

# *Revealing Non-Covalent Interactions*

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Theory  
Biological  
Nano  
Material

## **Funding**

NSF

NIH

ONR

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# Revealing Non-covalent interactions

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

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



**Erin Johnson (Duke,  
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**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)**

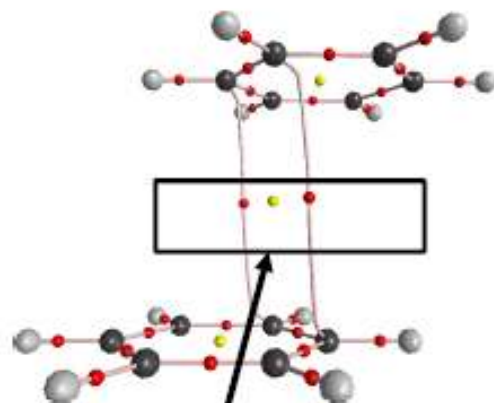
# Visualizing Non-Covalent Interactions

- **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

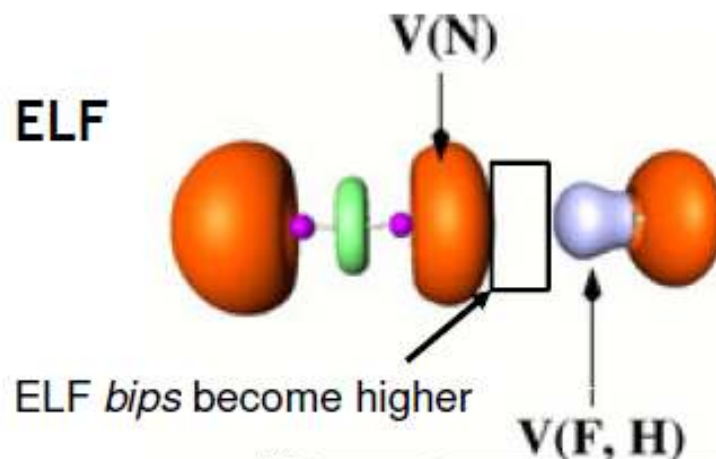
AIM



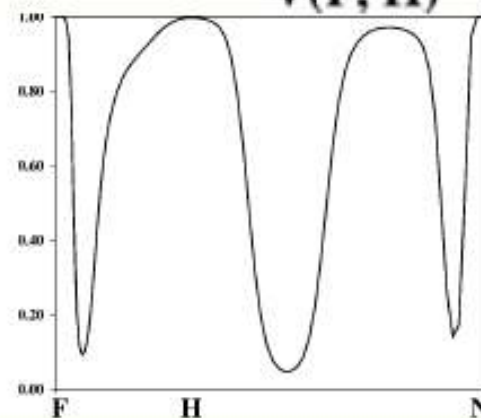
density critical points

But how can we actually see the weak interaction?

ELF



ELF bips become higher



# *Revealing Non-Covalent Interactions*

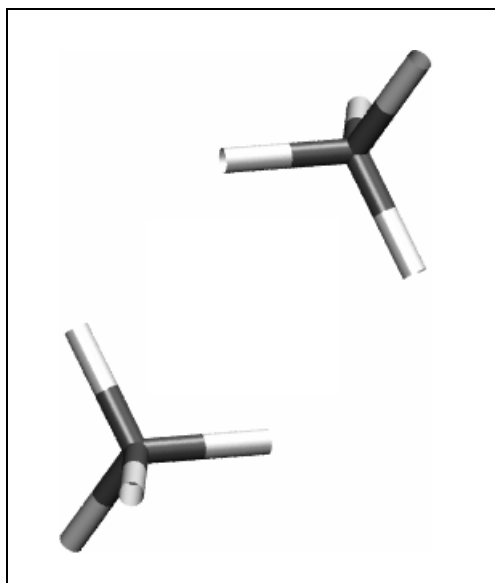
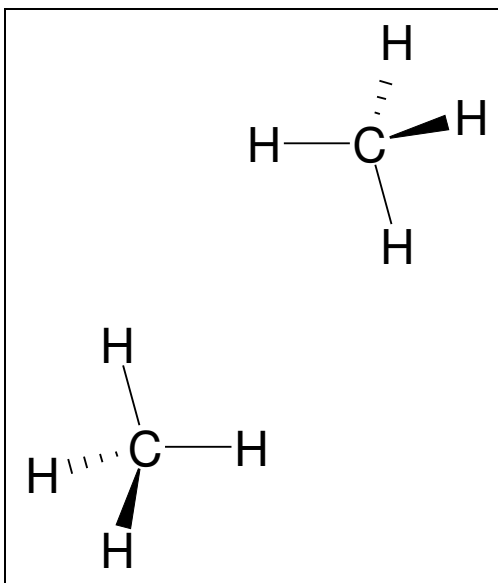
- Molecular structure does not identify the intricate non-covalent interactions that govern many areas of biology and chemistry.
- We develop an approach to detect non-covalent interactions in real space, based on the electron density and its gradient.
- Our approach reveals underlying chemistry that 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.

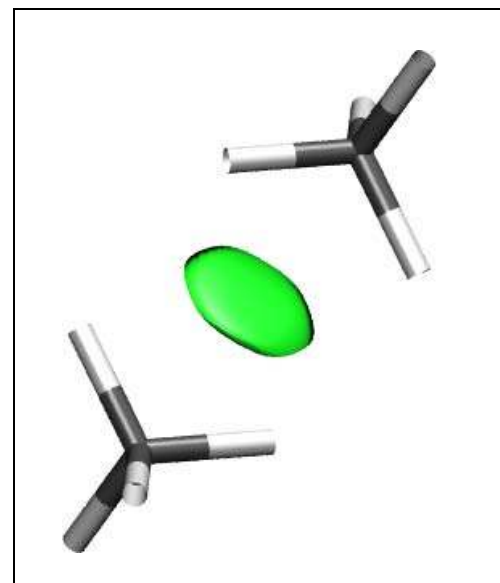
# INTERACTIONS IN REAL SPACE

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

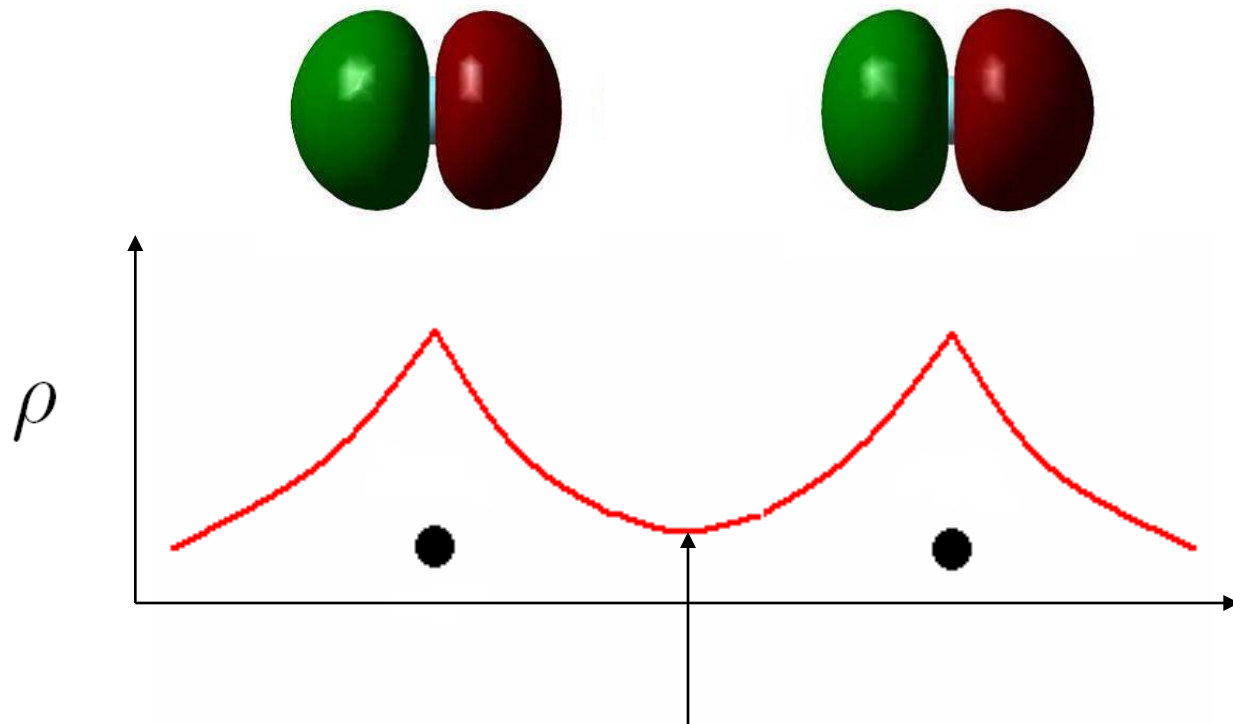
Covalent bonds: easy to represent



Dispersion?



# INTERACTIONS IN REAL SPACE



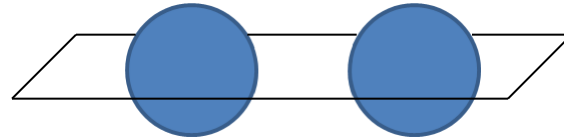
$$\rho > 0 \quad \text{and} \quad s = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla \rho|}{\rho^{4/3}} \longrightarrow 0$$

