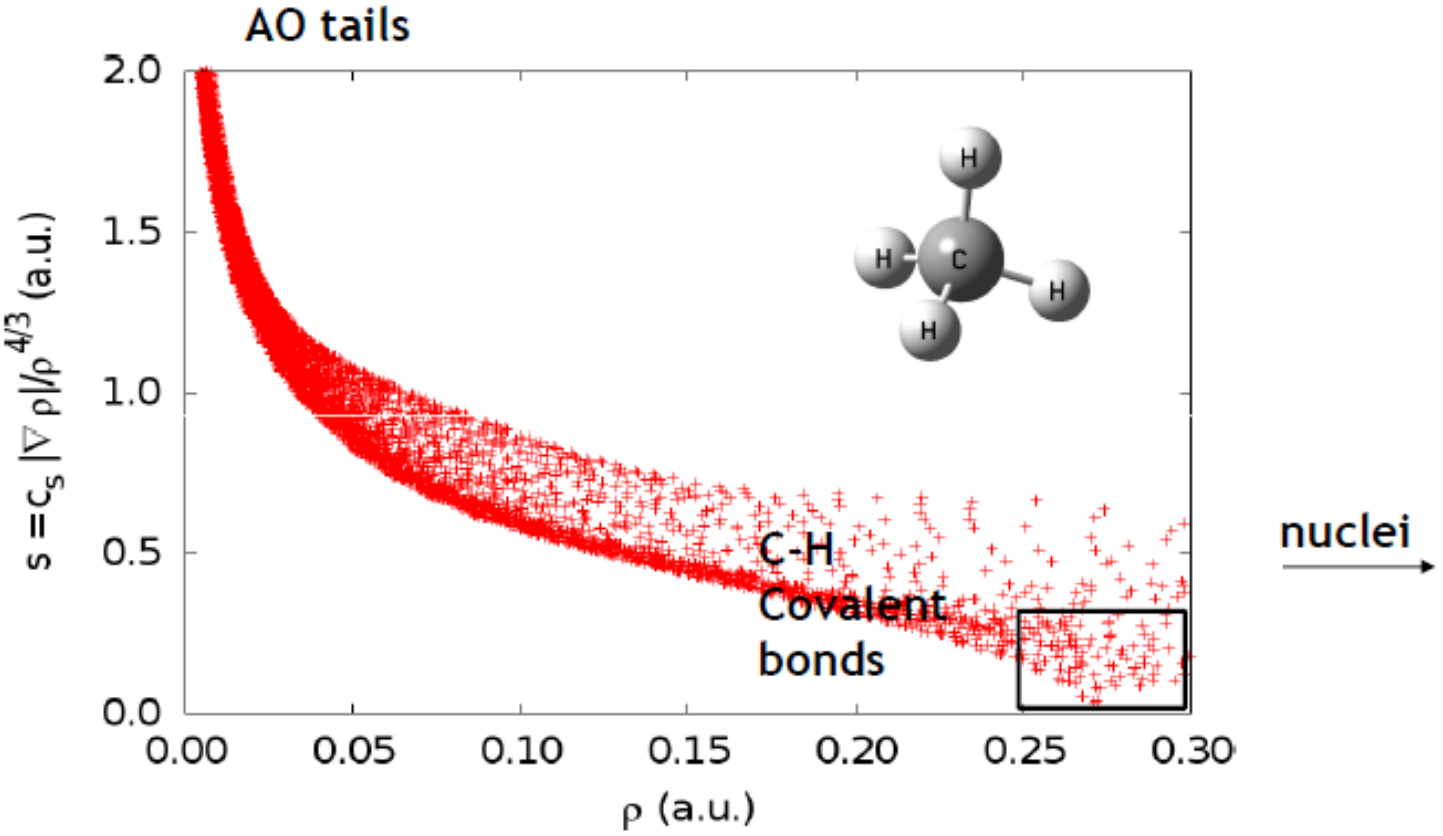
At all grid points, evaluate and plot



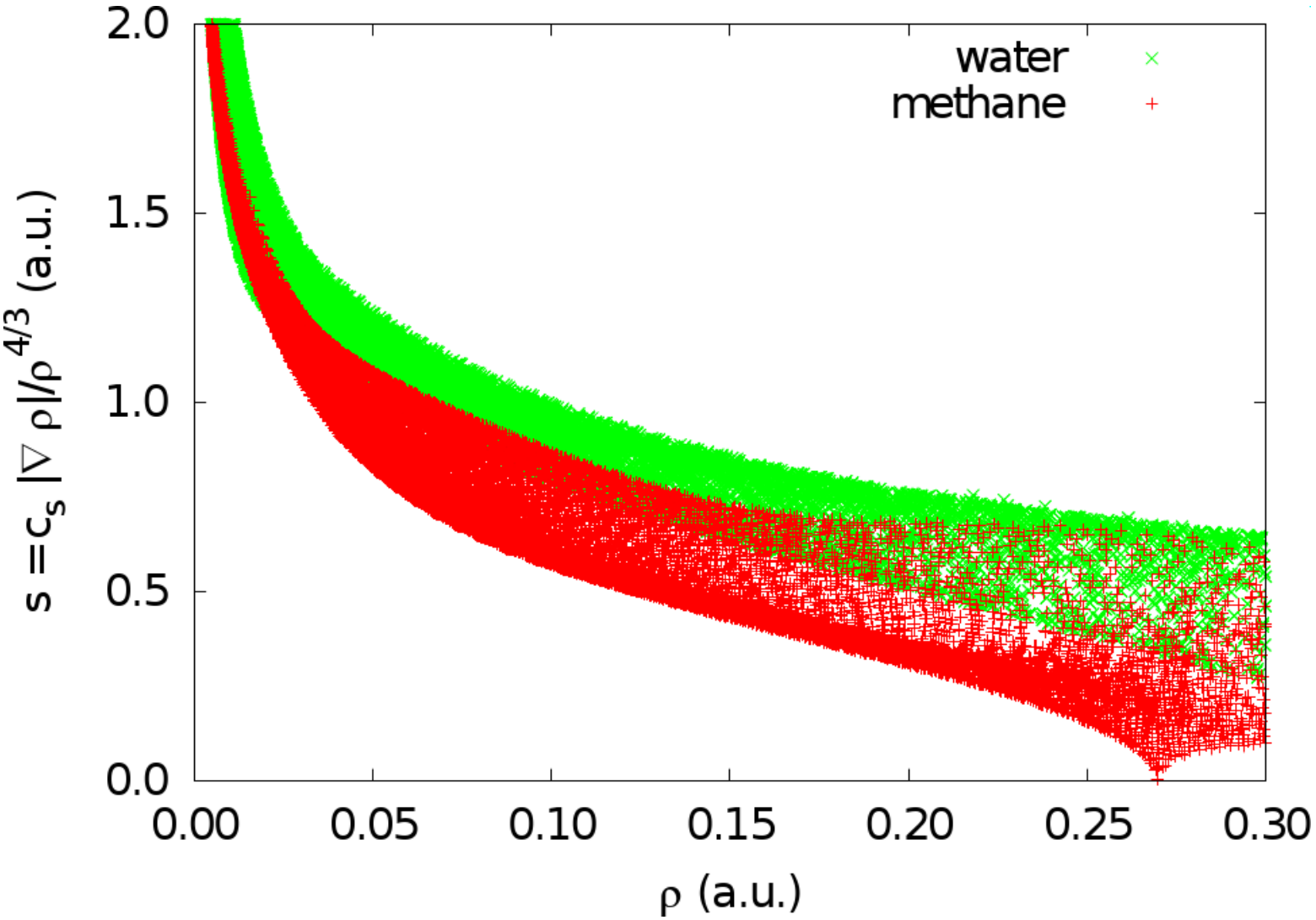
$$s(\rho(r))$$



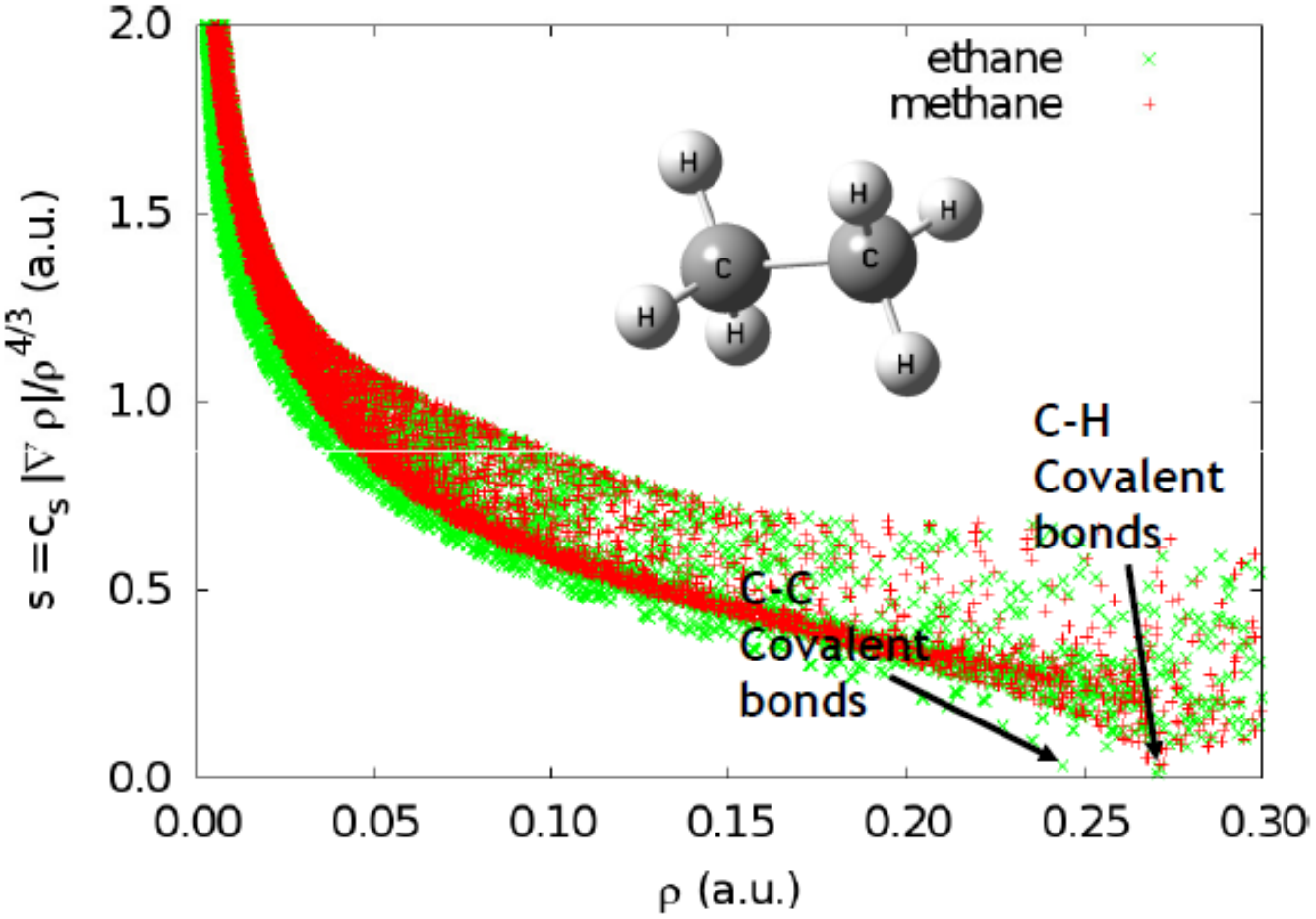
NCI


AO tails
2.0
1.5
1.0
0.5
0.0
0.00
0.05
0.10
0.15
0.20
0.25
0.30
$s = c_s |\nabla \rho| / \rho^{4/3}$ (a.u.)
ρ (a.u.)
H
H
C
H
H
C-H
Covalent
bonds
nuclei

