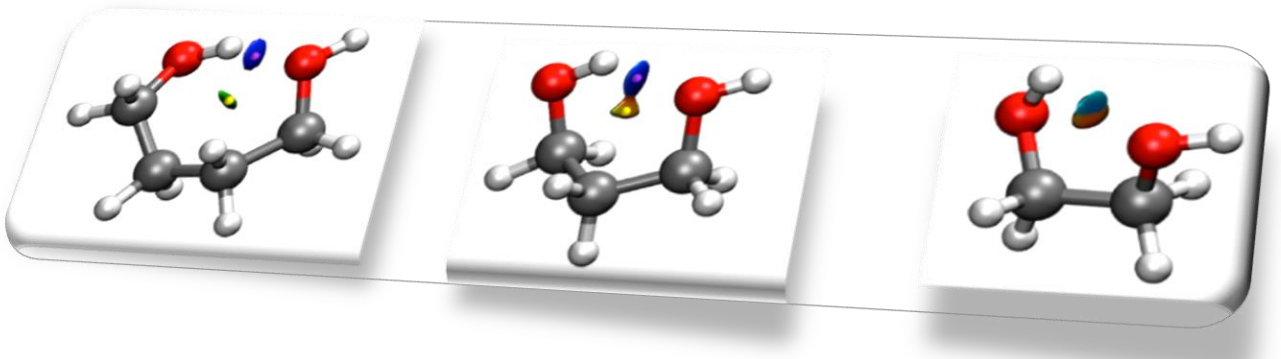
Non covalent interactions

Real space point of view



Julia Contreras García &

Peter Reinhardt

CNRS/Sorbonne Université

Outline

- Why are we still studying NCIs?
- QTAIM (Quantum Theory of Atoms in Molecules)
  - Critical points
  - Integrals
- NCI (Non covalent interaction index)
  - Definition
  - NCI vs AIM
  - Big systems
- Summary

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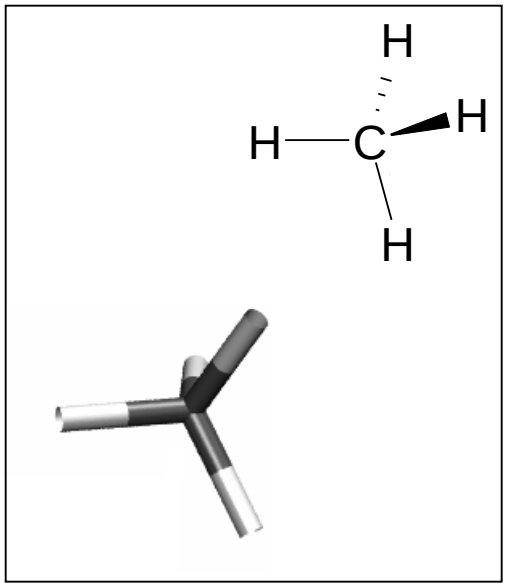
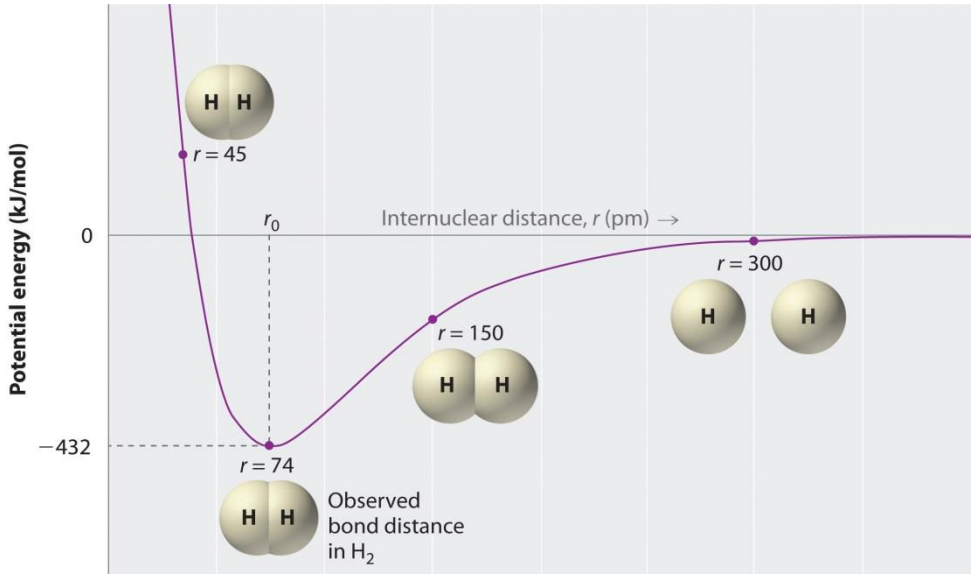
Motivation

Covalent bonds: easy to represent

Why?