# INTERACTIONS IN REAL SPACE

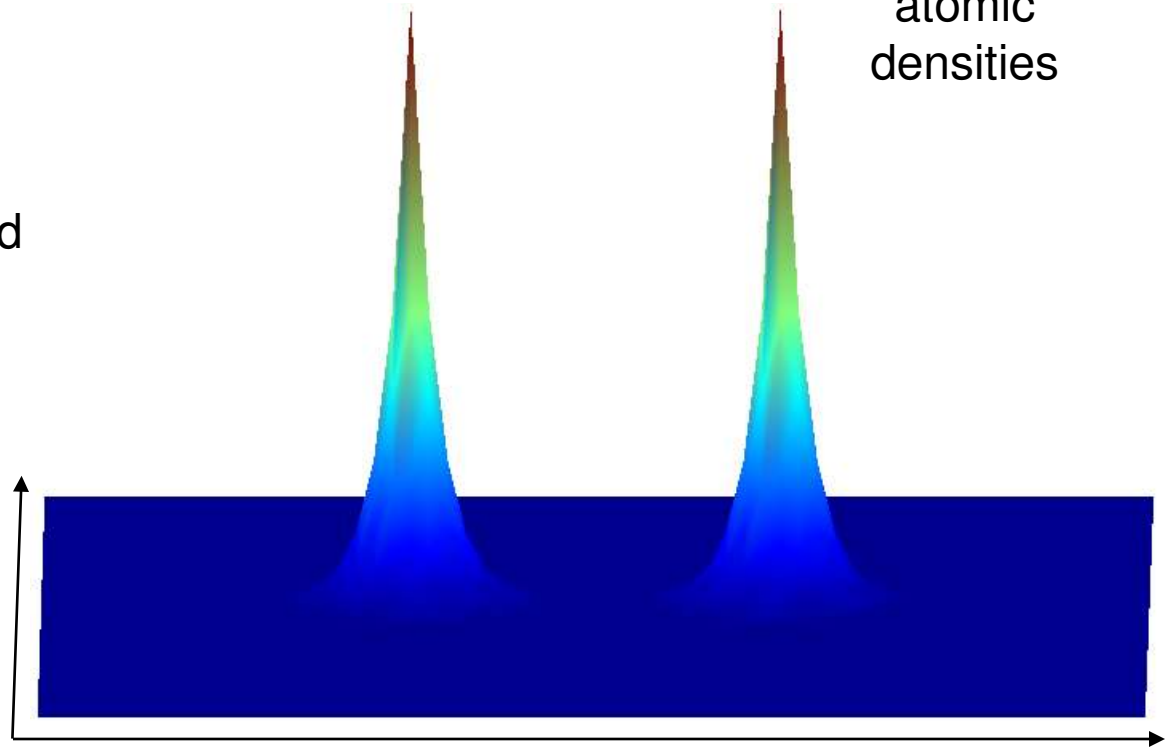
At all grid points, evaluate and plot

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

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

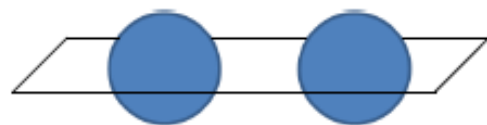


Simple DFT or  
atomic  
densities

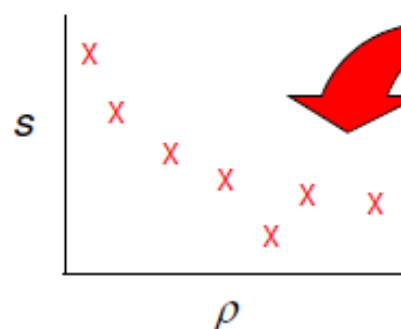


# NCI

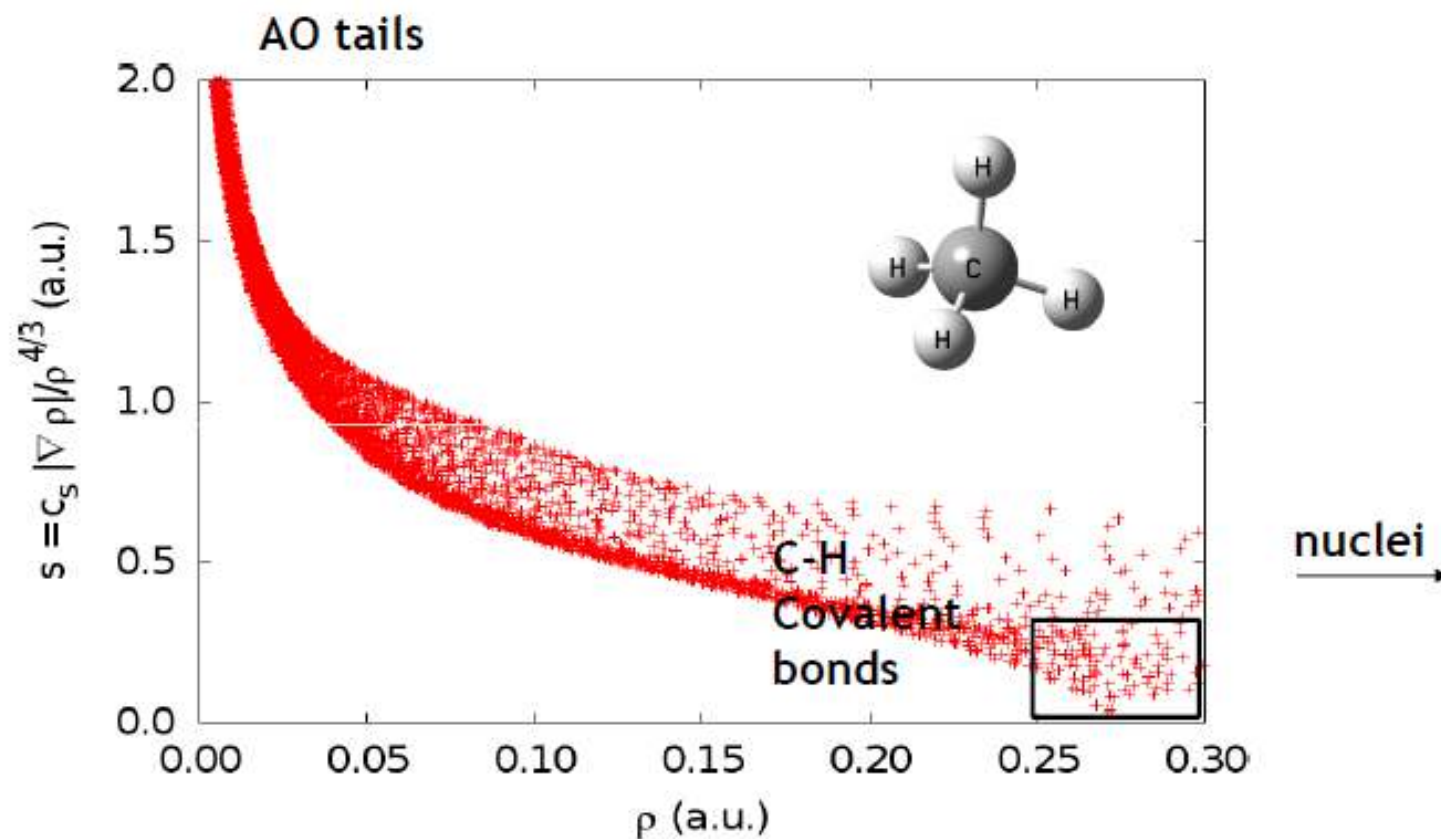
At all grid points, evaluate and plot