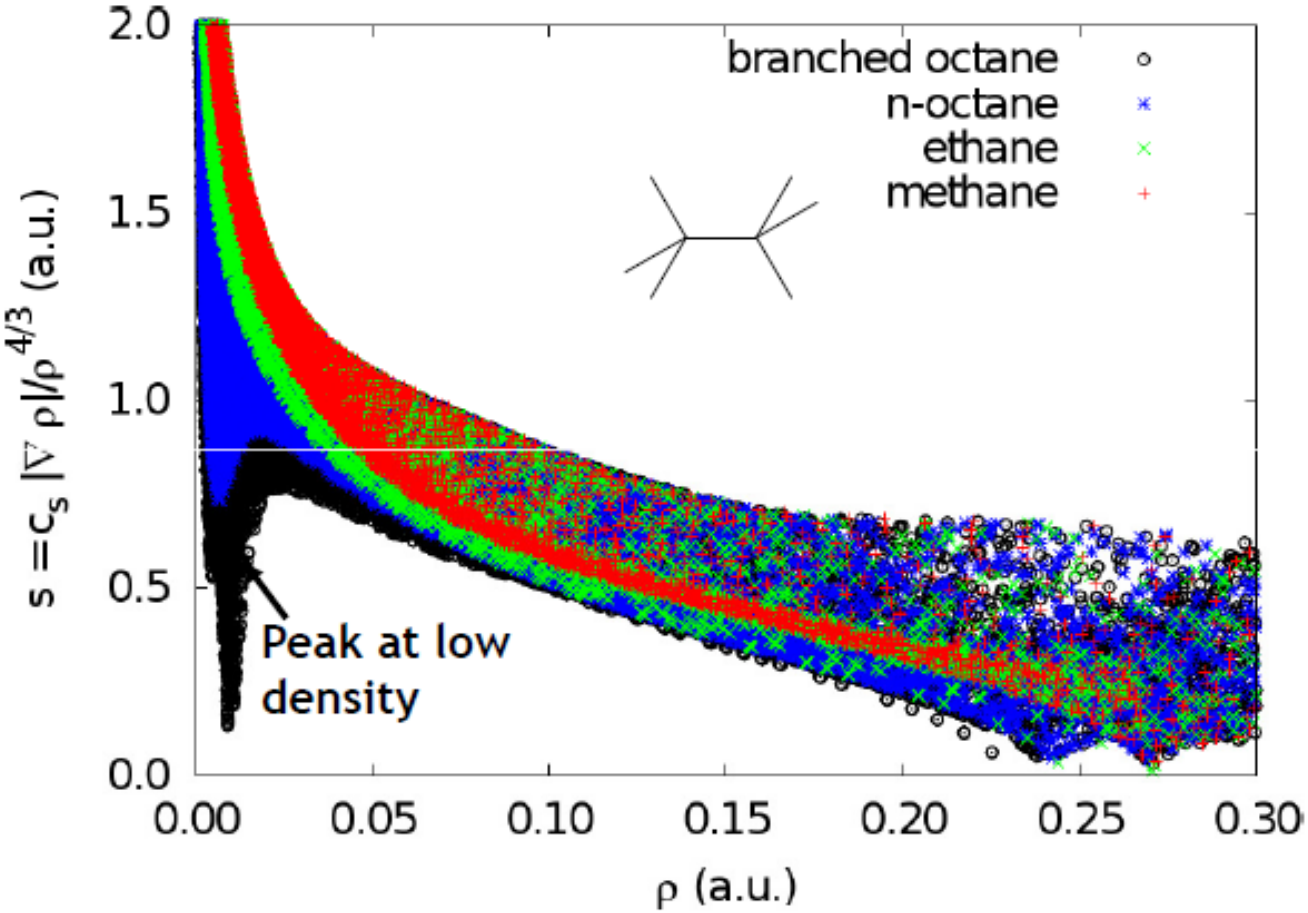
INTERACTIONS IN REAL SPACE

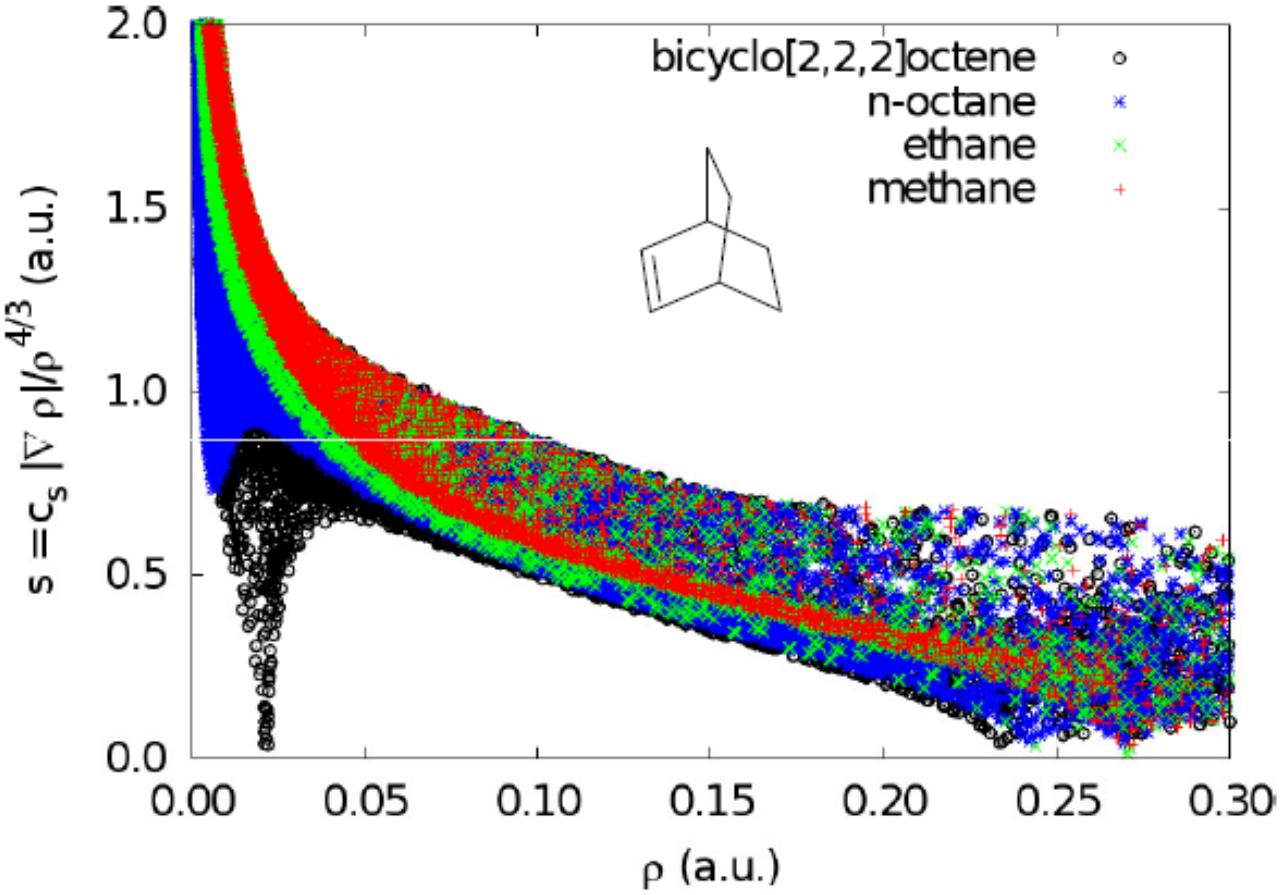


NCI

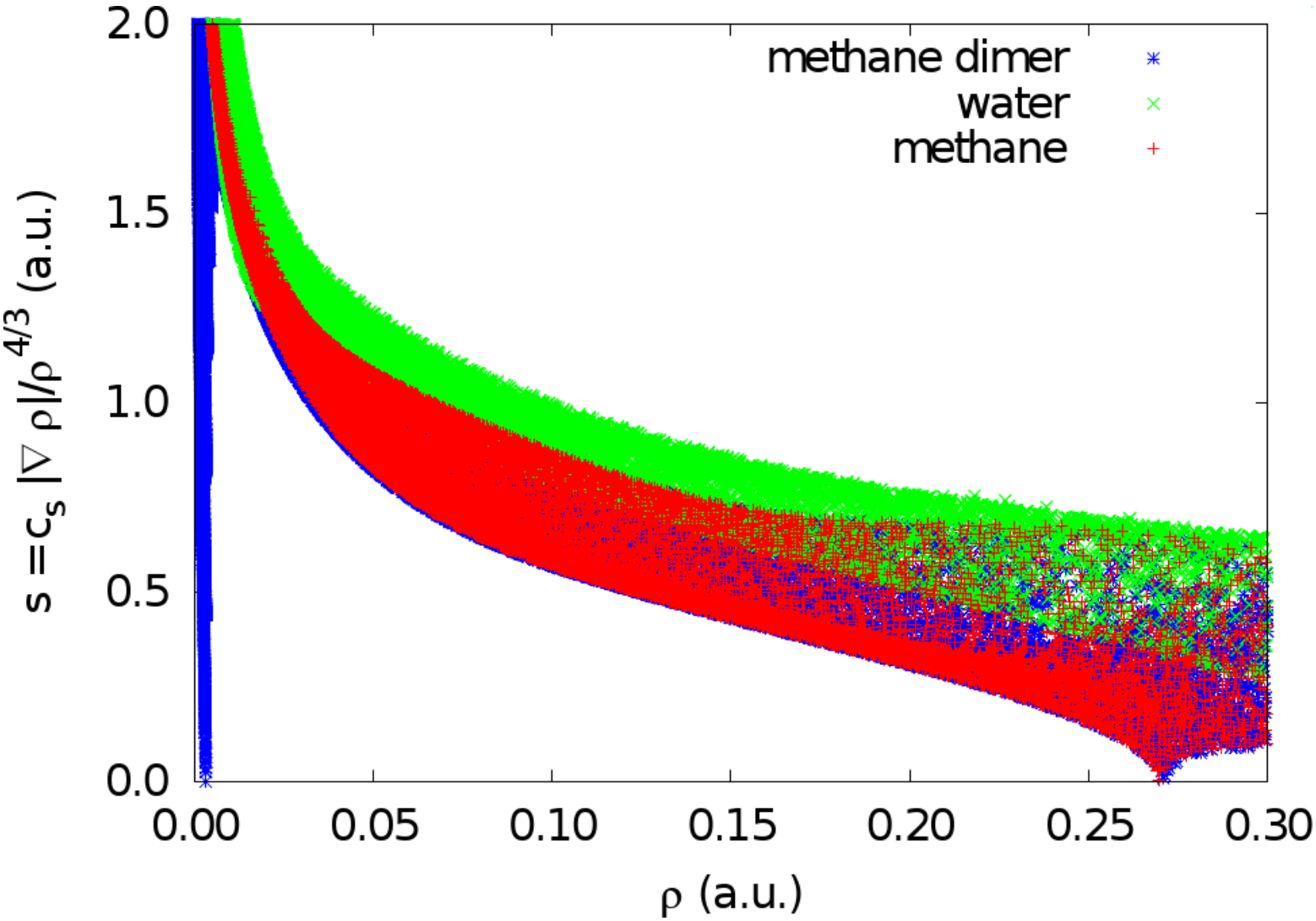

ethane
methane
C-H
Covalent
bonds
C-C
Covalent
bonds
$s = c_s |\nabla \rho| / \rho^{4/3}$ (a.u.)
ρ (a.u.)
0.0
0.5
1.0
1.5
2.0
0.00
0.05
0.10
0.15
0.20
0.25
0.30