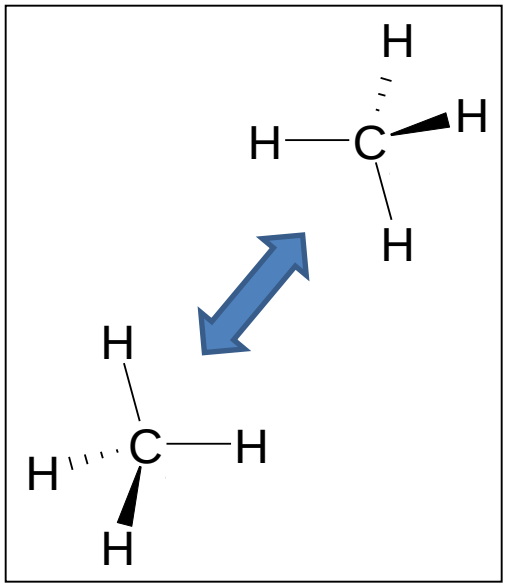


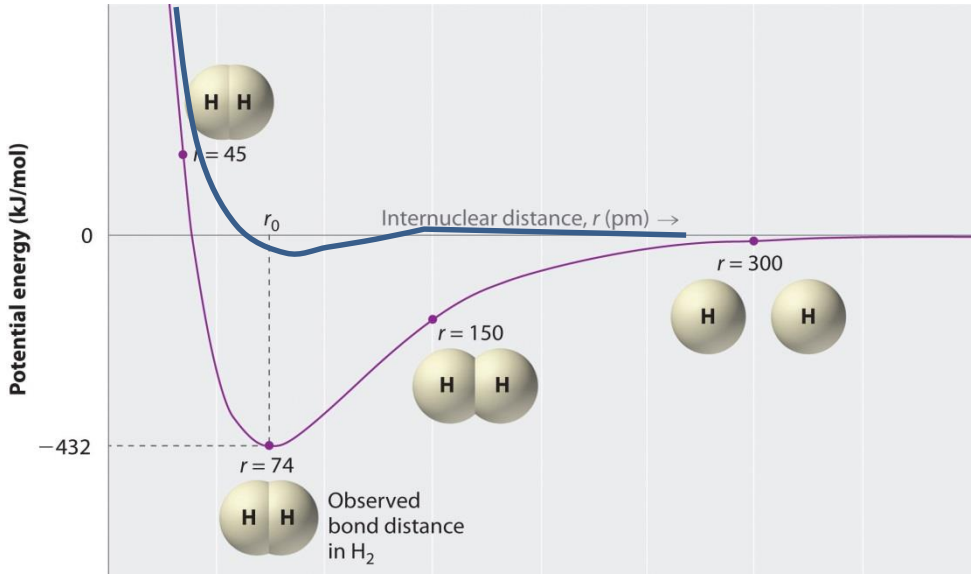
- The binding energy well is very steep
- Easy to parametrize

Motivation

Covalent bonds: easy to represent

Why?

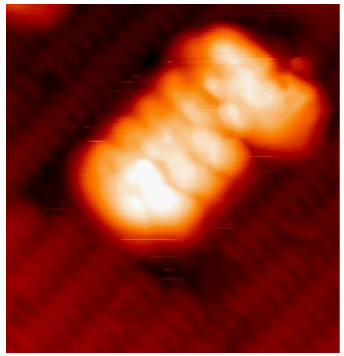




- The binding energy well is shallow (much more non local too!)
  - Less directional
  - Interactions between many atoms…
- This makes it more difficult to detect, calculate, model, add, …

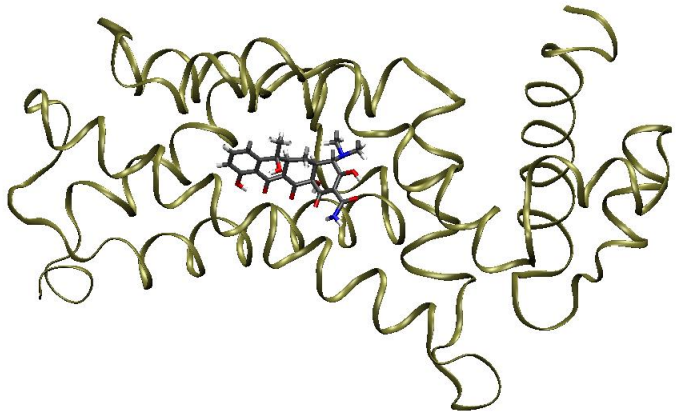
Motivation

Weak interactions are critical for:



- states of matter, water properties, solubility,

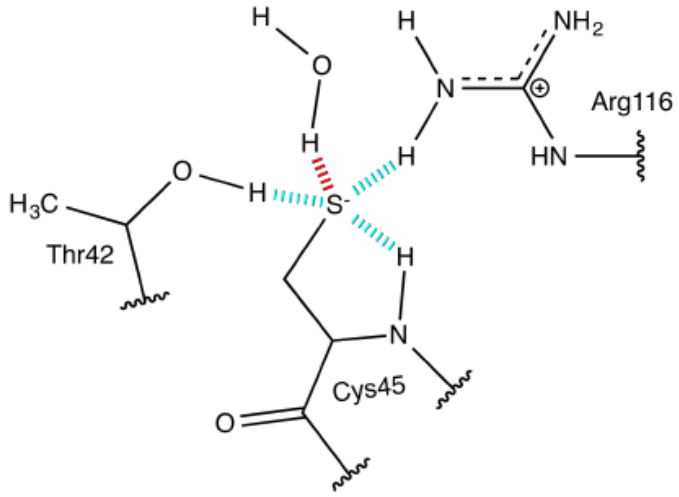
- surface chemistry,
- nano-scale and materials chemistry,
- biological chemistry
  - protein folding,
  - ligand-receptor binding,
  - drug interactions



Motivation

Weak interactions are usually based on geometrical factors: distances, distances+angles

Results can vary a lot, and these determine protonation states, etc



How can we develop a method that adapts to different environments?