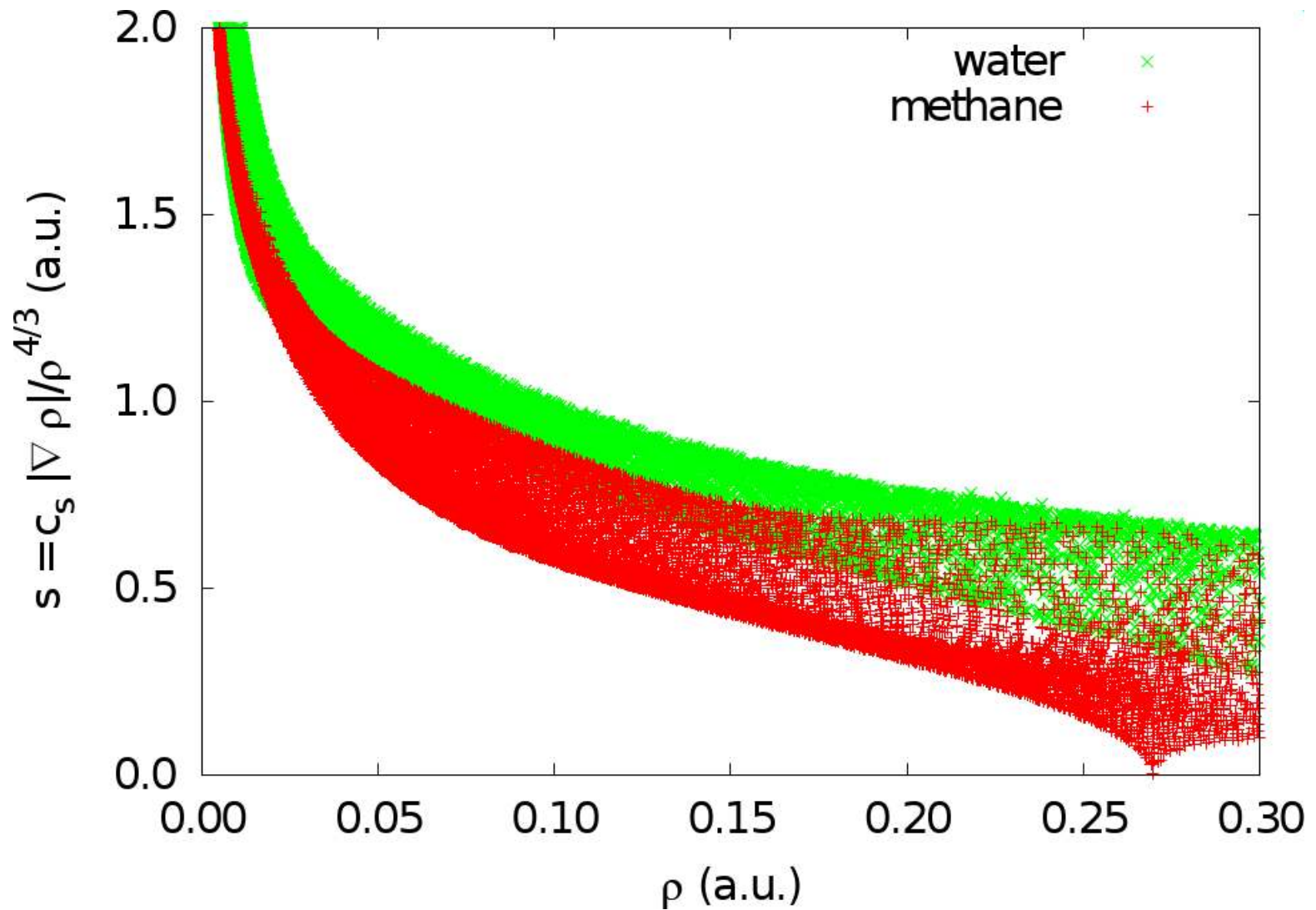
$$s(\rho(r))$$



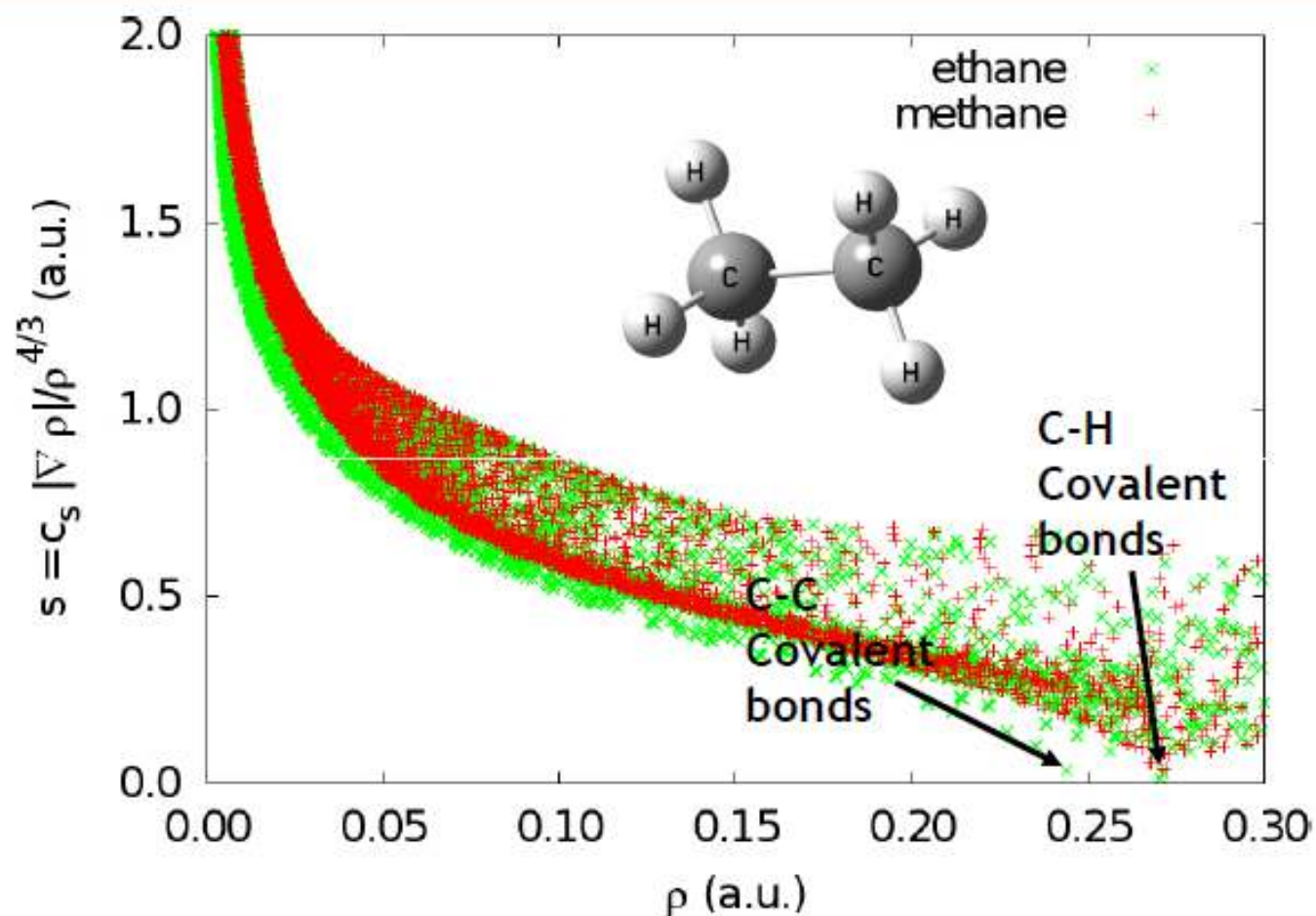
# NCI



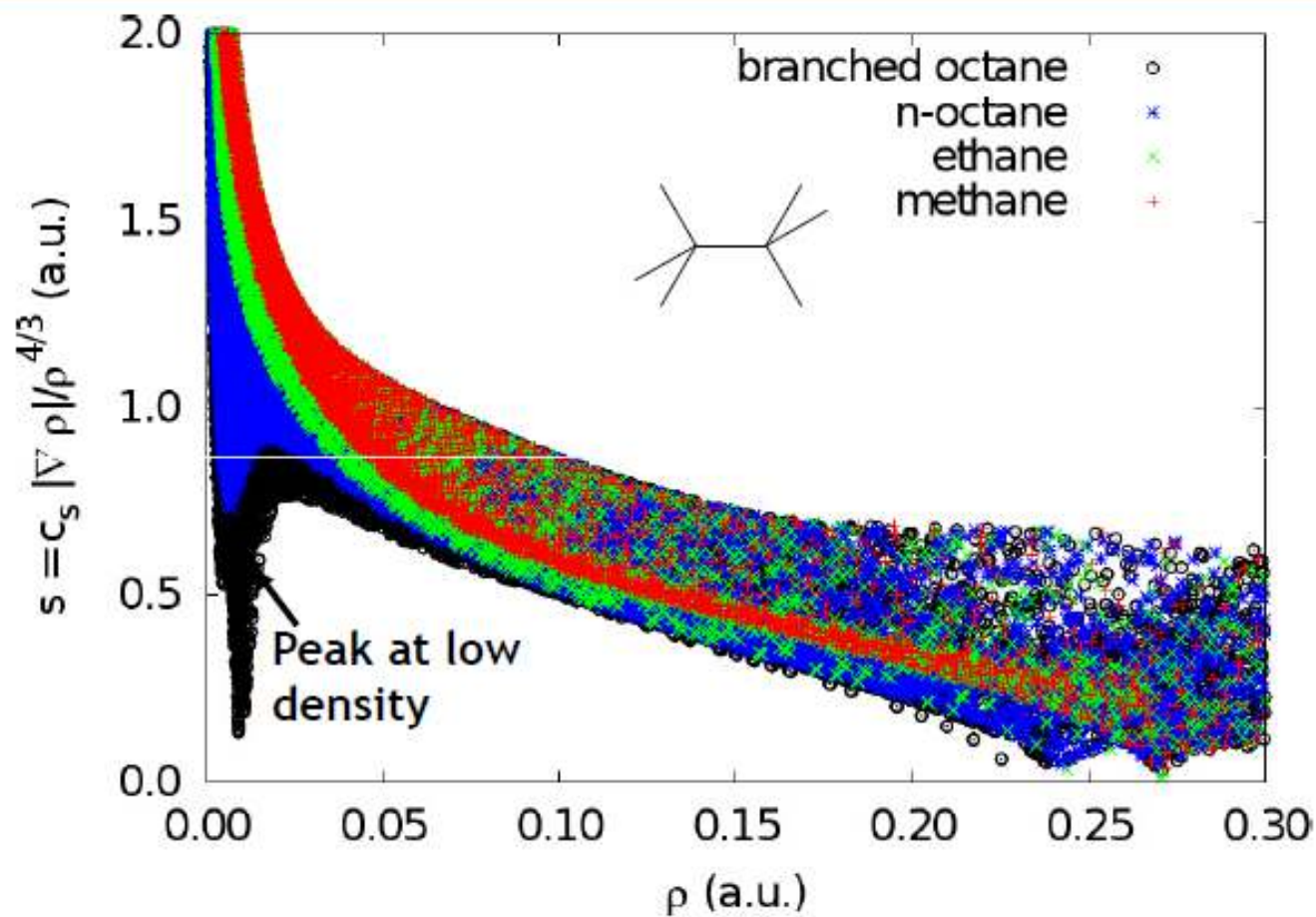
# INTERACTIONS IN REAL SPACE



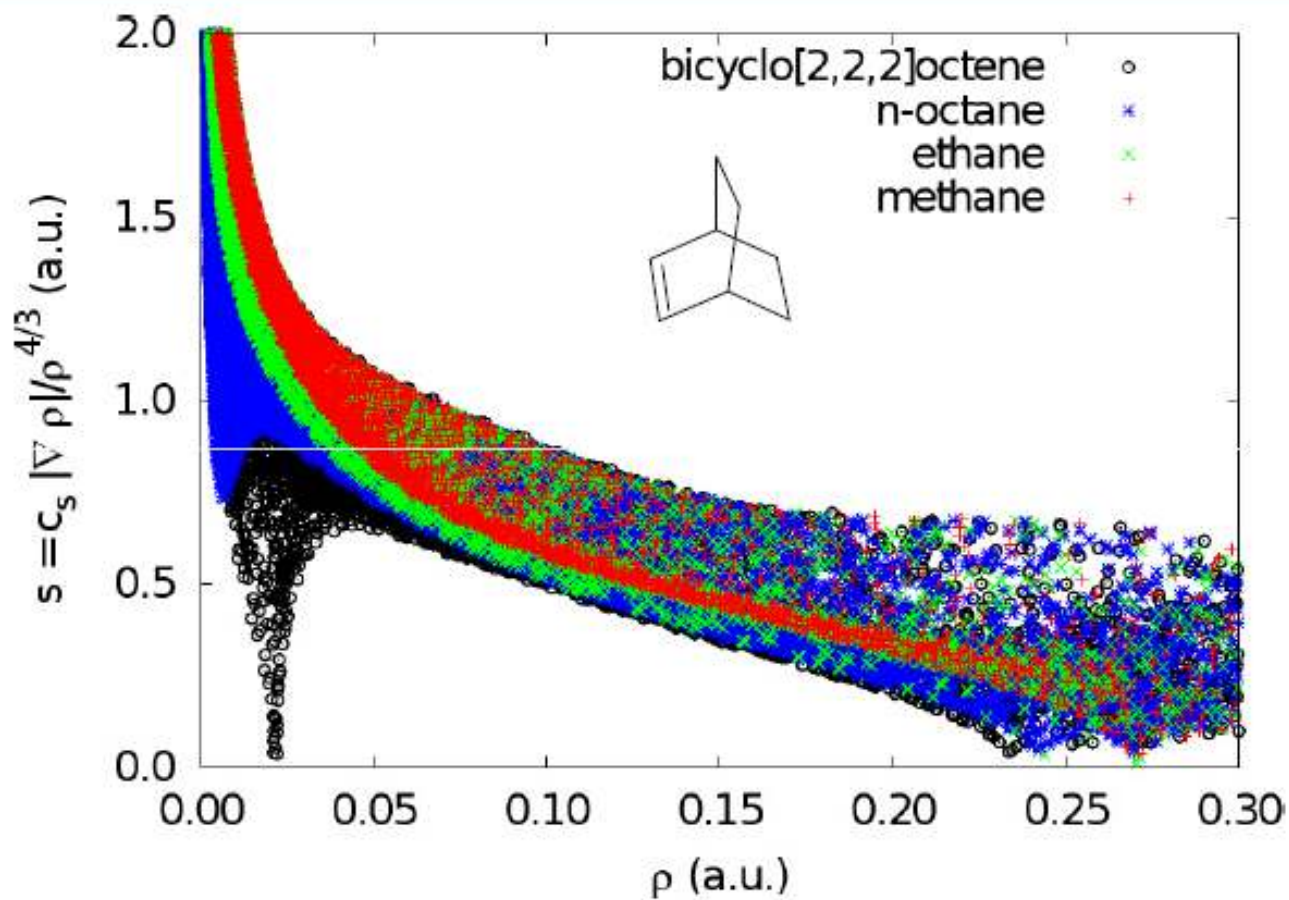
# NCI



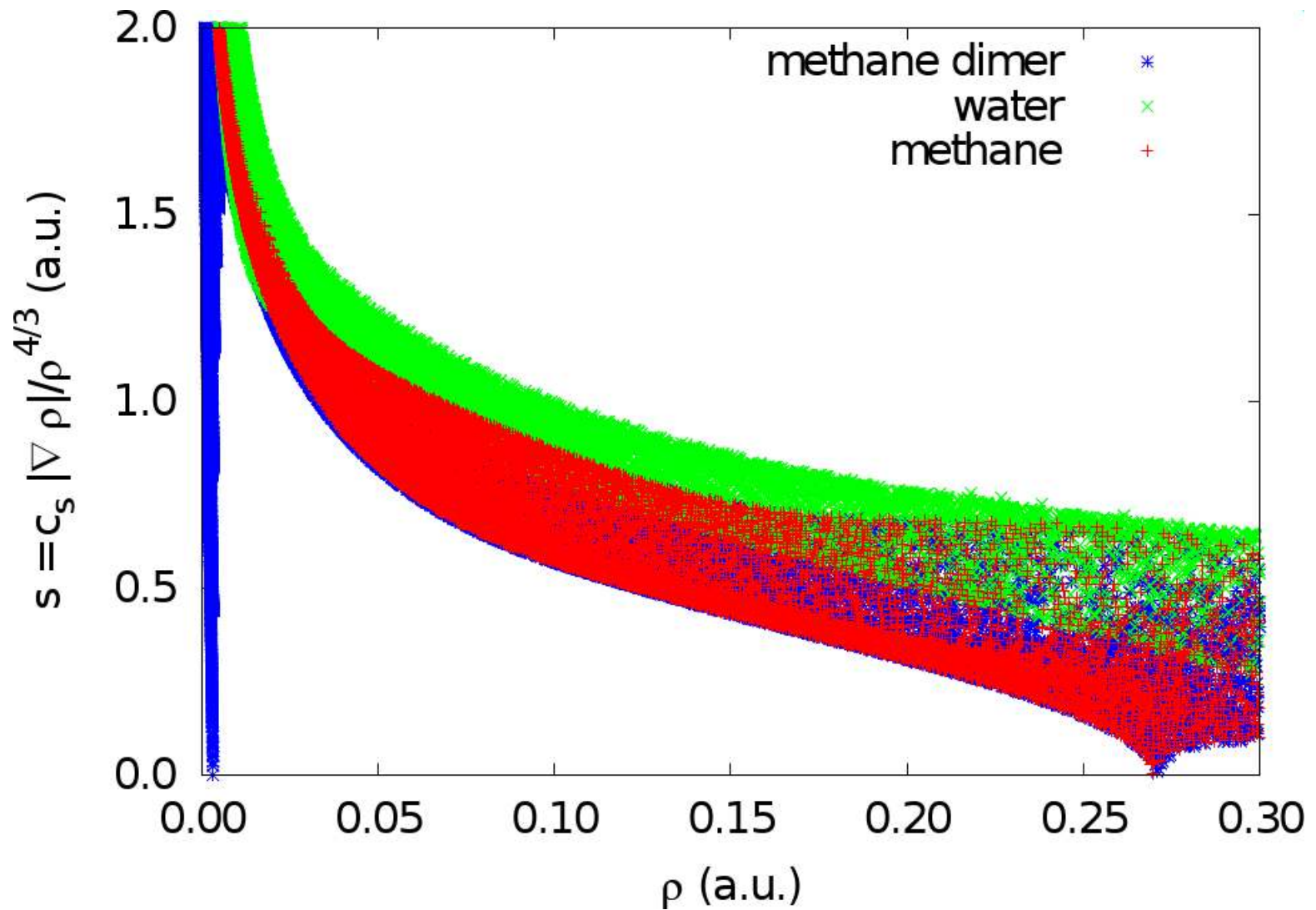
# NCI



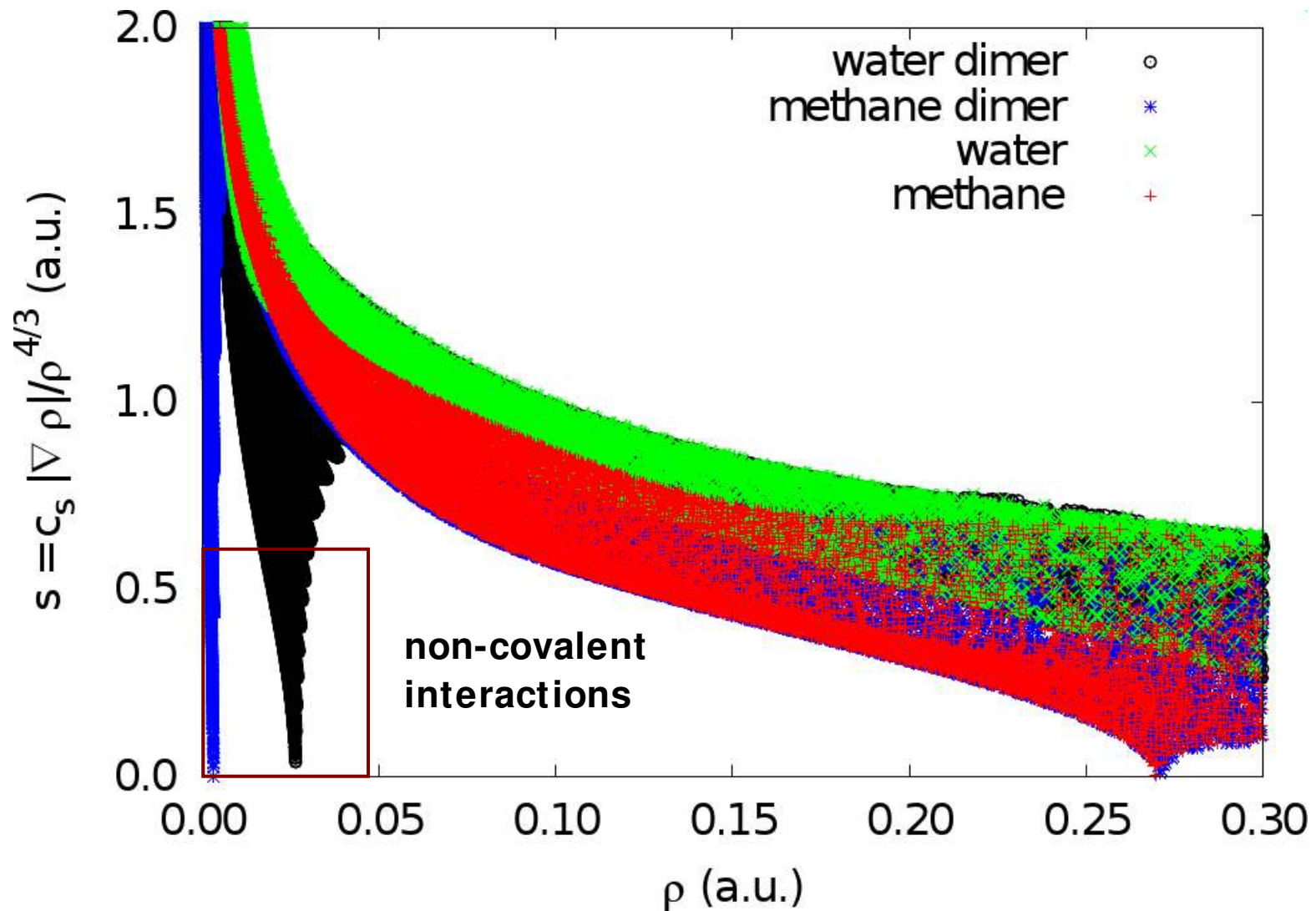
# NON-COVALENT INTERACTIONS



# INTERACTIONS IN REAL SPACE



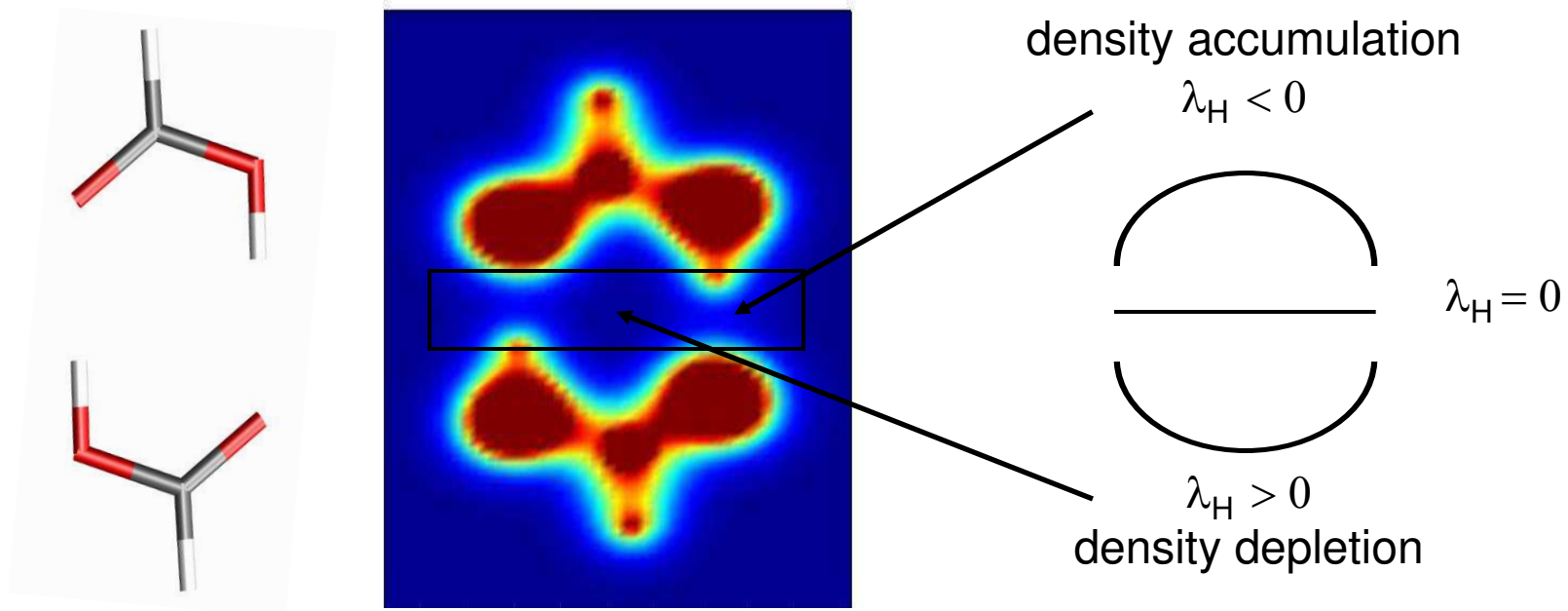