NCI

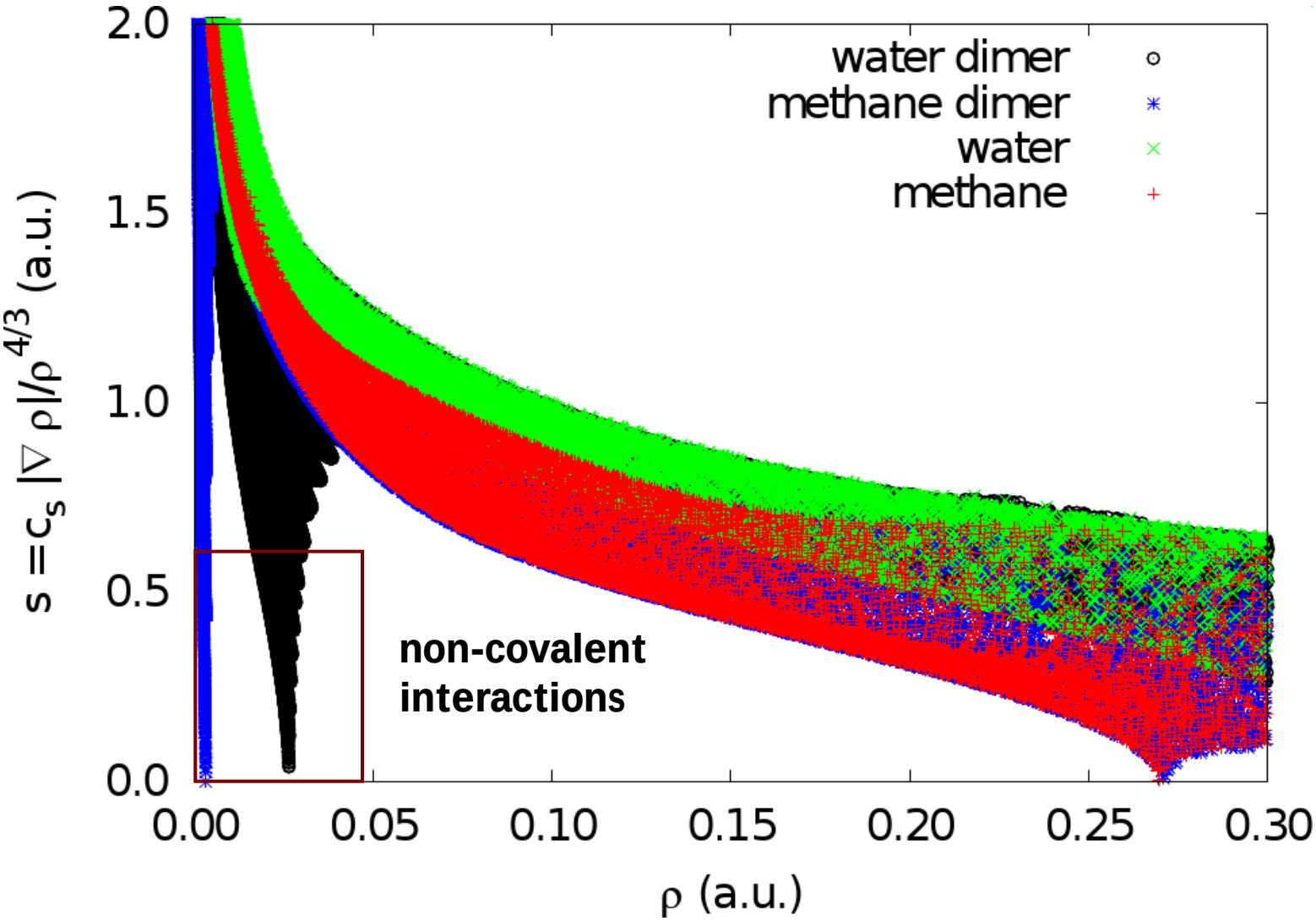

branched octane
n-octane
ethane
methane
Peak at low density
$s = c_s |\nabla \rho| / \rho^{4/3}$ (a.u.)
ρ (a.u.)
2.0
1.5
1.0
0.5
0.0
0.00
0.05
0.10
0.15
0.20
0.25
0.30


bicyclo[2,2,2]octene
n-octane
ethane
methane
2.0
1.5
1.0
0.5
0.0
0.00
0.05
0.10
0.15
0.20
0.25
0.30
s = c_s |∇ ρ|/ρ^4/3 (a.u.)
ρ (a.u.)

INTERACTIONS IN REAL SPACE



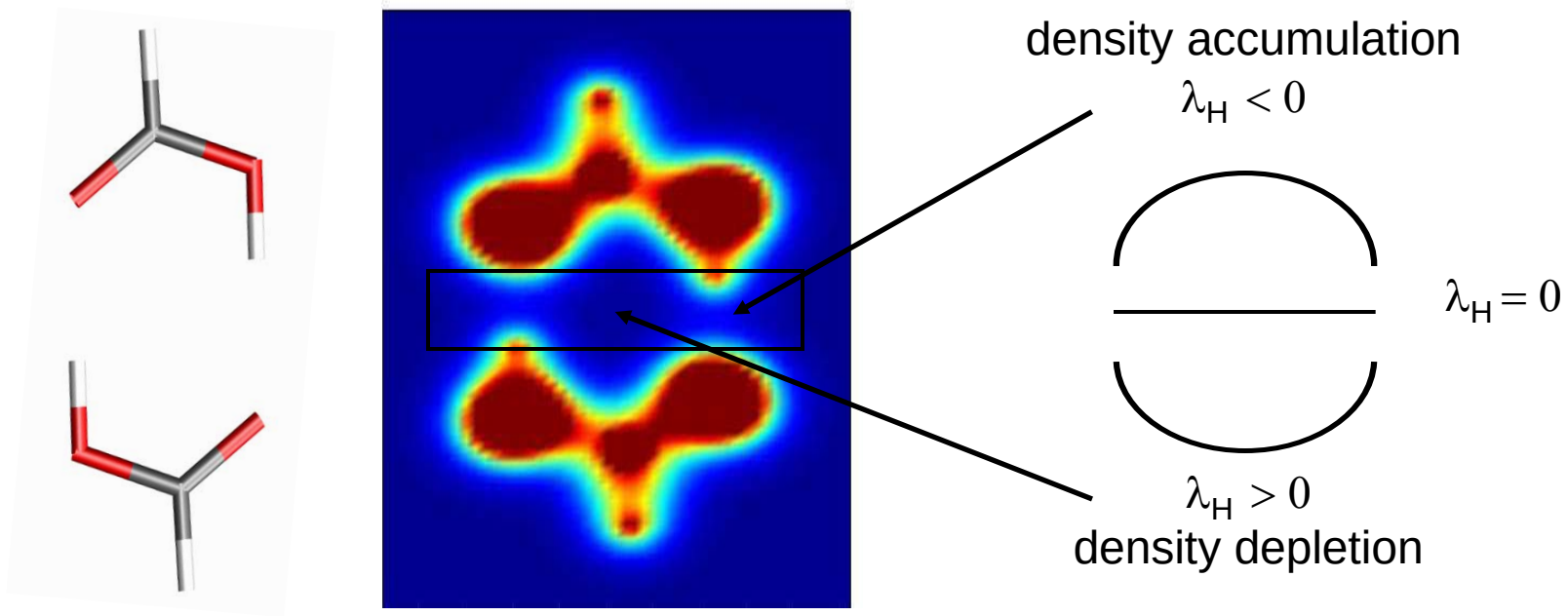
INTERACTIONS IN REAL SPACE



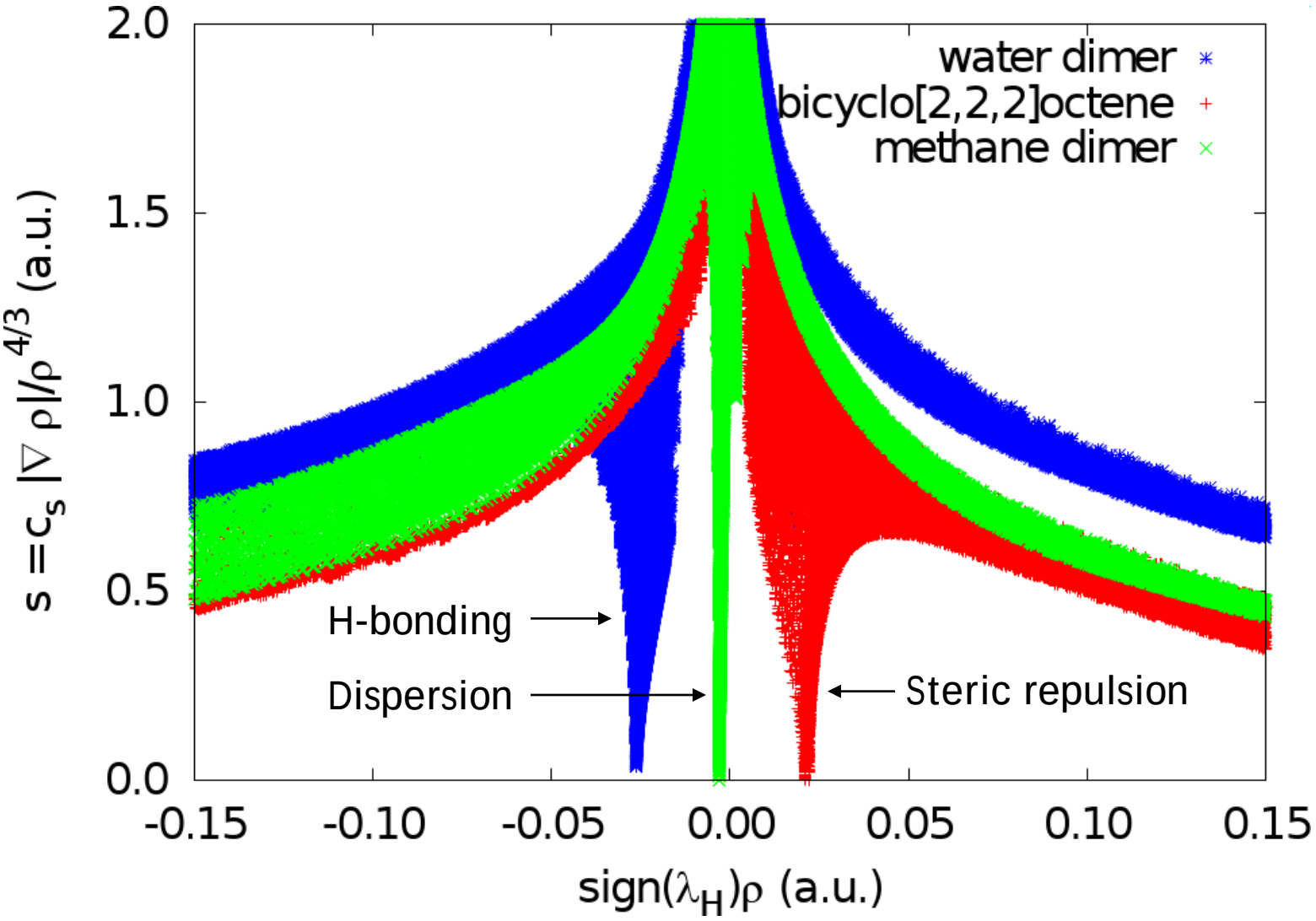
INTERACTIONS IN REAL SPACE

Attractive and repulsive interactions can be distinguished by the sign of the second Hessian eigenvalue (λ_H).