Electron density

- Quantum mechanical information in 3D… electron density!
  - ρ(r) is a fundamental property of any electronic system

$$\rho(\vec{r}) = N \int \ldots \int \left|\Psi(\vec{x}_1, \vec{x}_2, \ldots, \vec{x}_N)\right|^2 ds\, d\vec{x}_2 \ldots \vec{x}_N$$

  - ➢ is experimentally accessible
  - ➢ is defined within the exact many-body theory,
  - ➢ is supported by the Hohenberg−Kohn theorem

Electron density

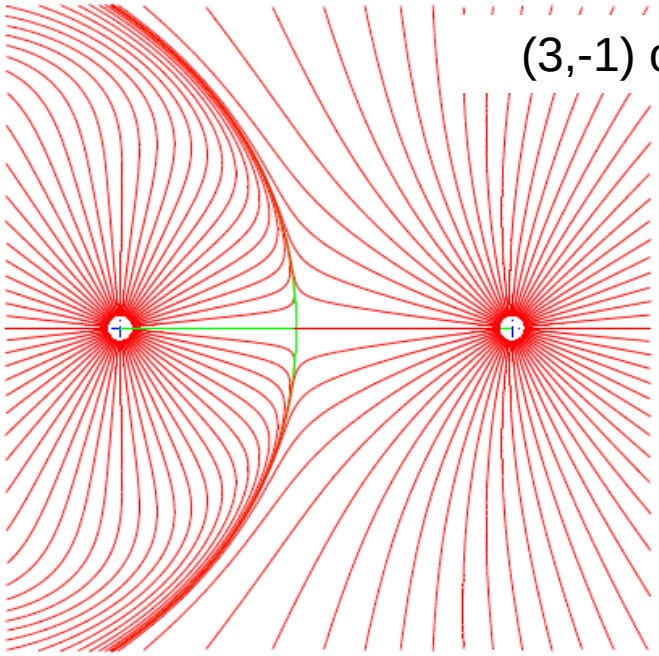
QTAIM: From electronic density to chemical structure

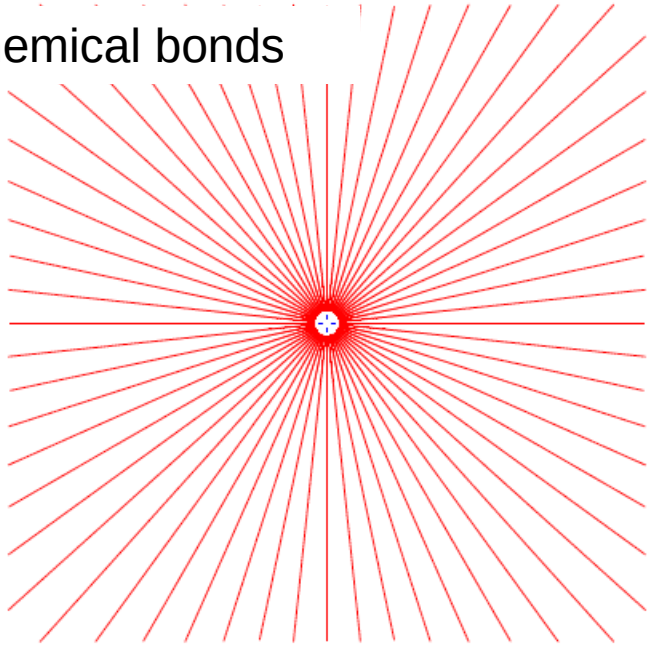
Density

- Maxima = nuclei

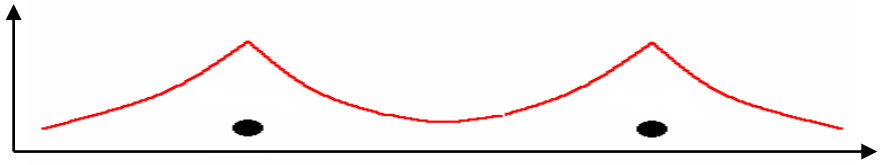
Electron density

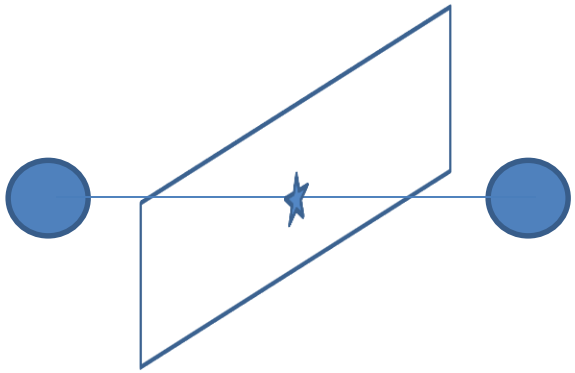
(3,-1) occur at chemical bonds





Plane that contains the nuclei

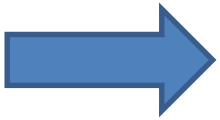


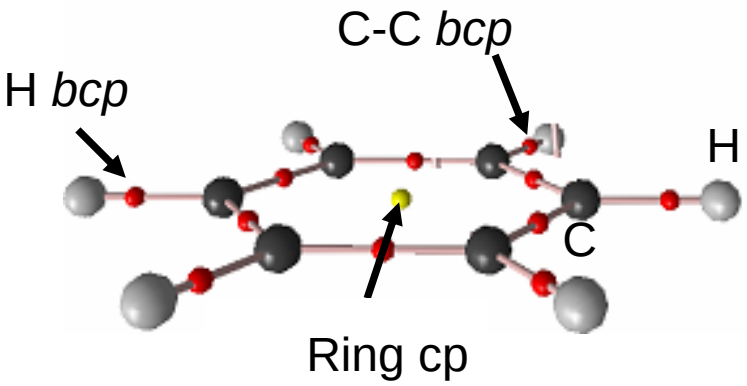


Electron density

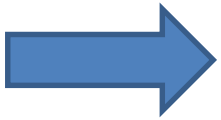
QTAIM: From electronic density to chemical structure