# INTERACTIONS IN REAL SPACE



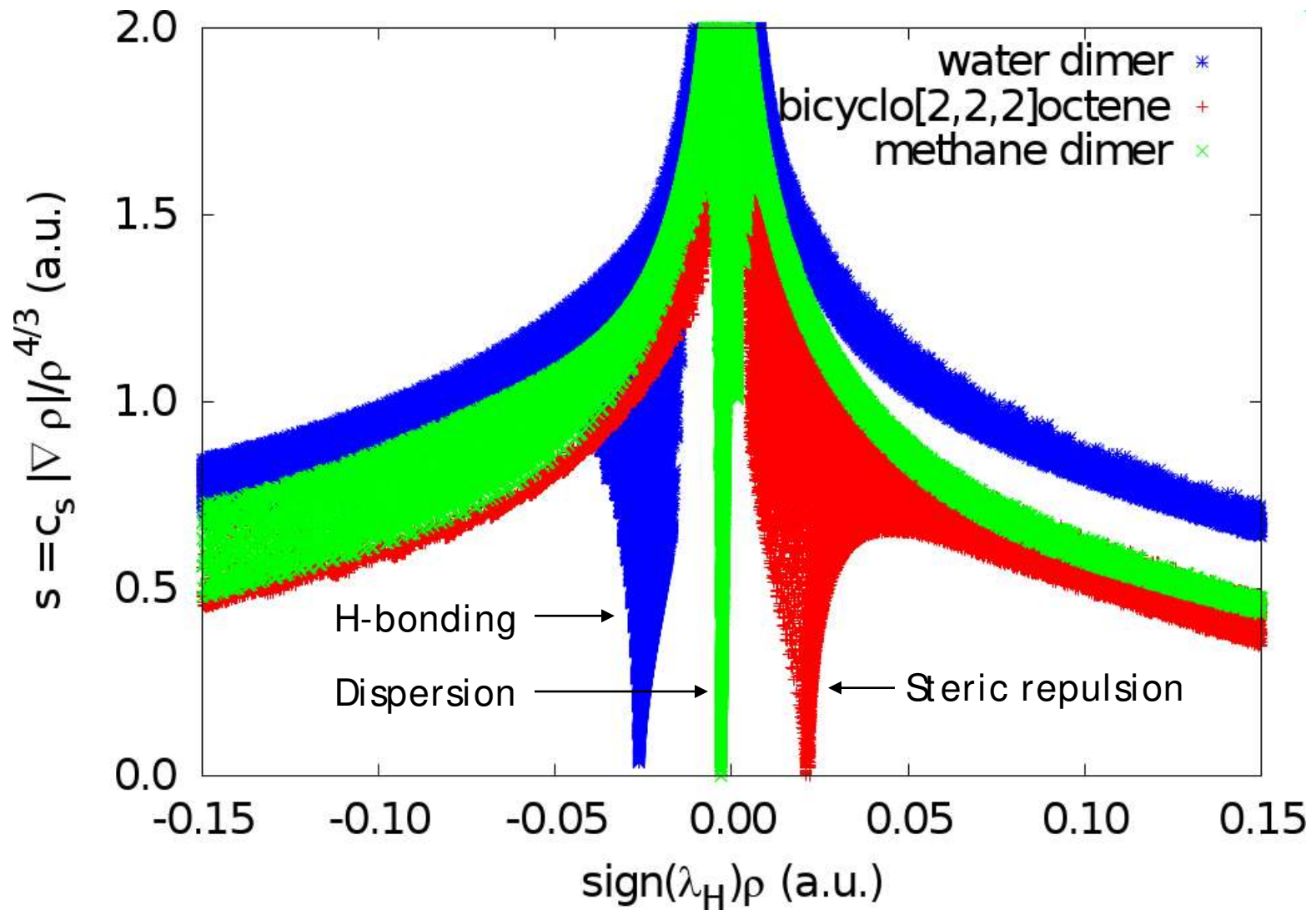
# INTERACTIONS IN REAL SPACE

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

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

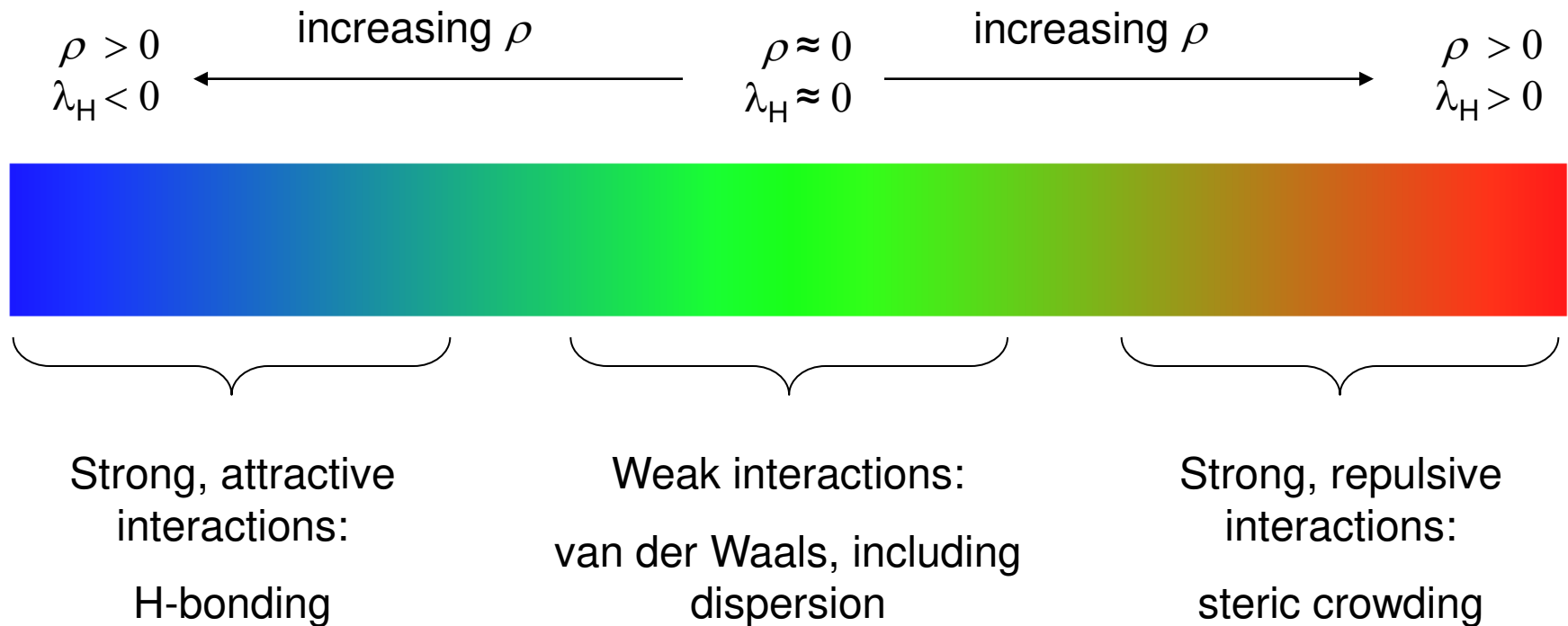


# INTERACTIONS IN REAL SPACE



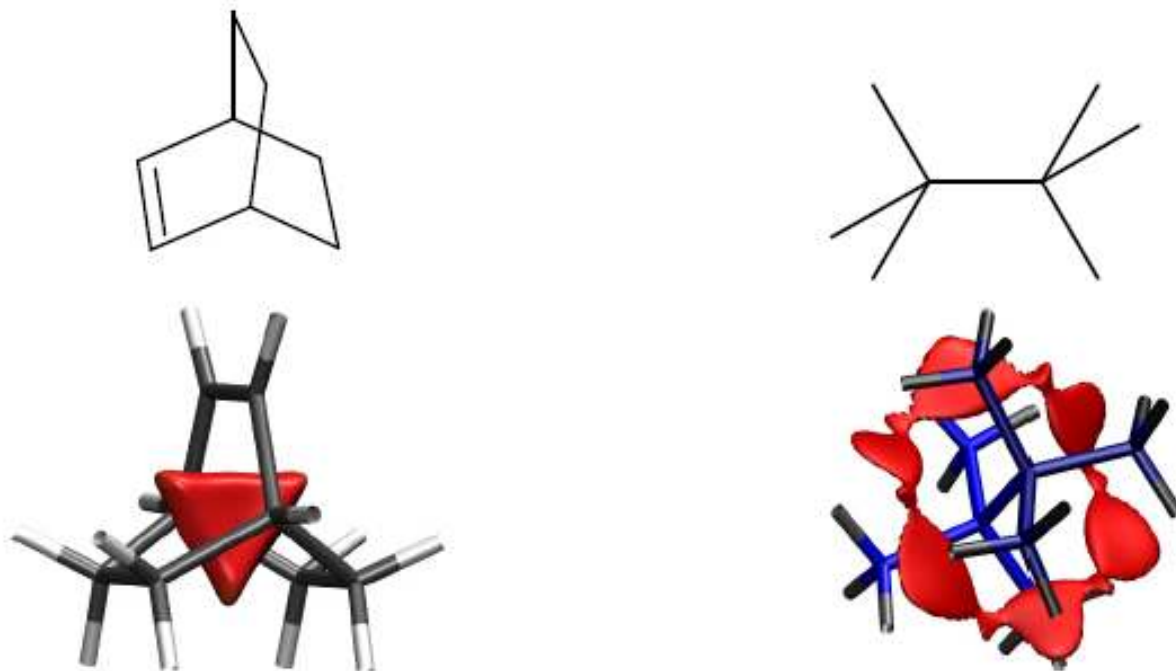
# INTERACTIONS IN REAL SPACE

Plot gradient isosurfaces in real space and colour by  $\text{sign}(\lambda_H)\rho$