This value corresponds to the variation of the density along the axes of maximal curvature.

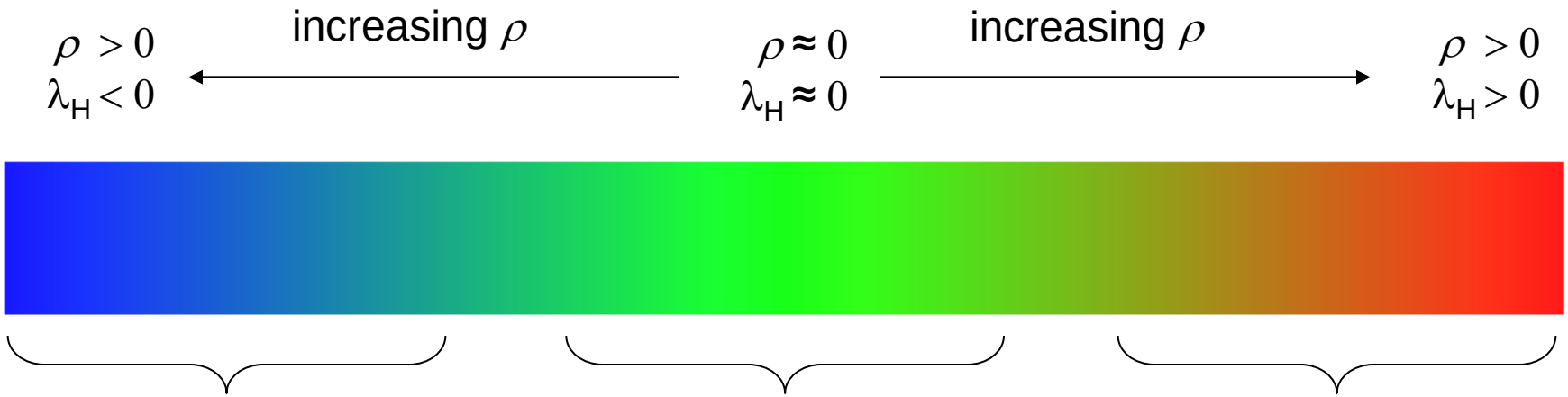


INTERACTIONS IN REAL SPACE



INTERACTIONS IN REAL SPACE

Plot gradient isosufaces in real space and colour by sign(λ_H)ρ



Strong, attractive interactions:

H-bonding

Weak interactions:

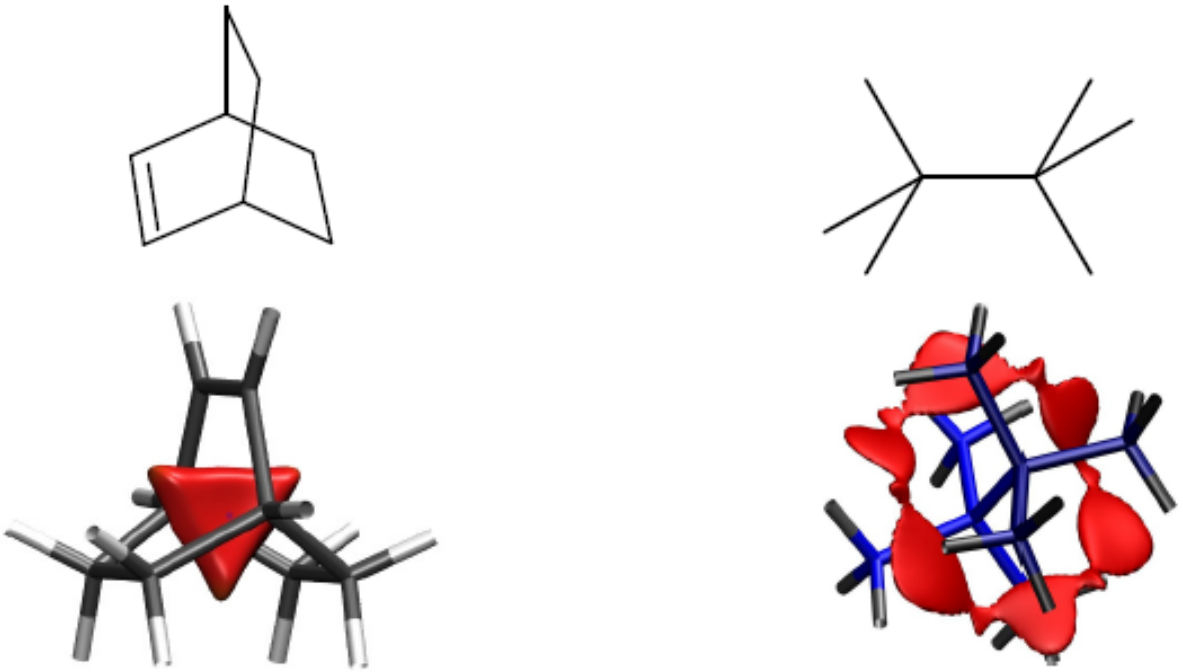
van der Waals, including dispersion

Strong, repulsive interactions:

steric crowding

NCI

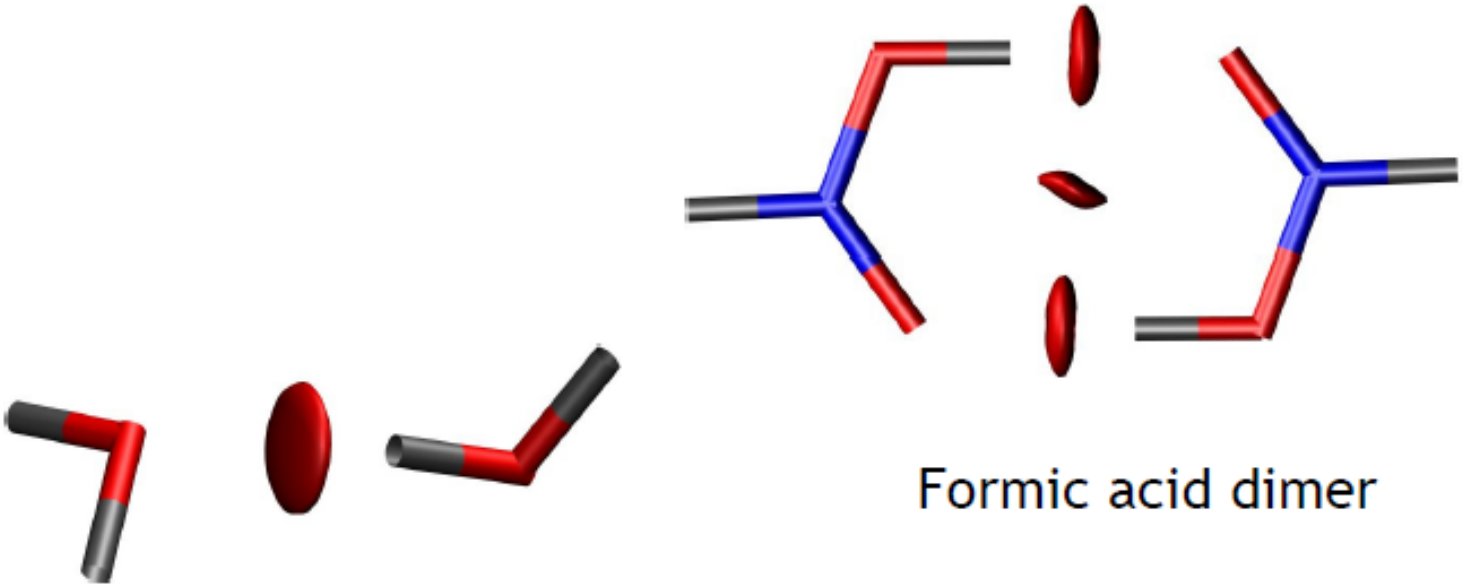
- We represent the in 3D the points from the peaks



Regions of steric clash!