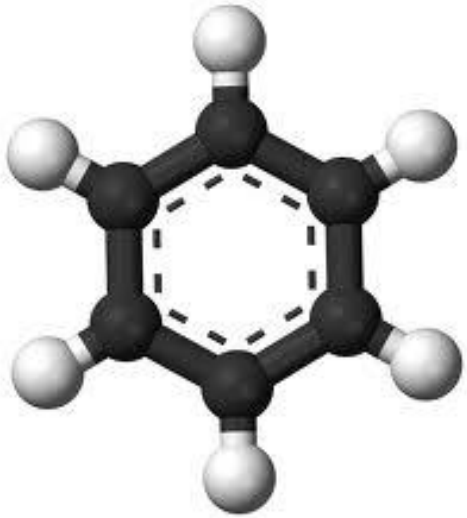
Density





ρ topology



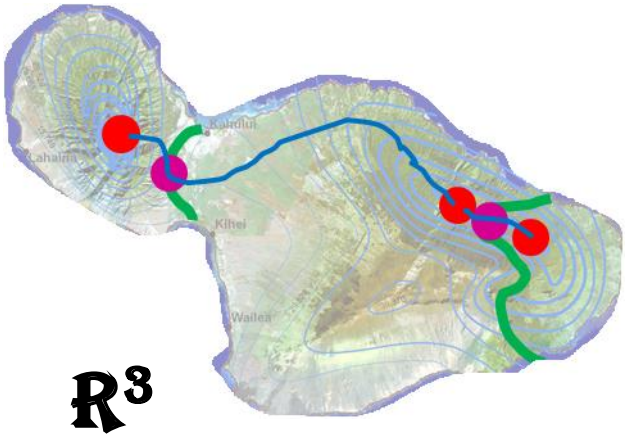


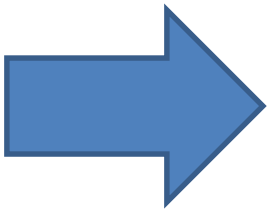
Chemical structure

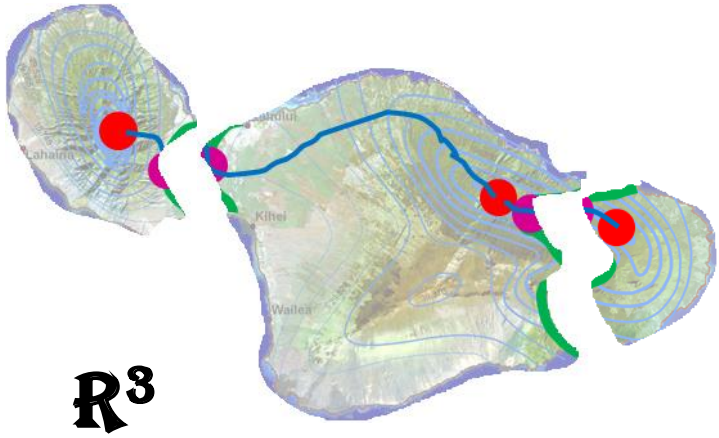
- Maxima = nuclei
- Bond = 1st order saddle point (*bcp*)

IMPORTANT PROPERTIES

- Each maximum has an associated region of space (basin)
  - Non overlapping
  - They fill up the volume