# NCI

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

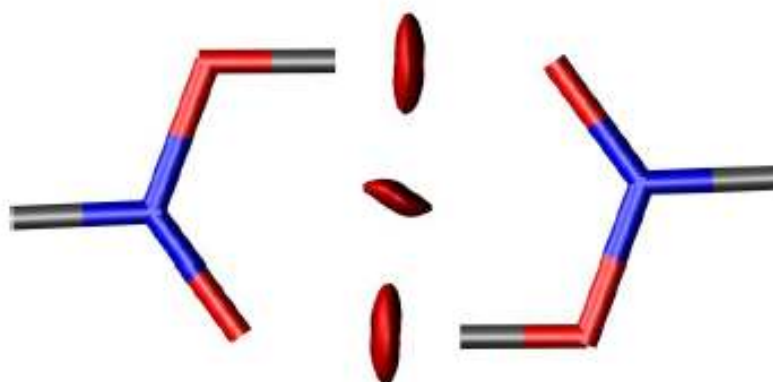


Regions of steric clash!

- Hydrogen bonds



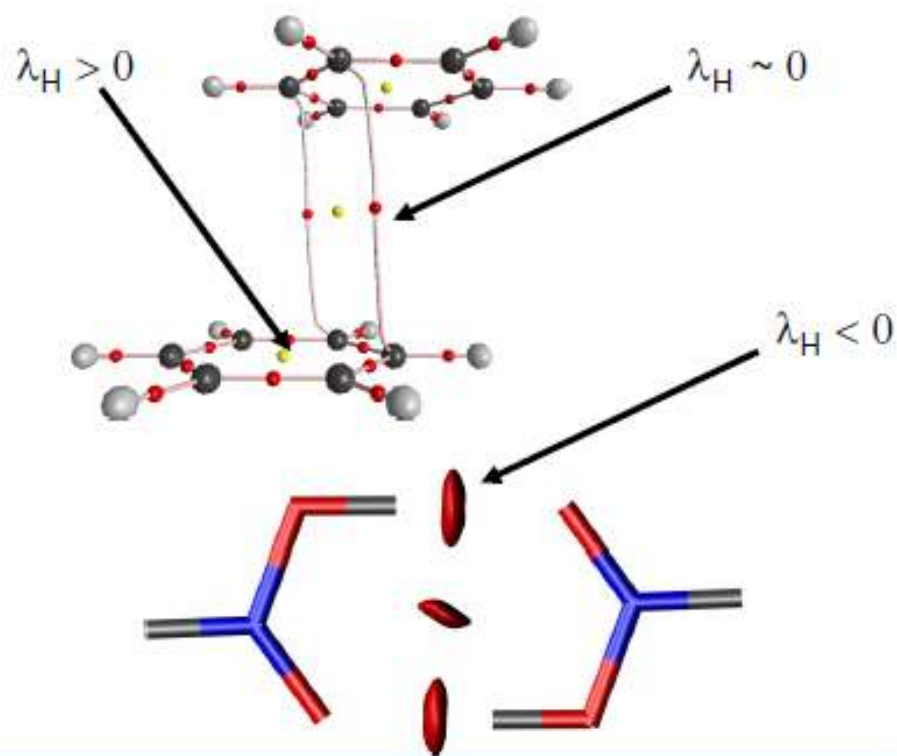
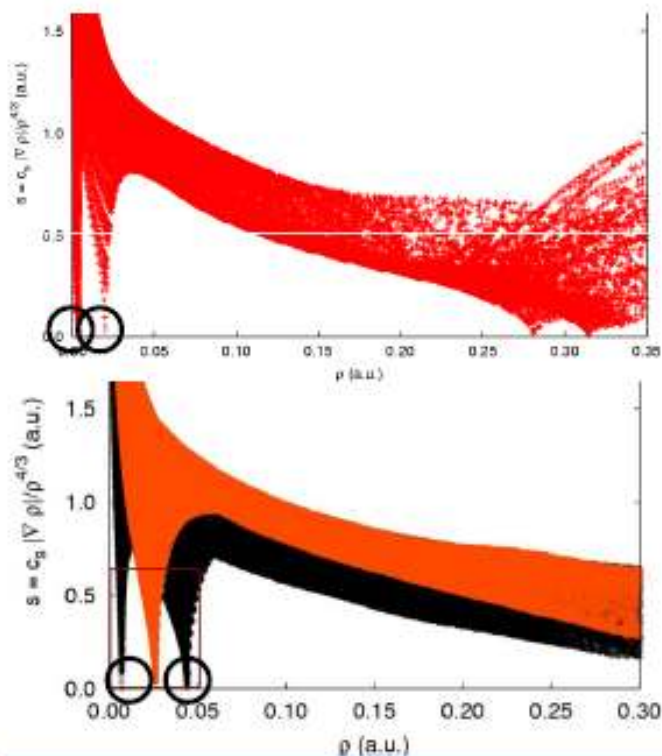
Water dimer



Formic acid dimer

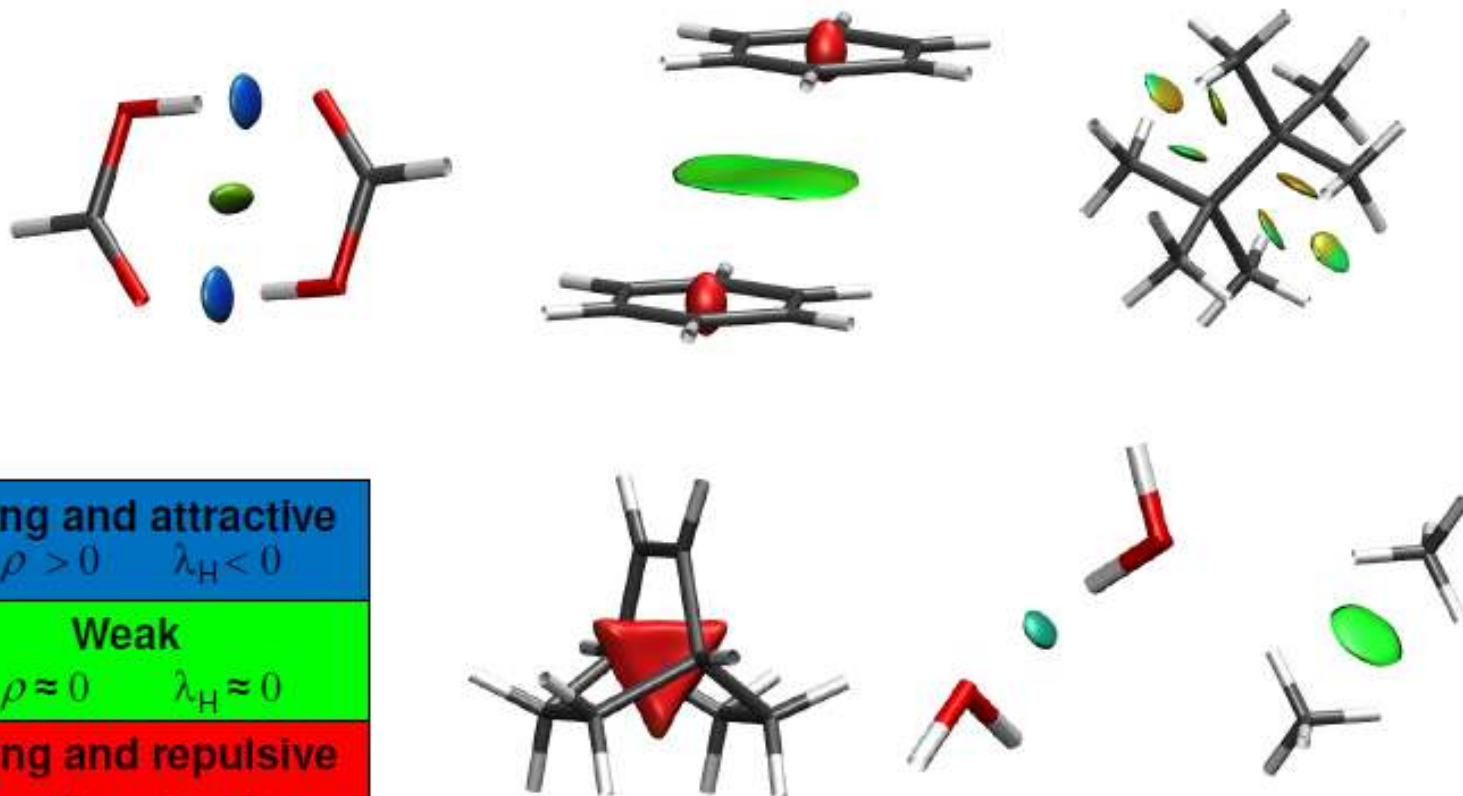
# NCI

- 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  $\text{sign}(\lambda_H) \times \rho$