NCI

- Hydrogen bonds

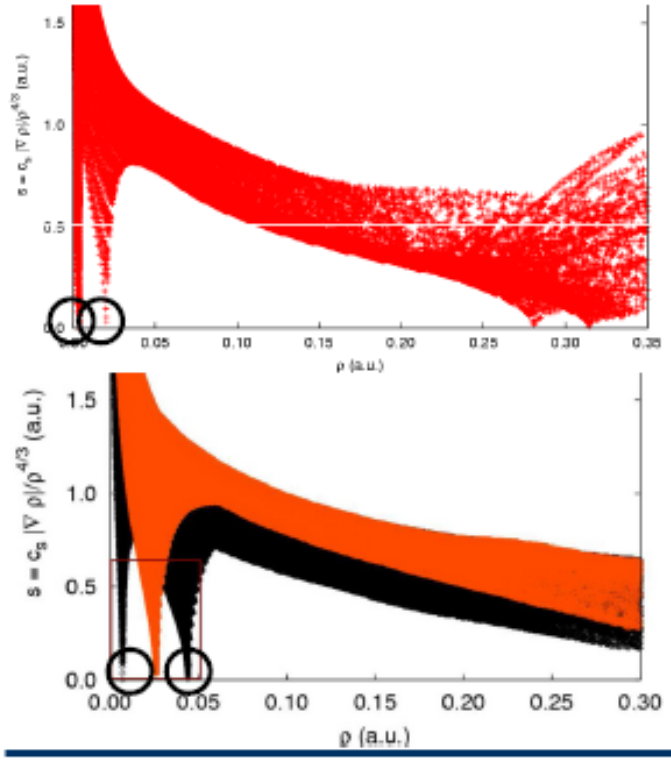


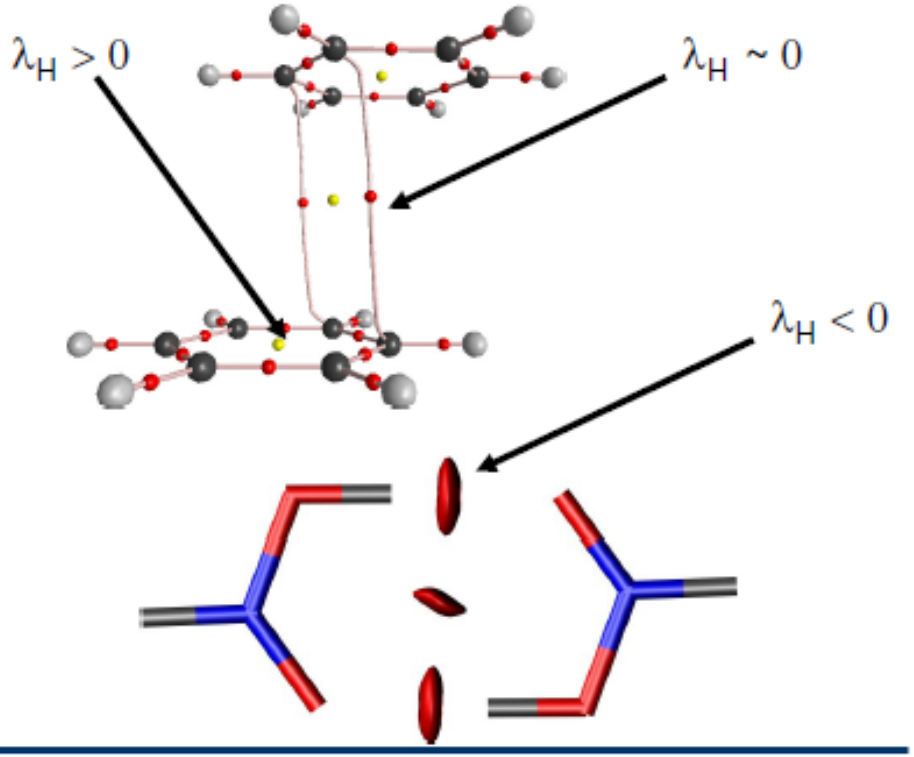
Water dimer

Formic acid dimer

NCI

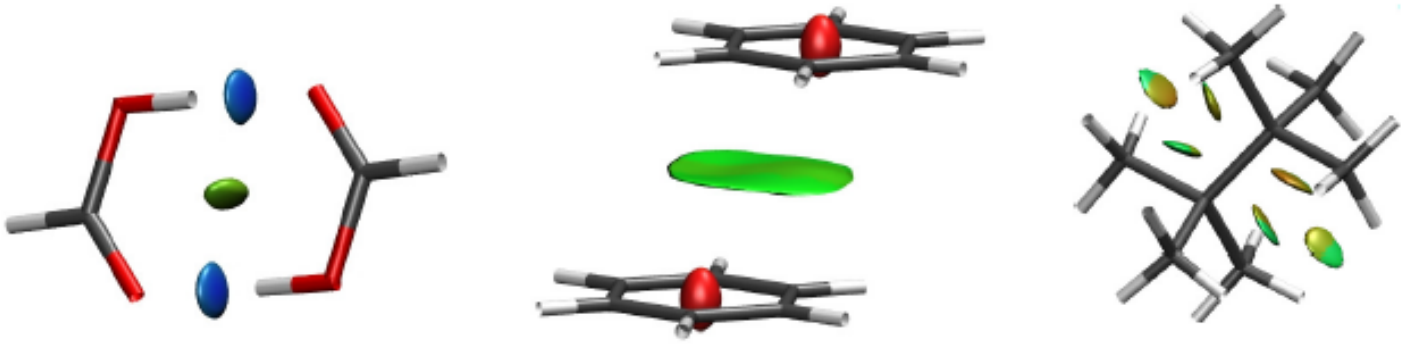
- Density is proportional to the strength of the interaction
- Bonding interactions give rise to charge accumulation ($\lambda_H < 0$)
- Antibonding interactions give rise to charge depletion ($\lambda_H > 0$)



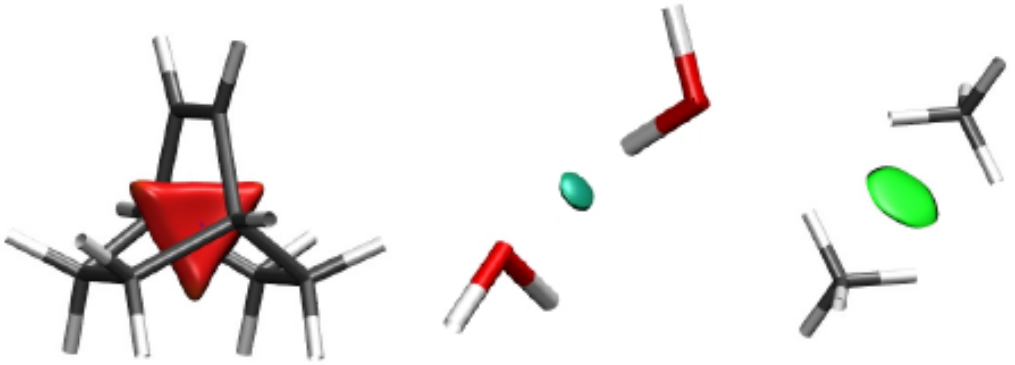


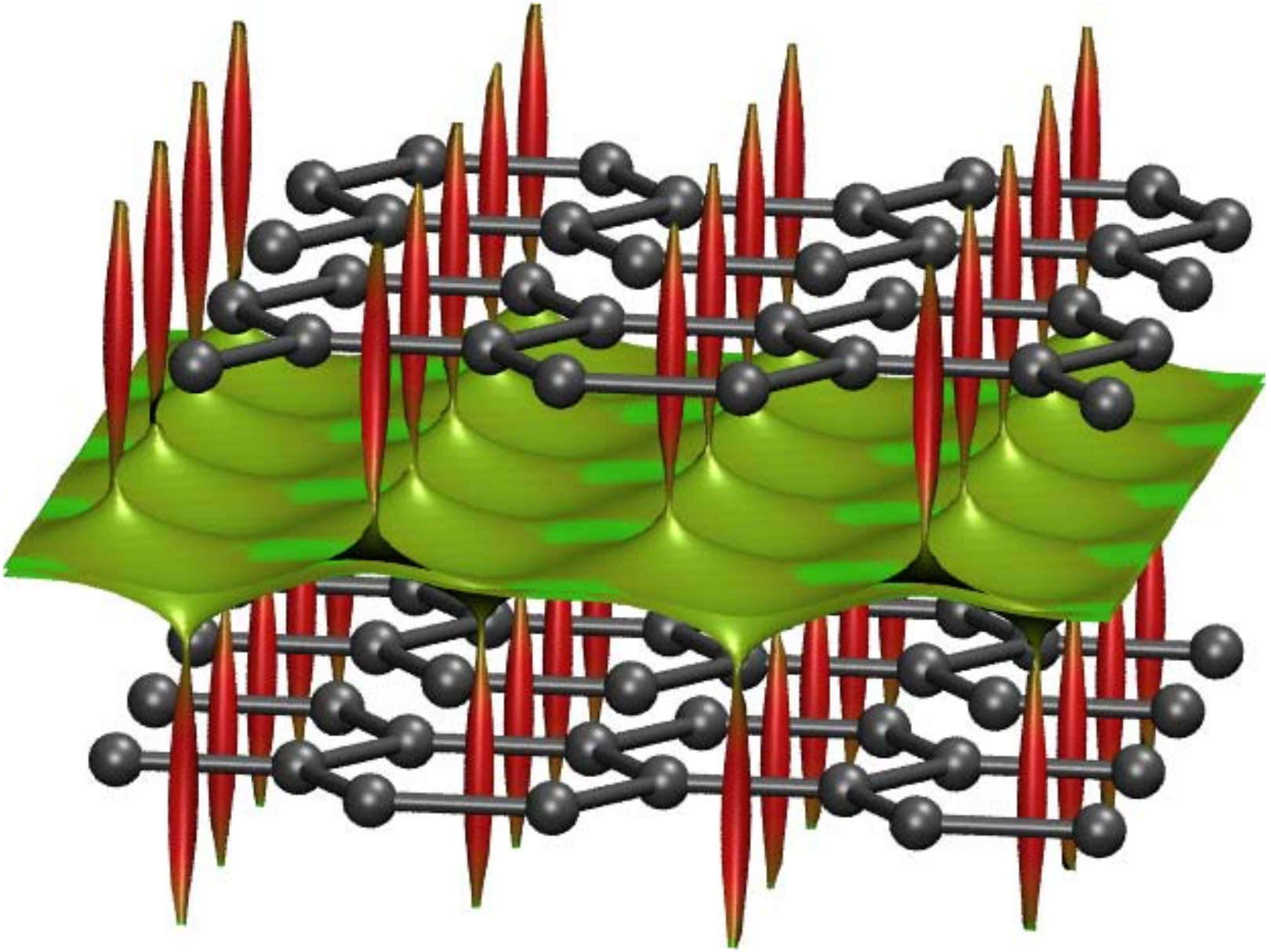
SMALL MOLECULES

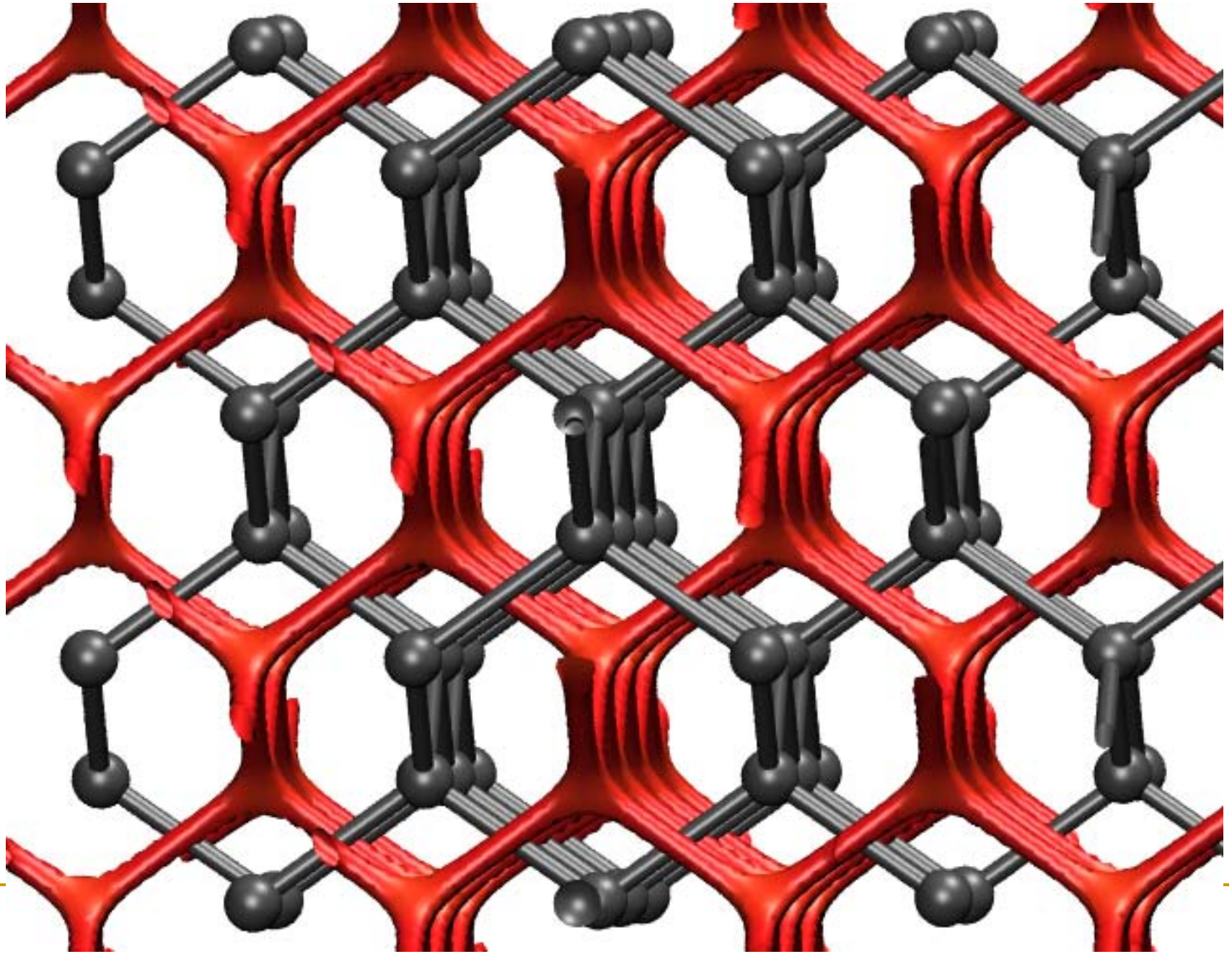
We represent NCI surfaces and color them in terms of sign(λ_H) x ρ



Strong and attractive	$\rho > 0$ $\lambda_H < 0$
Weak	$\rho \approx 0$ $\lambda_H \approx 0$
Strong and repulsive	$\rho > 0$ $\lambda_H > 0$







INTERACTIONS IN REAL SPACE

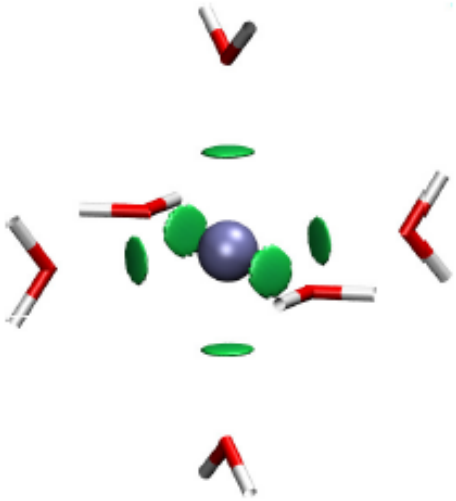
Low-density, low-gradient isosurfaces reveal non-covalent interactions.