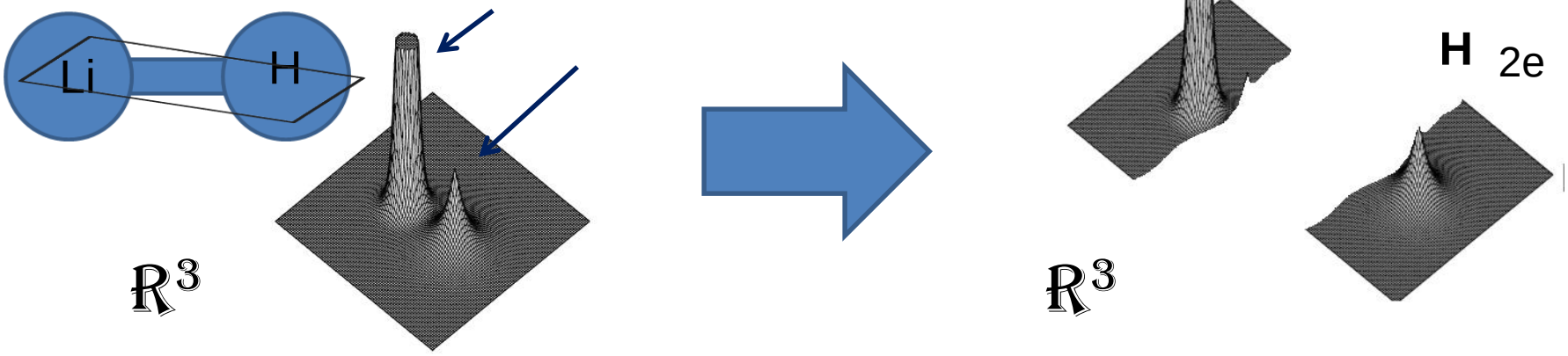




•Electron density

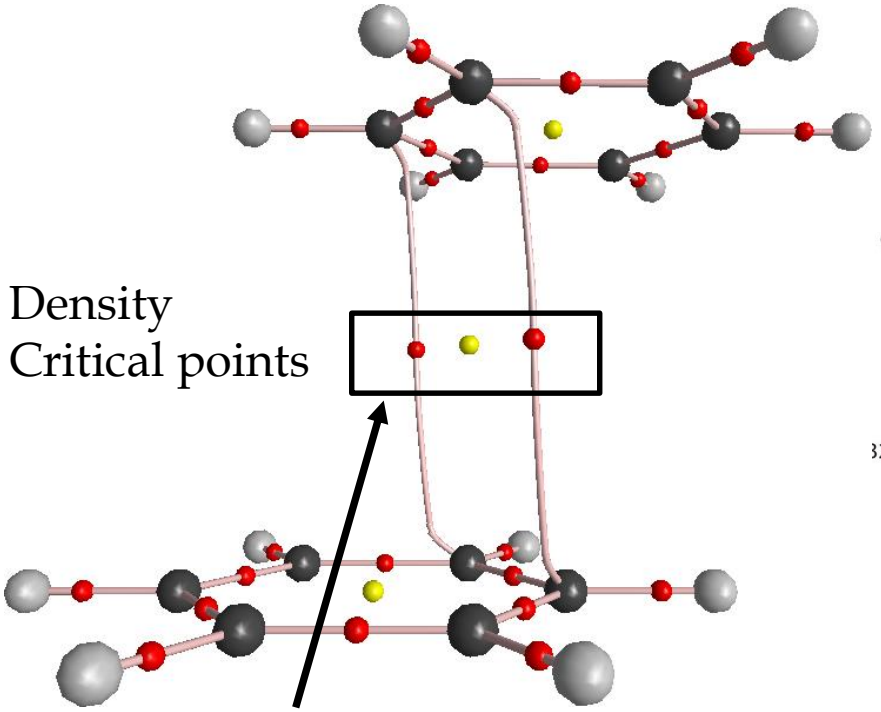
- Each maximum has an associated region of space (basin)
  - Non overlapping
  - They fill up the volume
  - Have a chemical meaning

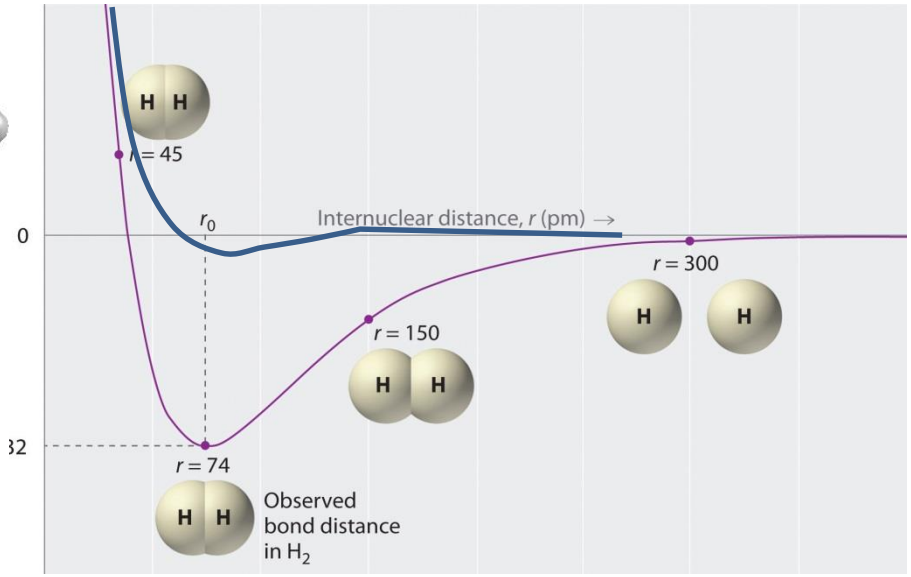
We can integrate properties!



Electron density

The topology of the density alone is not able to provide a satisfactory picture of **weak bonds**





Pair interactions are not well described by critical points

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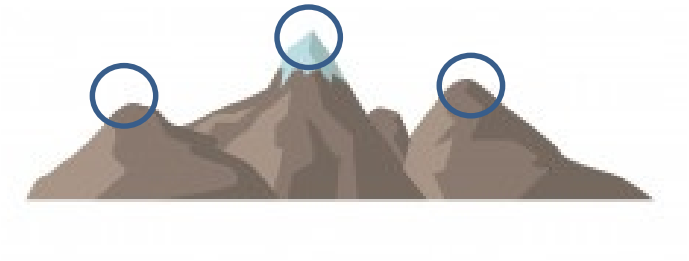
Mathematical description of interactions

Identifying a general shape

Critical point : $\nabla\rho = 0$



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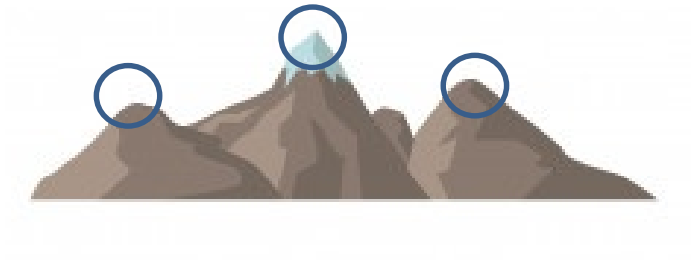
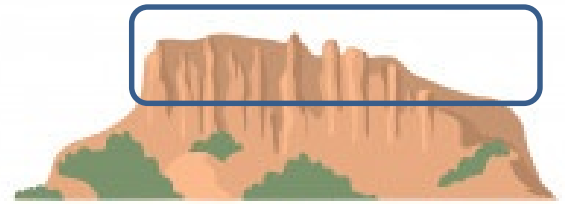