**Strong and attractive**

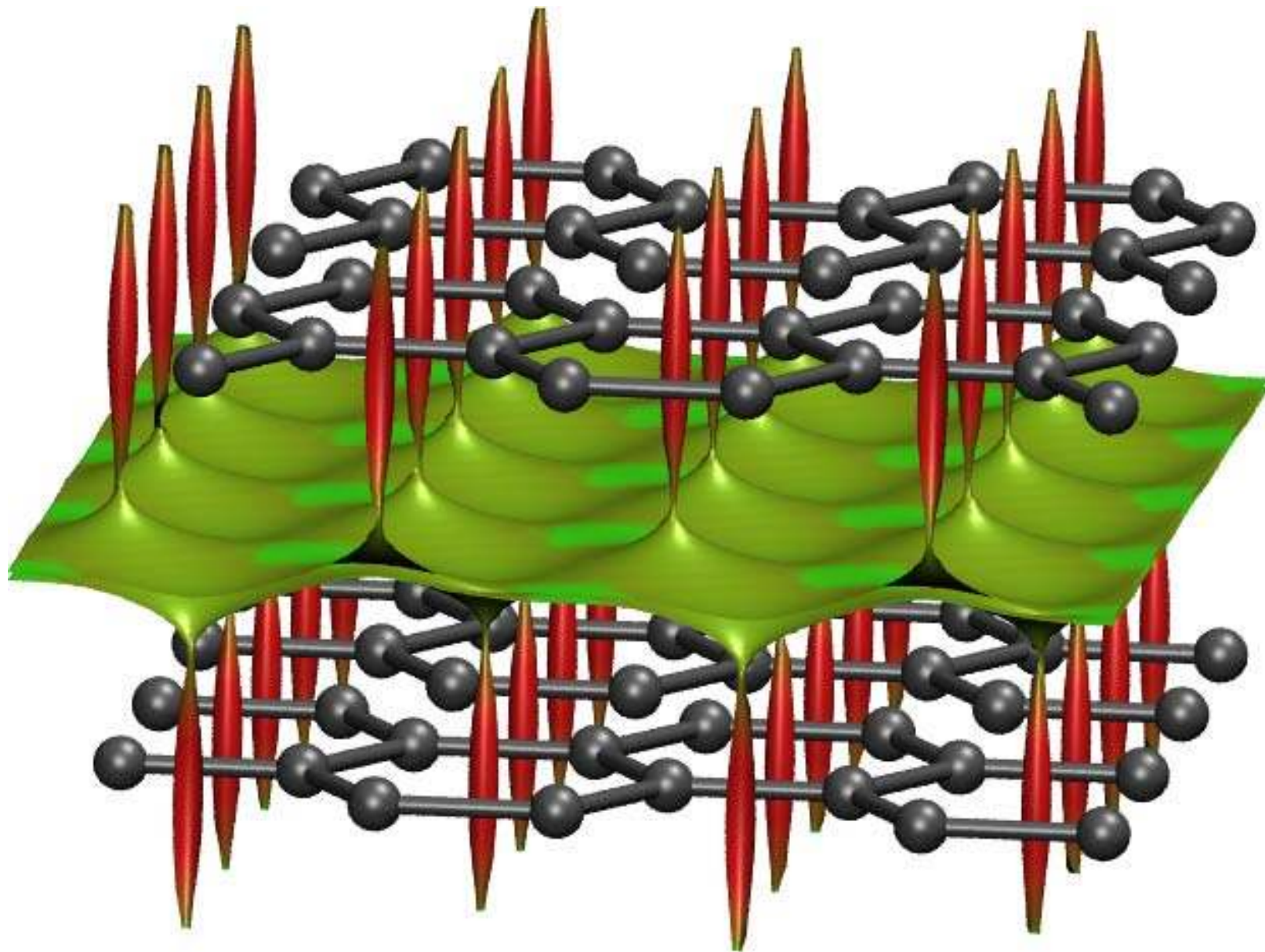
$$\rho > 0 \quad \lambda_H < 0$$

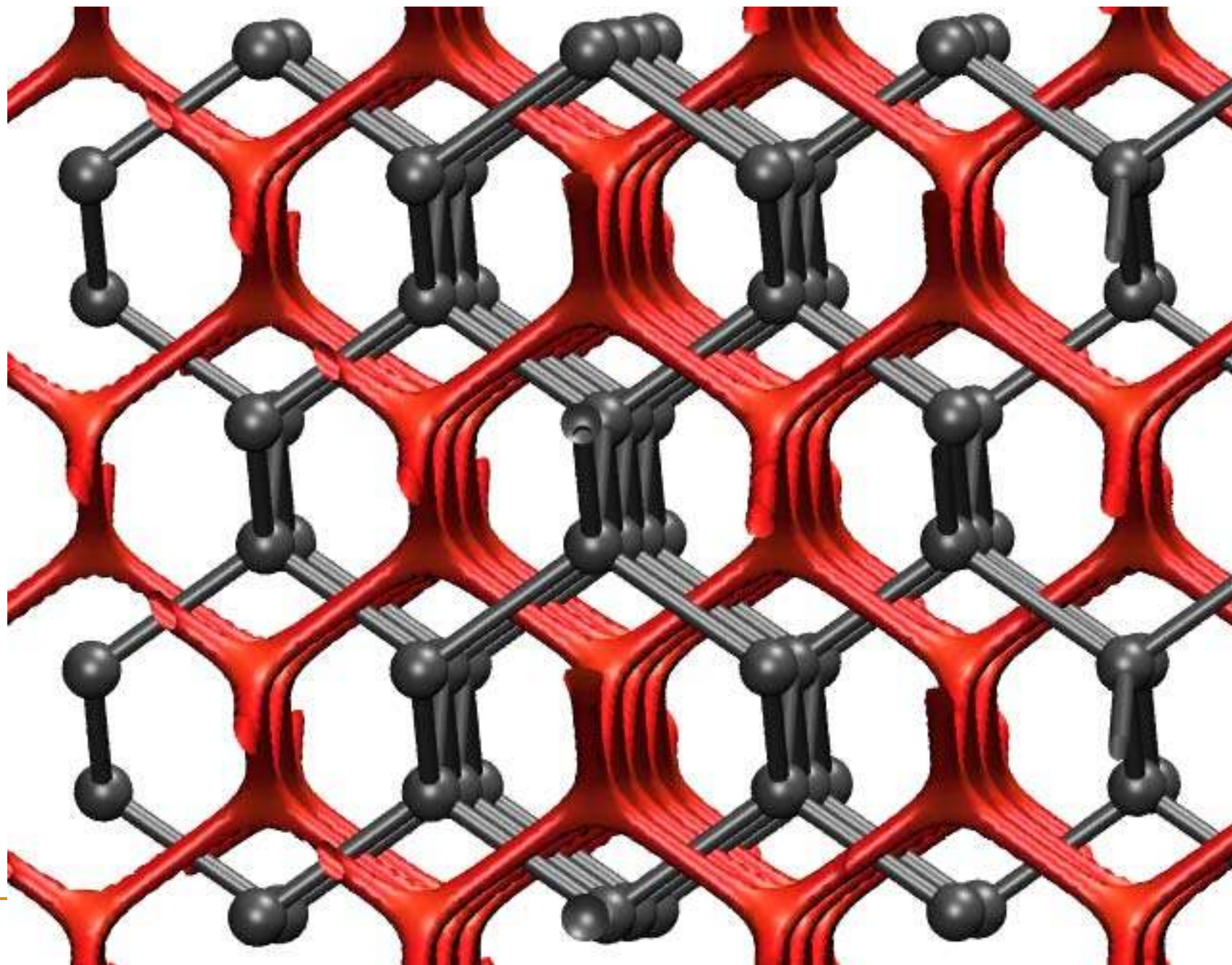
**Weak**

$$\rho \approx 0 \quad \lambda_H \approx 0$$

**Strong and repulsive**

$$\rho > 0 \quad \lambda_H > 0$$





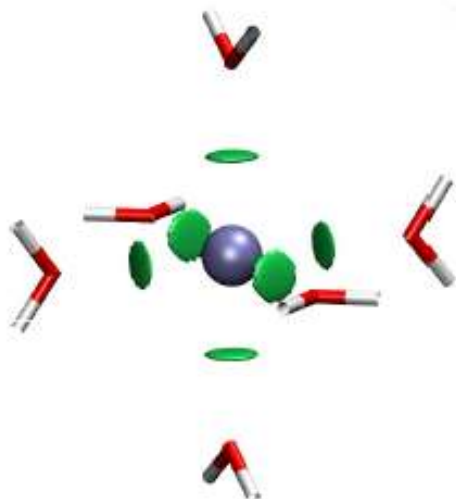
Low-density, low-gradient isosurfaces reveal non-covalent interactions.