- ***Any*** reasonable electron density can be used,
- only requires input atomic coordinates,
- shows continuous surfaces rather than pair-wise contacts.

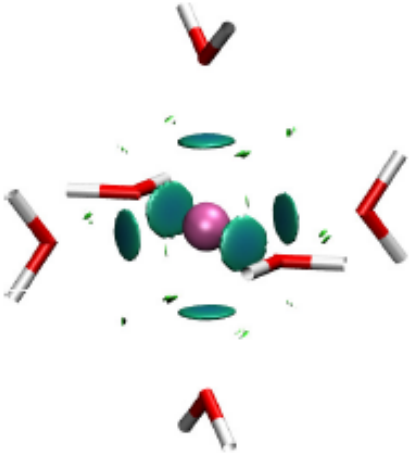
This offers exciting possibilities for

- analysis of interactions in, and between, biomolecules,
- design of ligands and catalysts,
- self-assembled materials.

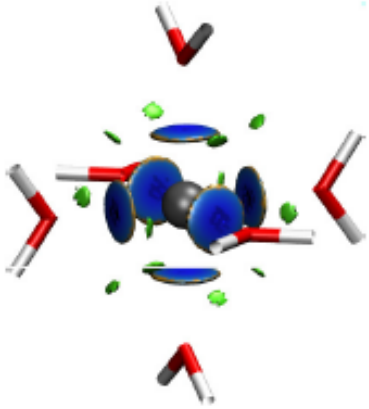
METALLIC HYDRATES



K^+



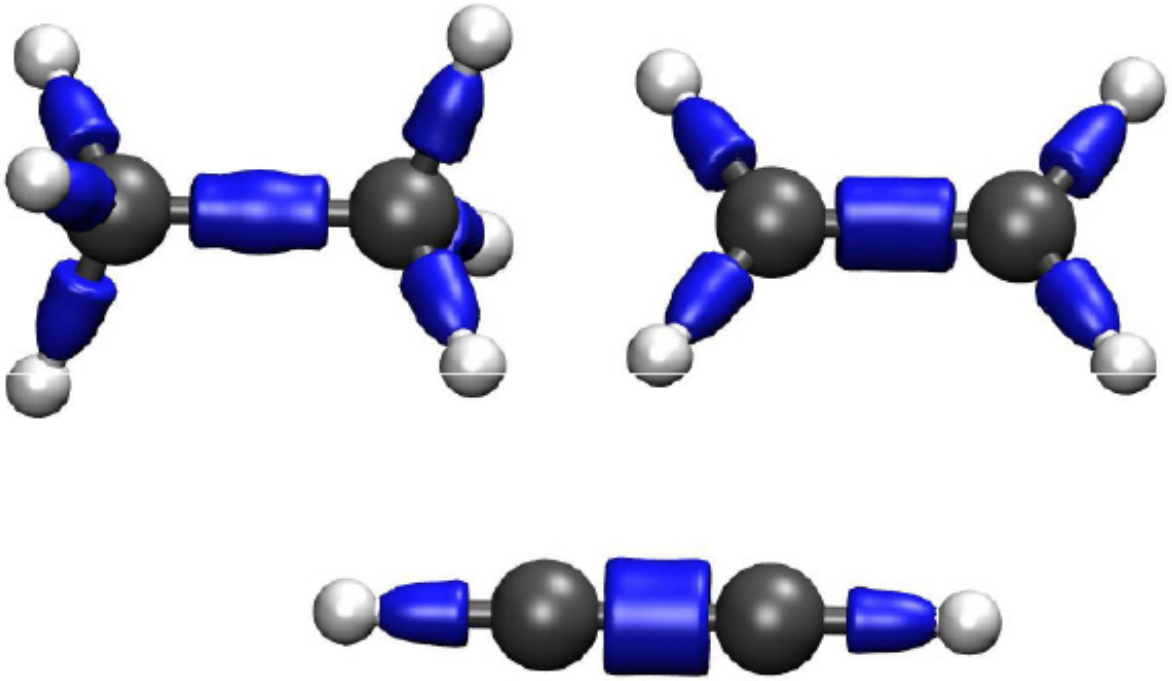
Ca^{2+}



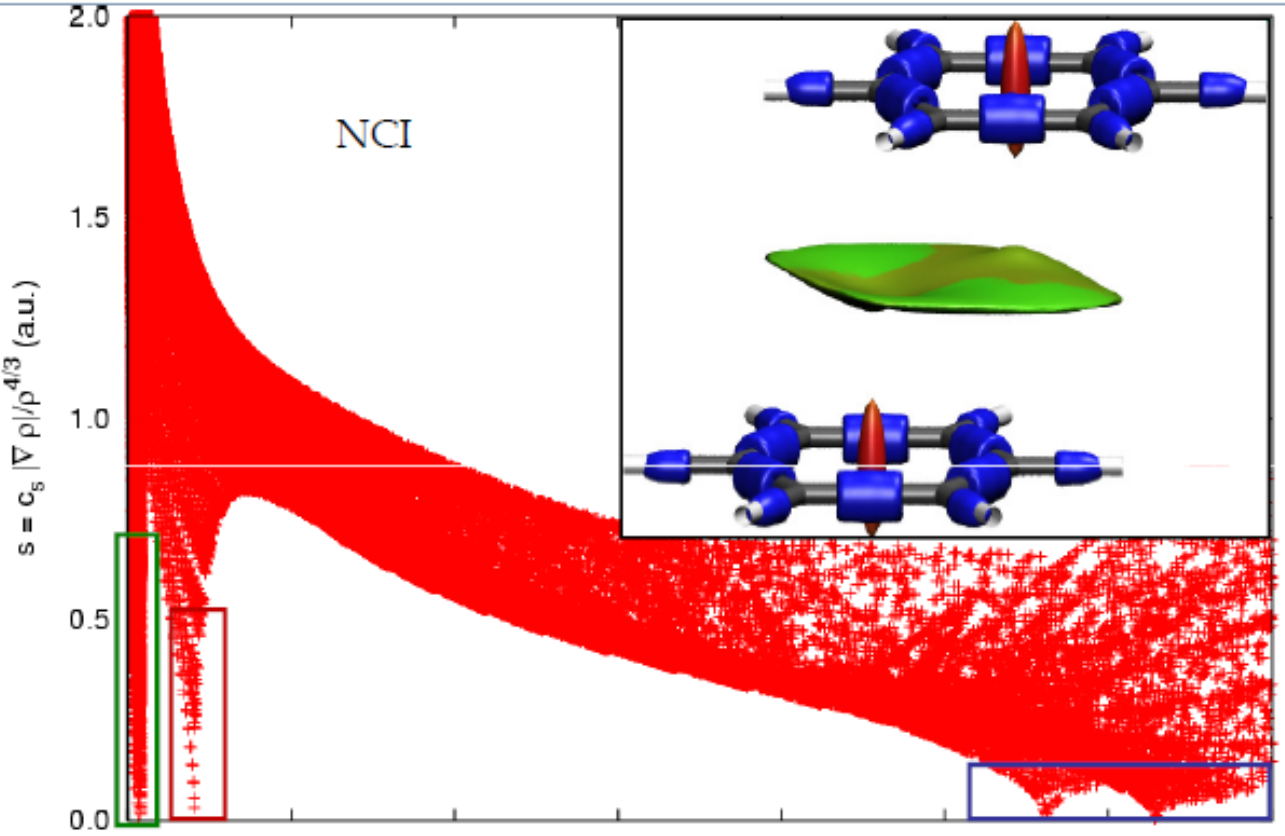
Zn^{2+}

Covalent Bonds seen at higher densities

NCI



COMPARISON W/ OTHER BONDING THEORIES

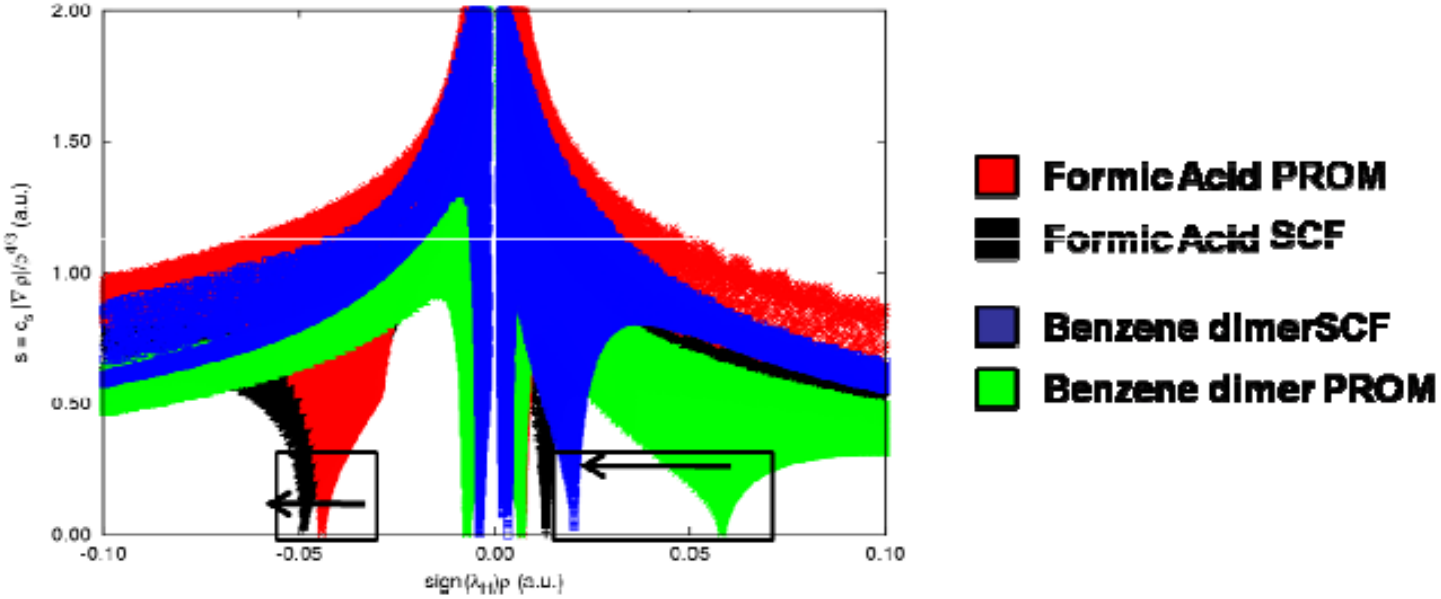


Covalent bonds

Web, Jmol, blog
VMD

BIOMOLECULES

- One of the major areas of application of weak interactions are biomolecules
- HOWEVER, SCF calculations are extremely expensive
- s(ρ) characteristics are preserved from promolecular to SCF density