If the profile is flat…

Let's look at the region $\nabla\rho \to 0$



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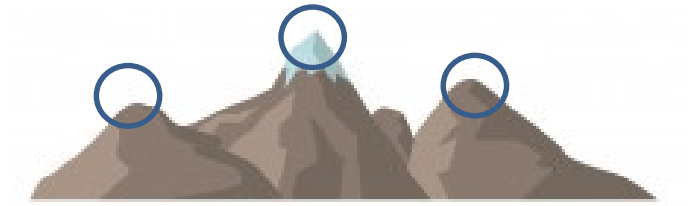

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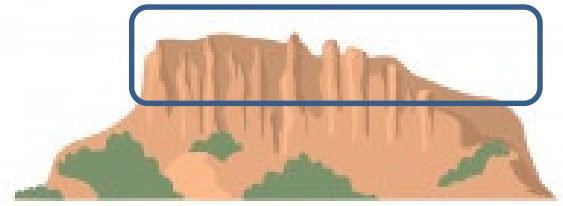
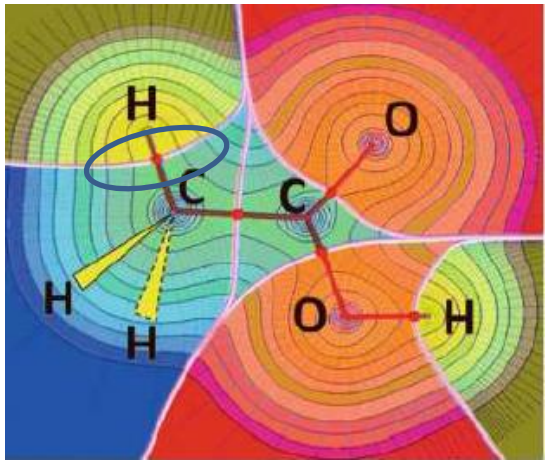


NCI:

analysis of the reduced density gradient at low densities

$$s = \frac{1}{c_s}\frac{|\nabla\rho|}{\rho^{4/3}} \quad \text{with } c_s = 2(3\pi^2)^{1/3}$$



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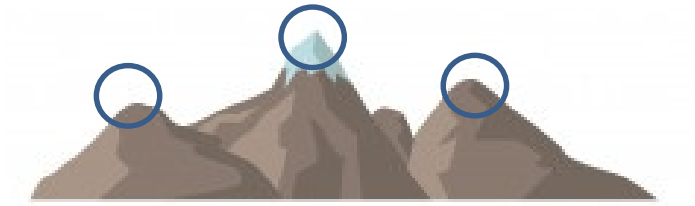

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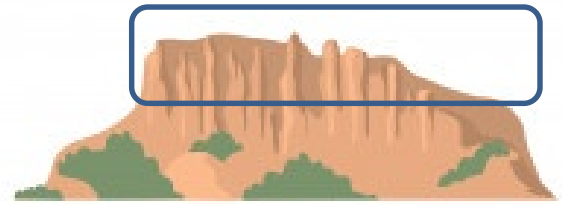

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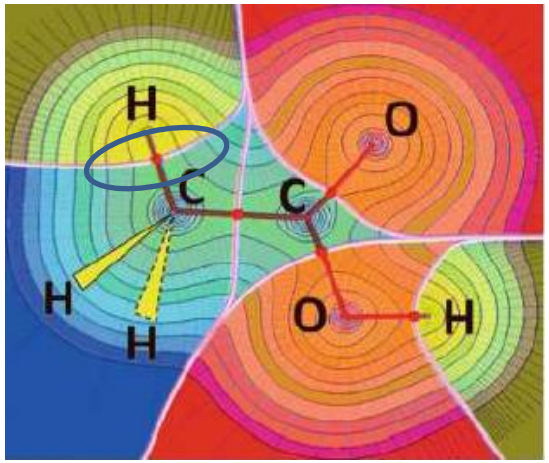
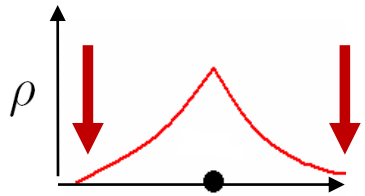


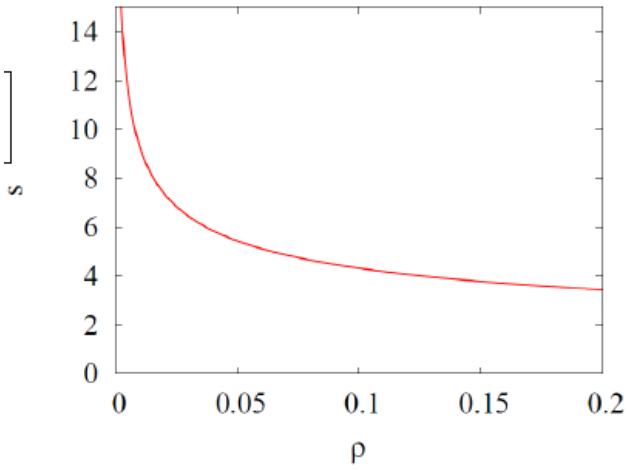
How does it work?