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

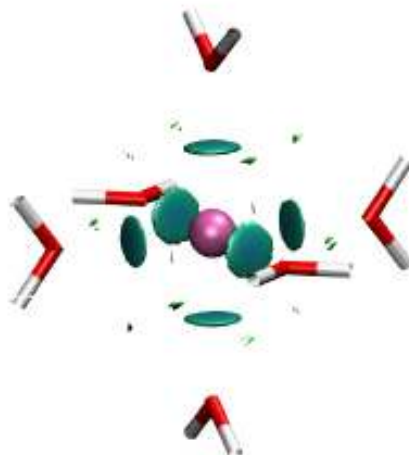
This offers exciting possibilities for

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

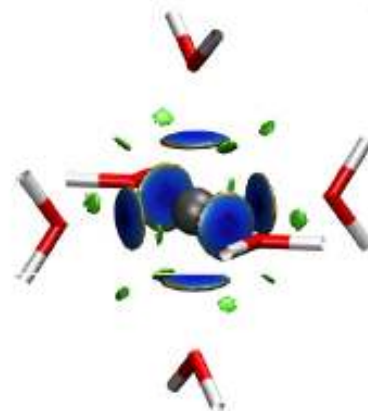
# METALLIC HYDRATES



$K^+$



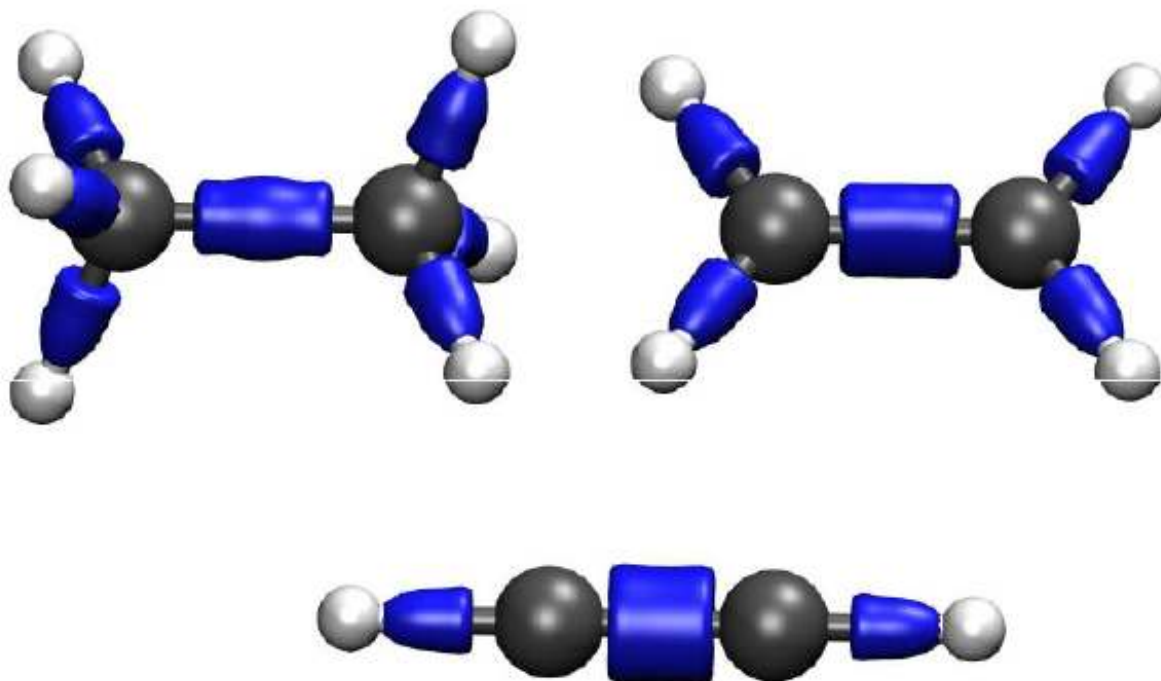
$Ca^{2+}$



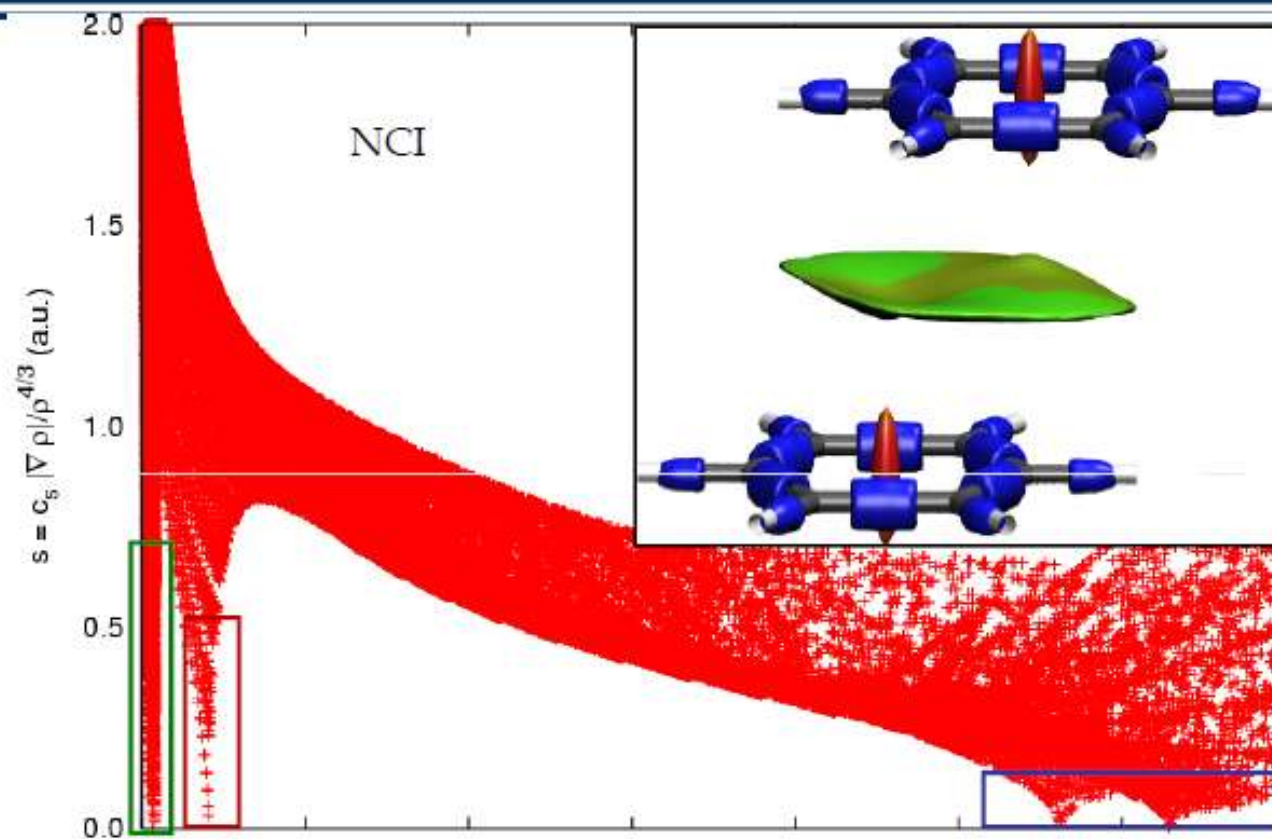
$Zn^{2+}$

## Covalent Bonds seen at higher densities

NCI



# COMPARISON W/ OTHER BONDING THEORIES



Covalent bonds

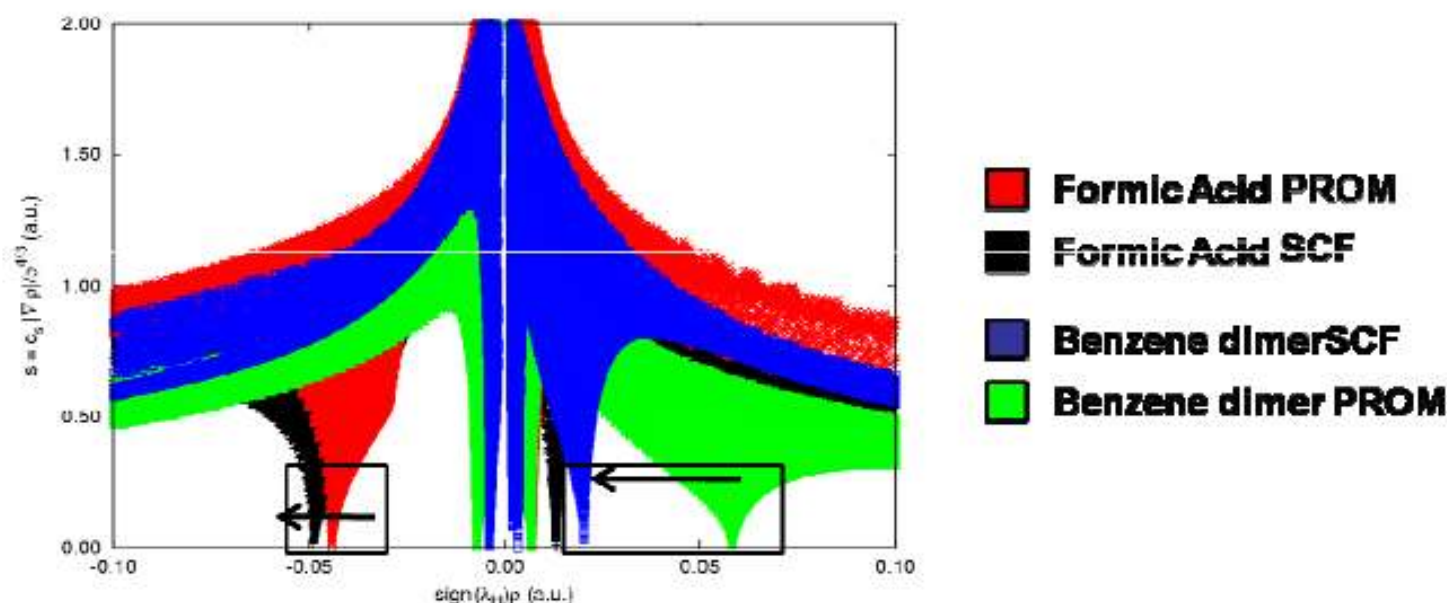
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Web, Jmol, blog  
VMD

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# BIOMOLECULES

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



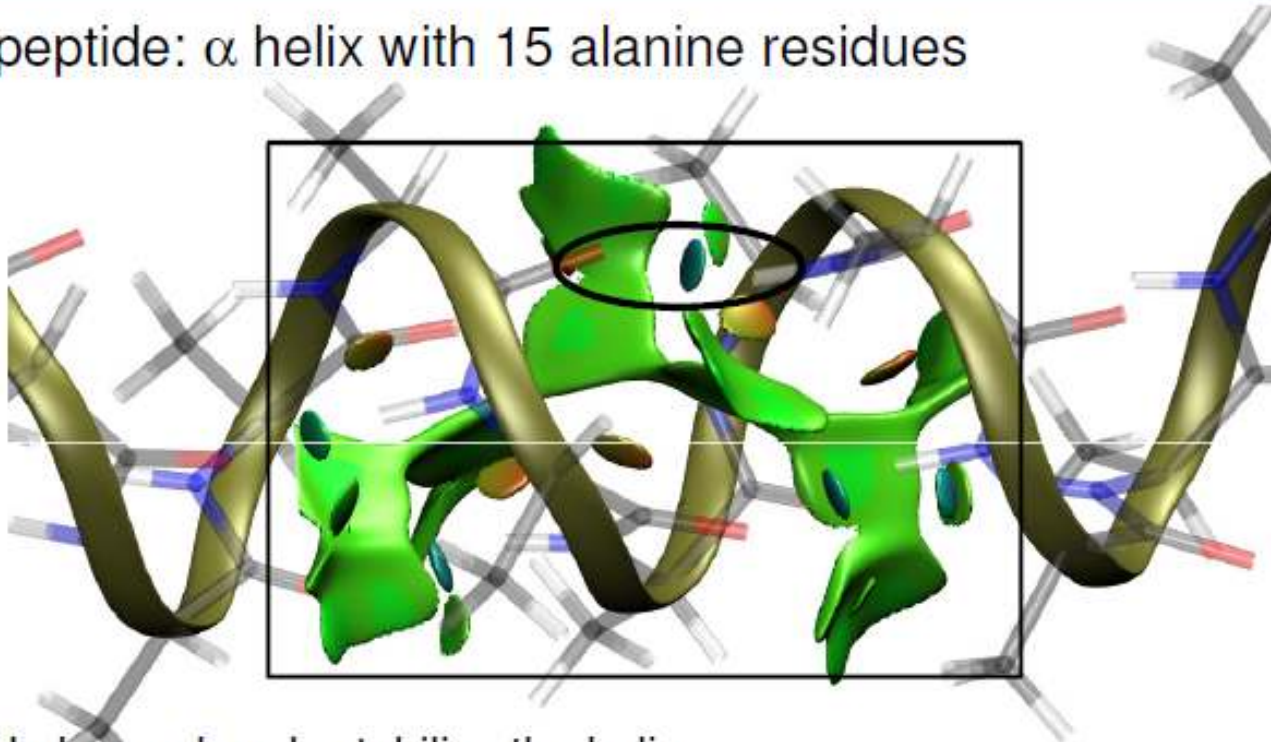
- It only requires atomic coordinates as input
- very fast calculation; applicable to large systems

Use promolecular densities

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

# BIOMOLECULES

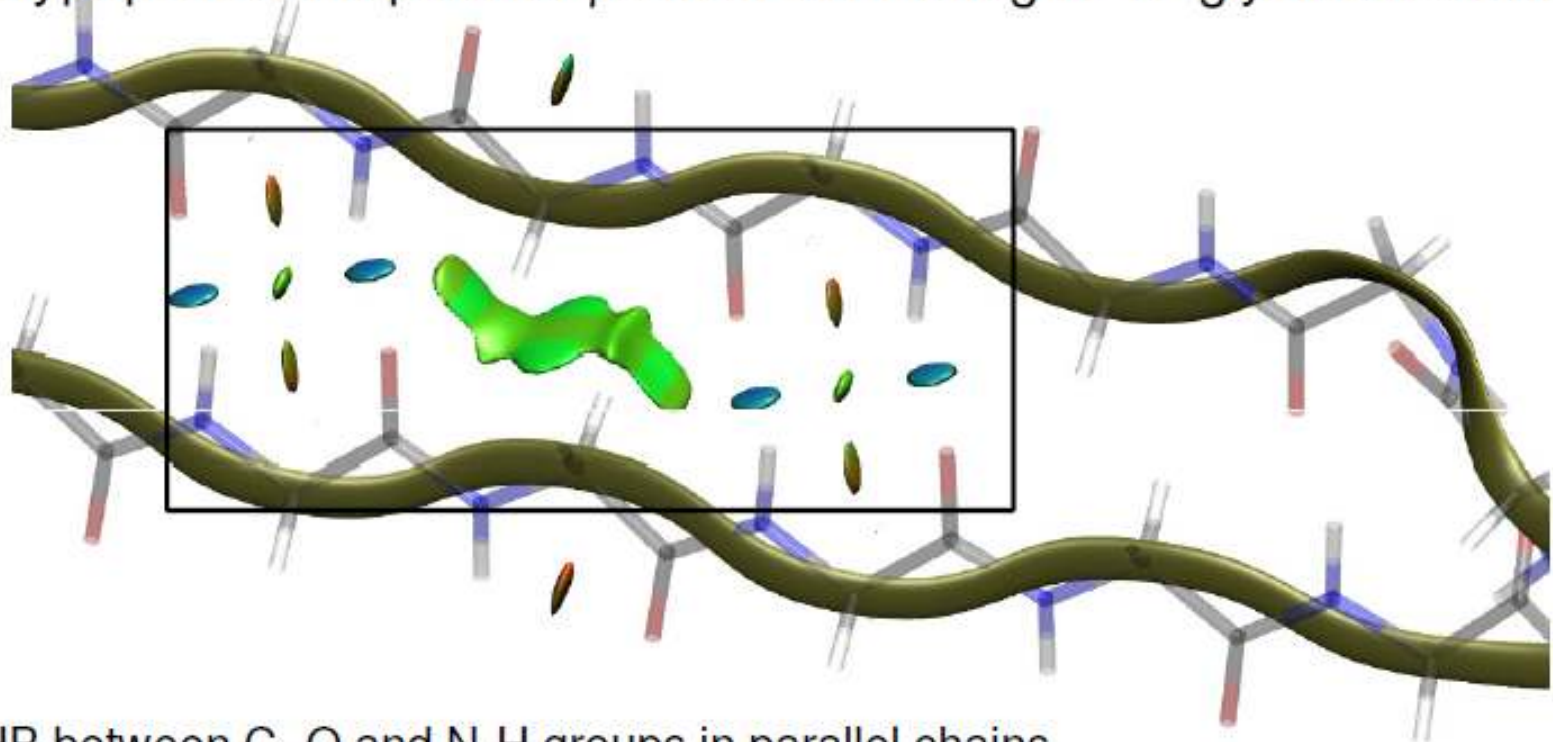
Poliptide:  $\alpha$  helix with 15 alanine residues