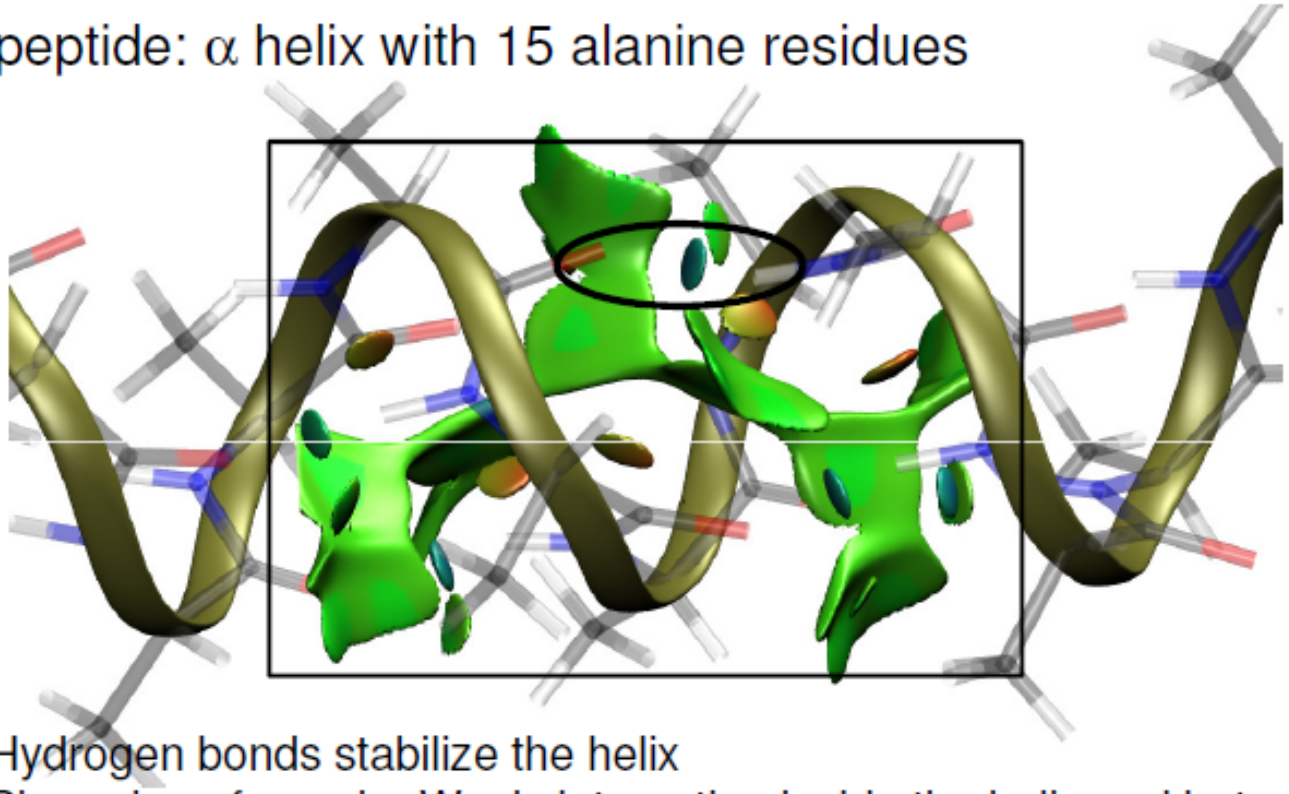
- It only requires atomic coordinates as input
- very fast calculation; applicable to large systems

Use promolecular densities

$$\rho^{pro} = \sum_i \rho_i^{atom}$$

BIOMOLECULES

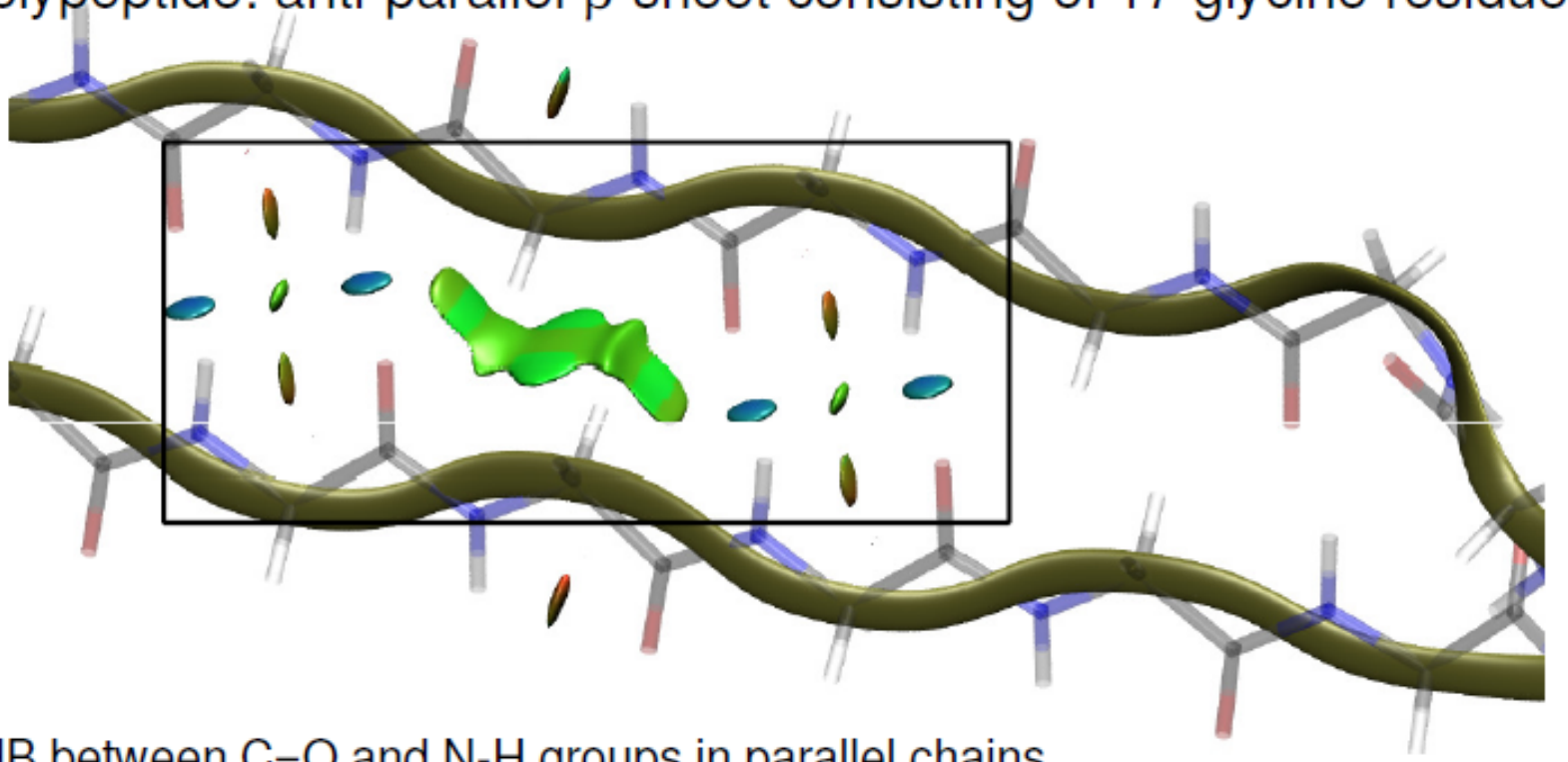
Polipeptide: α helix with 15 alanine residues



- Hydrogen bonds stabilize the helix
- Big region of van der Waals interaction inside the helix and between methyle lateral chains one step away