The reduced density gradient

Non-interacting densities



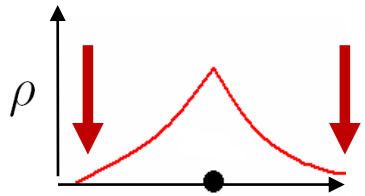
$$s(\rho) \propto \rho^{-1/3} \xrightarrow{\rho \to 0} \infty$$



$$\rho(x,y,z) = \left(\frac{\zeta^{3/2}}{\sqrt{\pi}} e^{-\zeta \sqrt{x^2+y^2+(z-R)^2}} \right)^2$$

The reduced density gradient

Non-interacting densities



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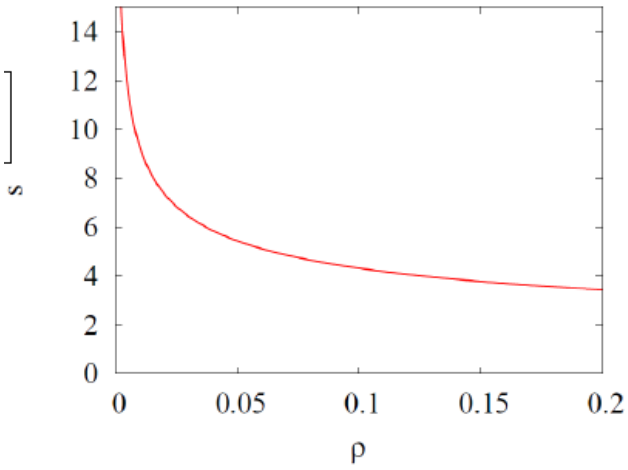

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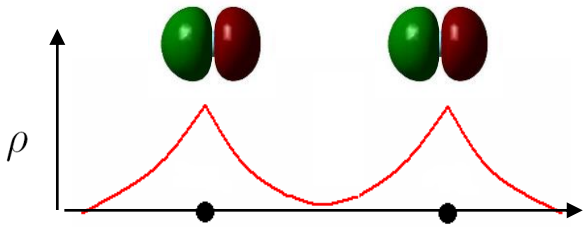
Interacting densities



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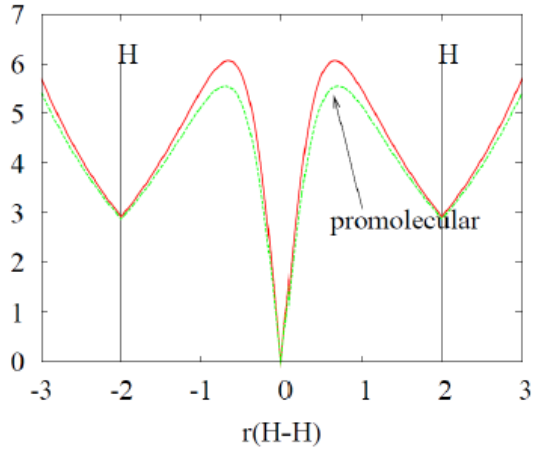

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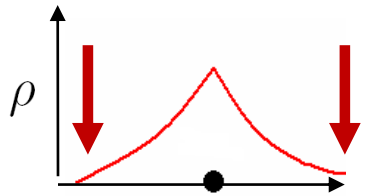
The reduced density gradient

Non-interacting densities



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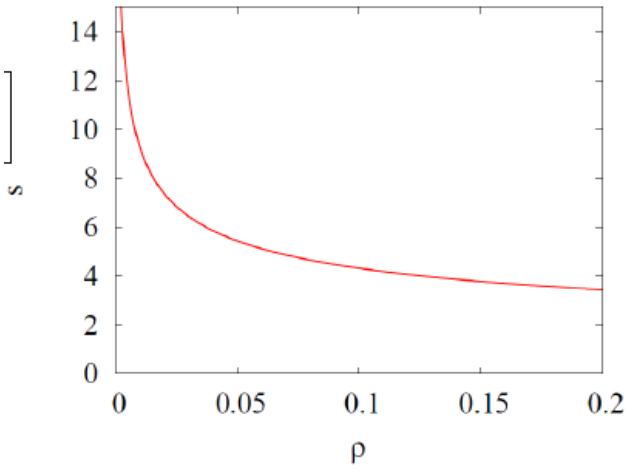

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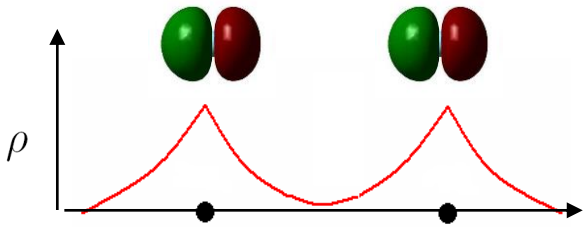

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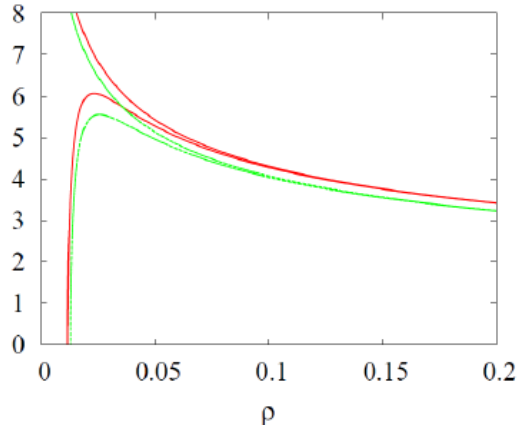

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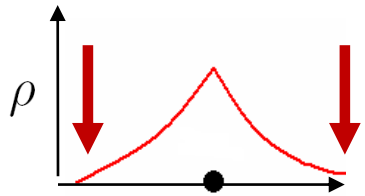