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

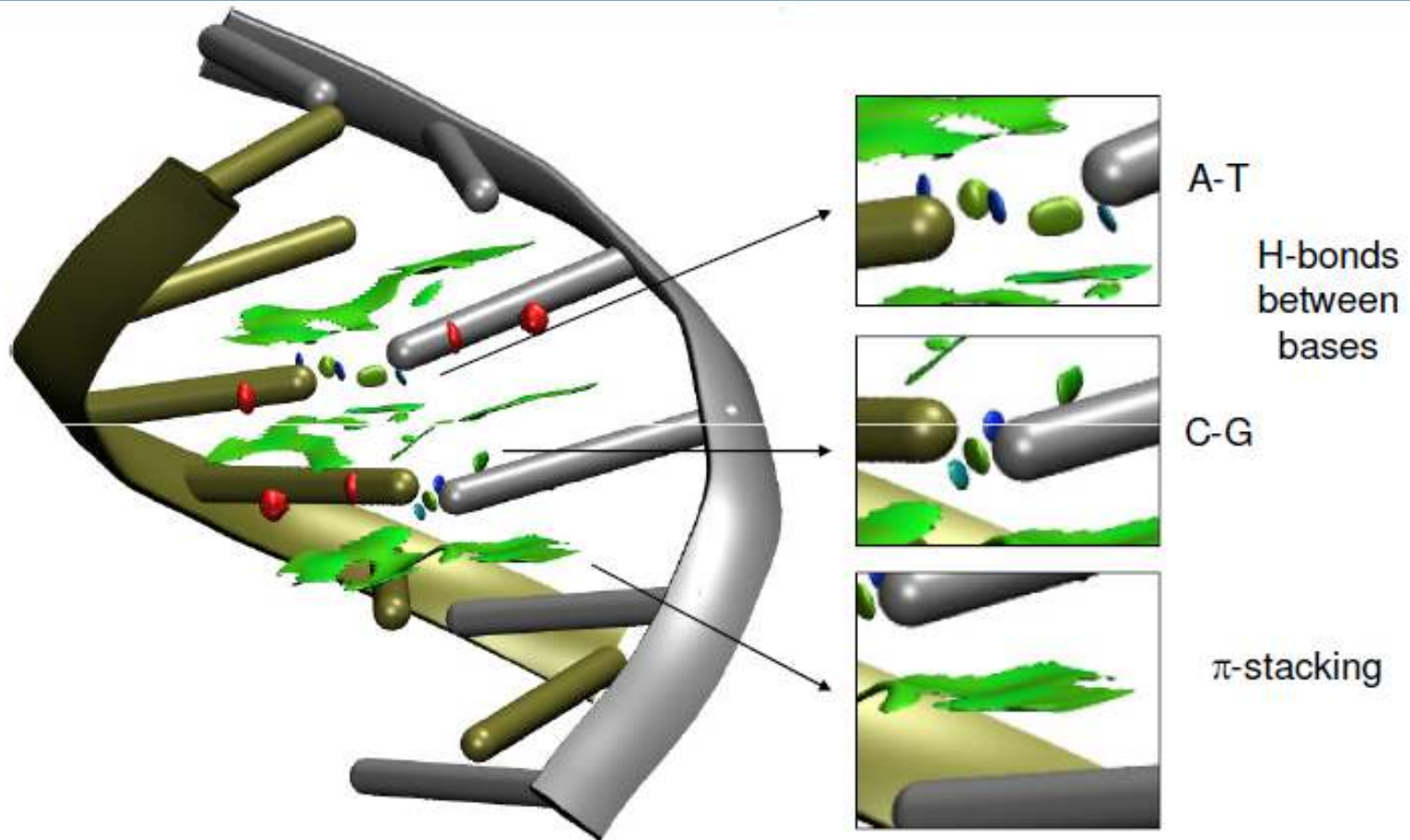
# BIOMOLECULES

polypeptide: anti-parallel  $\beta$ -sheet consisting of 17 glycine residues

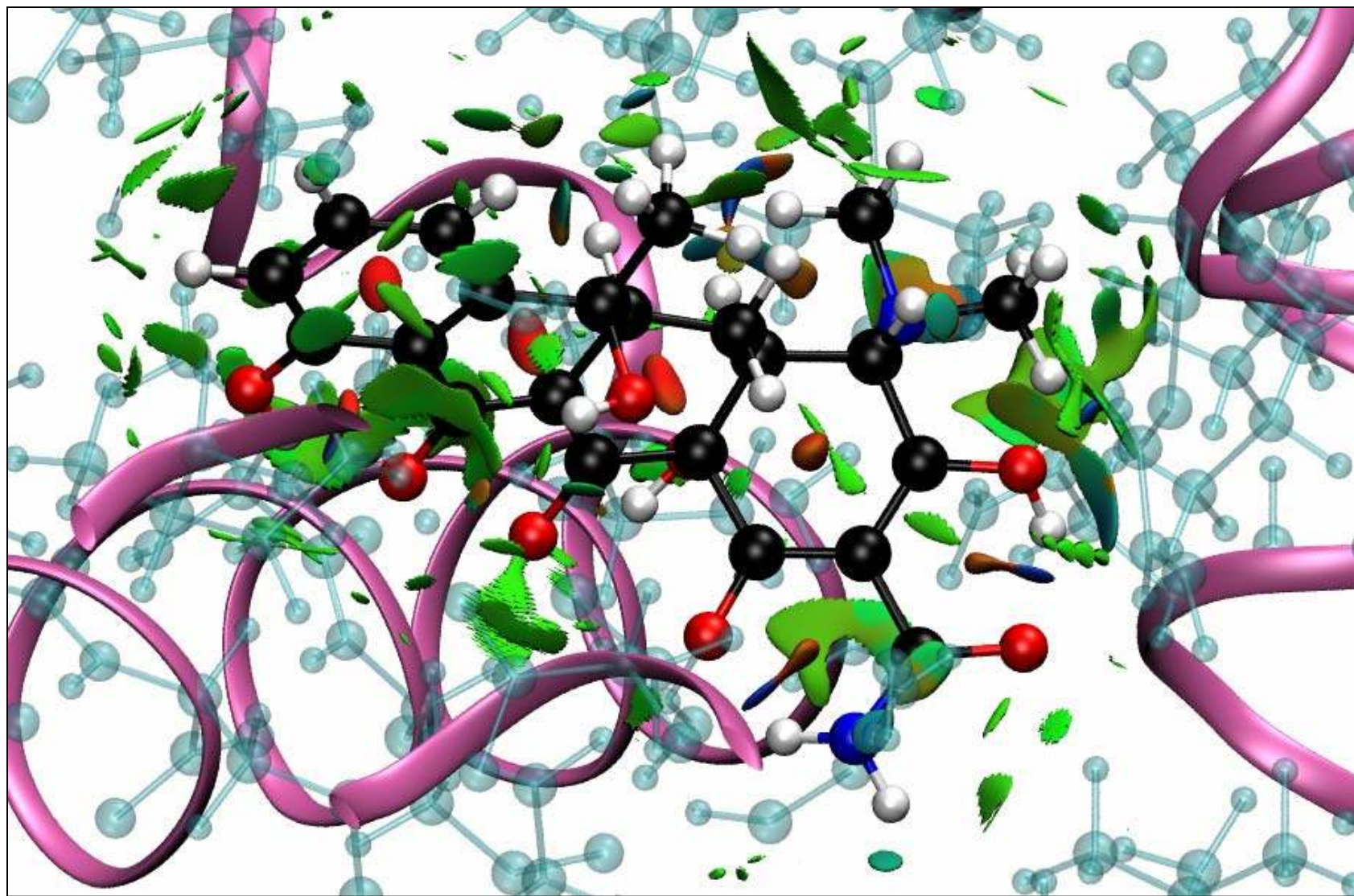


- HB between C=O and N-H groups in parallel chains
- van der Waals interactions between  $\text{CH}_3$  groups

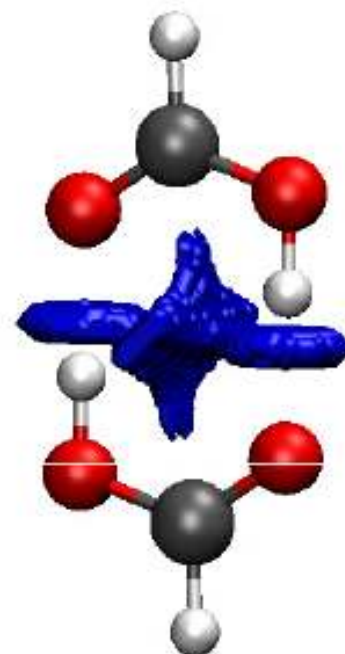
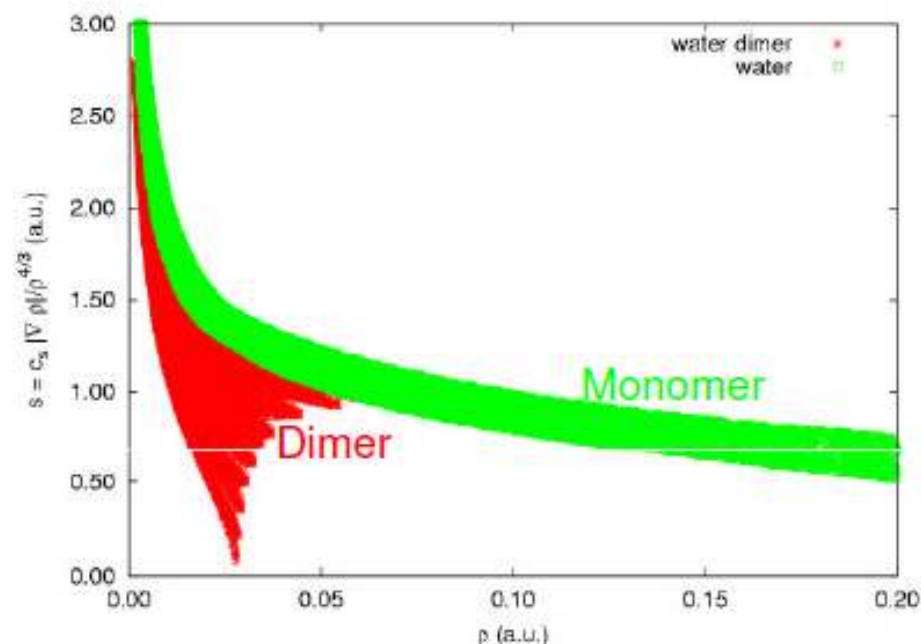
# BIOMOLECULES



# Small molecules interacting with protein

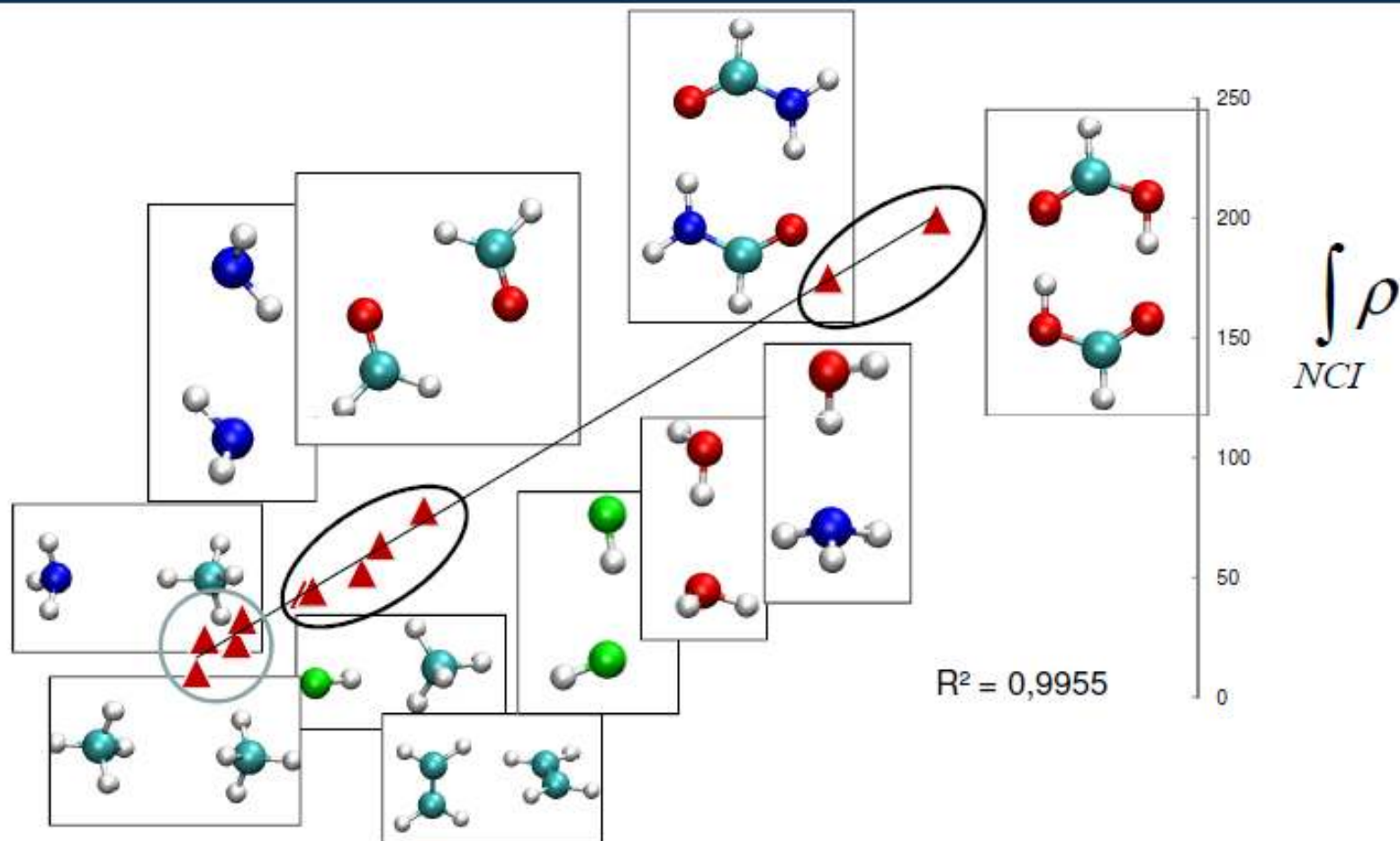


# ENERGETICS



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.htm>