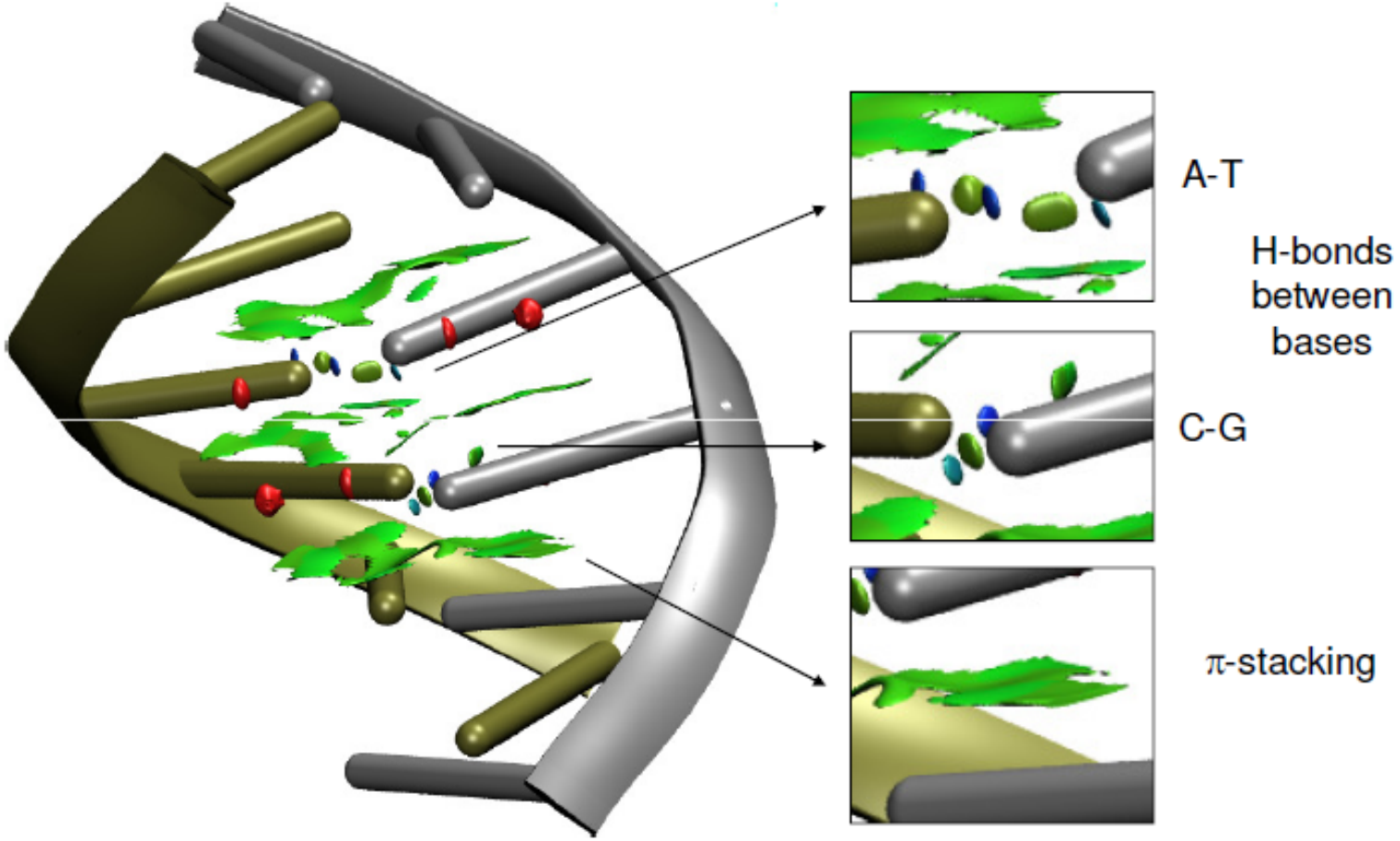
BIOMOLECULES

polypeptide: anti-parallel β-sheet consisting of 17 glycine residues

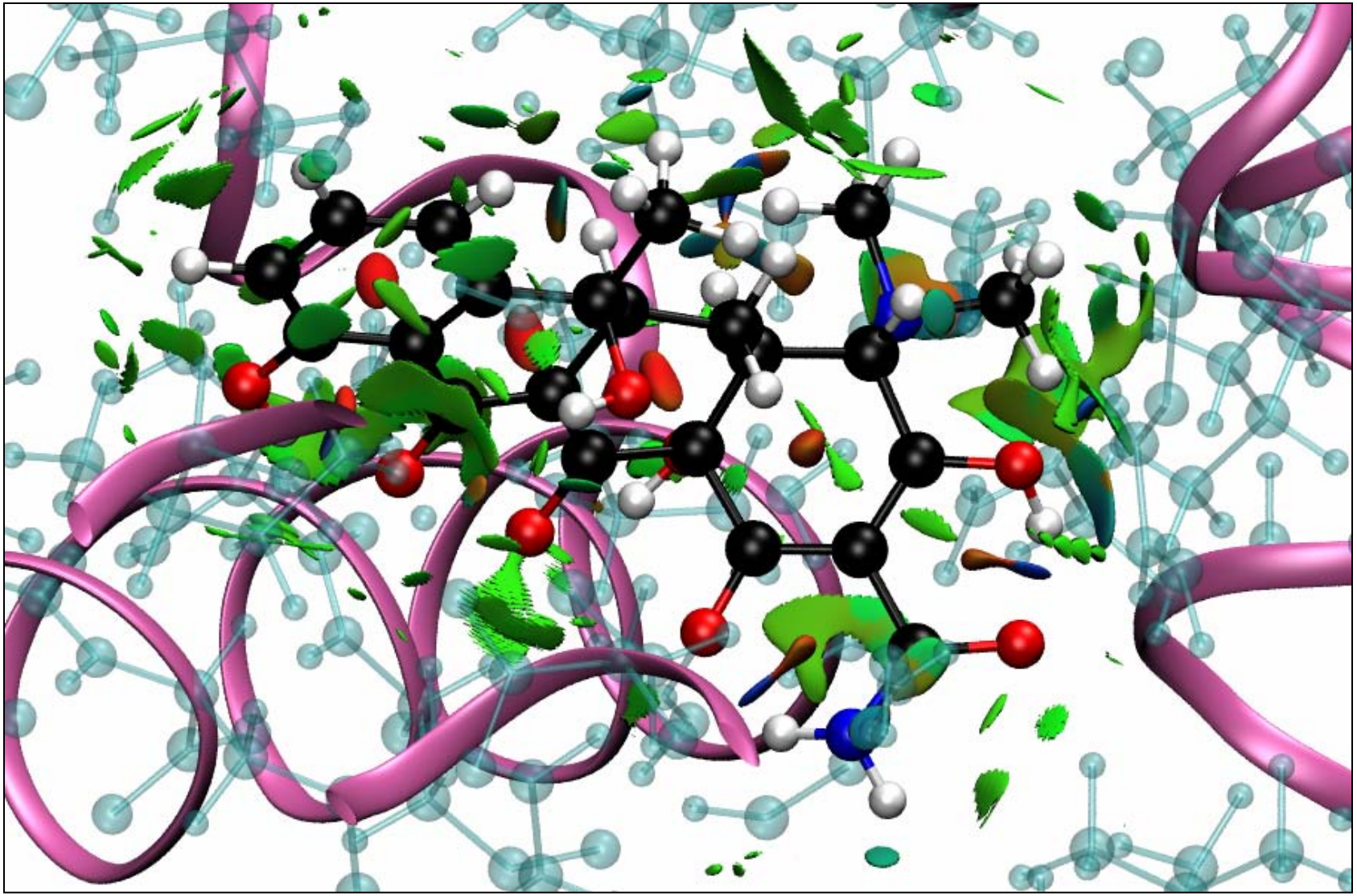


- HB between C=O and N-H groups in parallel chains
- van der Waals interactions between CH_3 groups

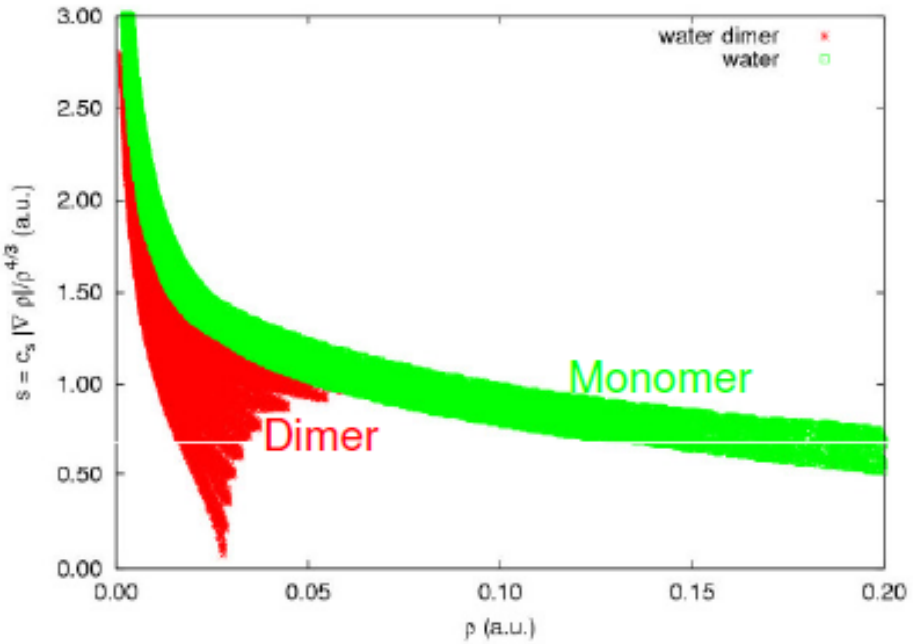
BIOMOLECULES

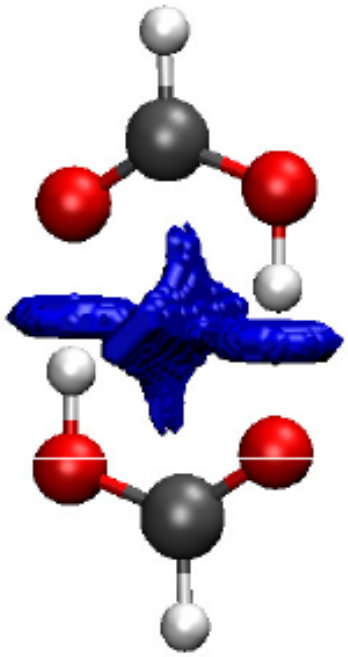


Small molecules interacting with protein



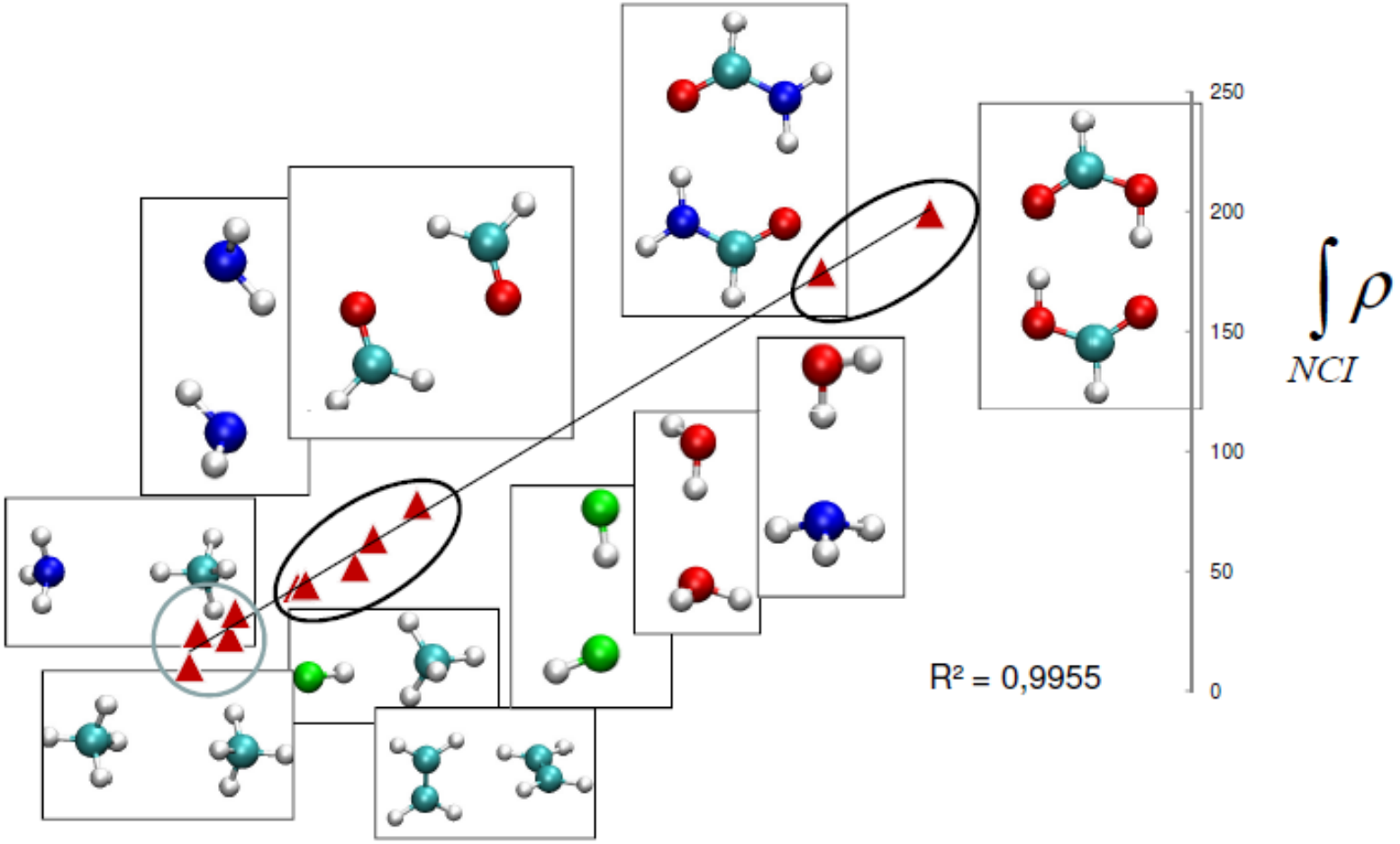
ENERGETICS





1. We localize the interaction region as the one where the dimer and the monomer differ
2. We integrate the density in the interaction region

ENERGETICS



Summary on NCI

•Non-covalent interactions have a unique signature and their presence can be revealed solely from the electron density.

•Non-covalent interactions are highly non-local and manifest in real space as low-gradient isosurfaces with low densities.

•This approach provides a rapid and rich representation of van der Waals interactions, hydrogen-bonds, and steric repulsion, requiring only the atomic coordinates as input.

•Many possible applications

•Programs freely available: http://www.chem.duke.edu/~yang/Software/softwareNCI.html