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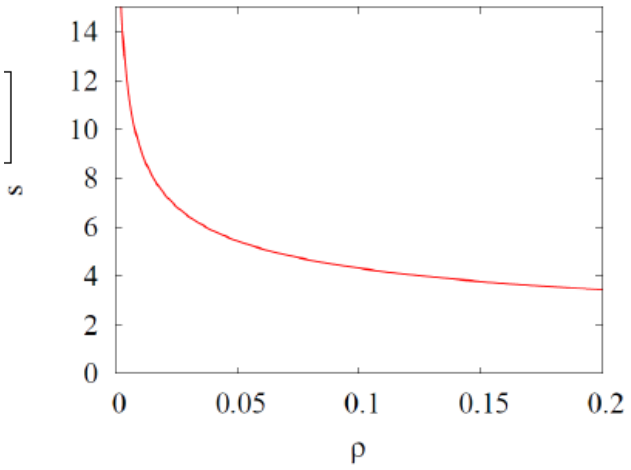

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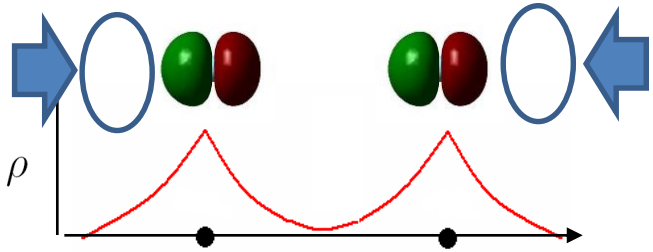

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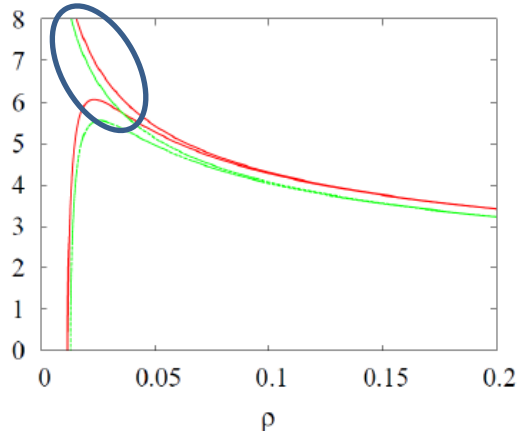
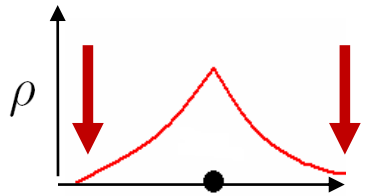


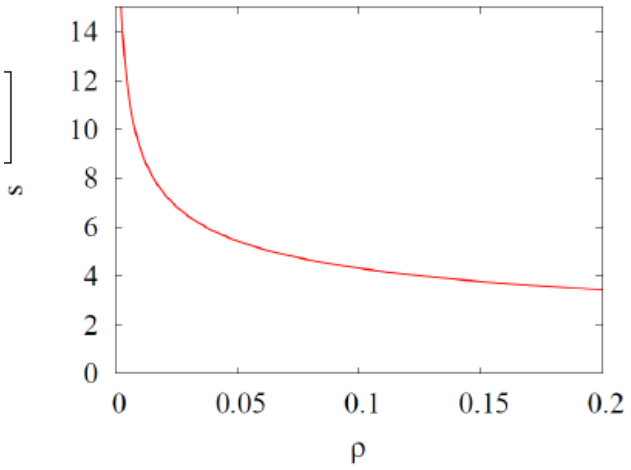
$$\rho(x,y,z) = \left(\frac{\zeta^{3/2}}{\sqrt{\pi}} e^{-\zeta \sqrt{x^2+y^2+(z-R/2)^2}} \right)^2 + \left(\frac{\zeta^{3/2}}{\sqrt{\pi}} e^{-\zeta \sqrt{x^2+y^2+(z+R/2)^2}} \right)^2$$

The reduced density gradient

Non-interacting densities

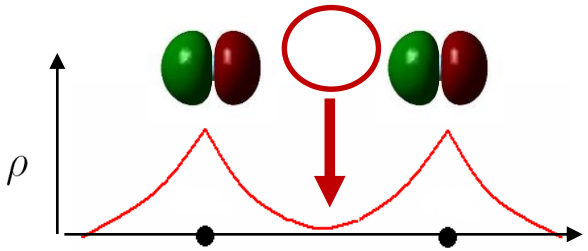


$$s(\rho) \propto \rho^{-1/3} \xrightarrow{\rho \to 0} \infty$$

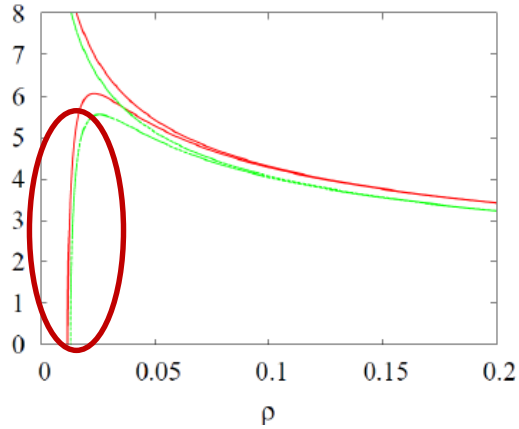


$$\rho(x,y,z) = \left(\frac{\zeta^{3/2}}{\sqrt{\pi}} e^{-\zeta \sqrt{x^2+y^2+(z-R)^2}} \right)^2$$

Interacting densities



$$s(\rho) \xrightarrow{r \to 0} e^{R/3} r + O[r]^3 \to 0$$



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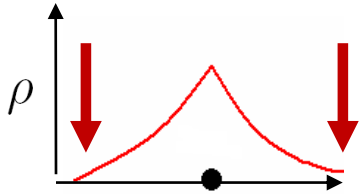
The reduced density gradient

Non-interacting densities



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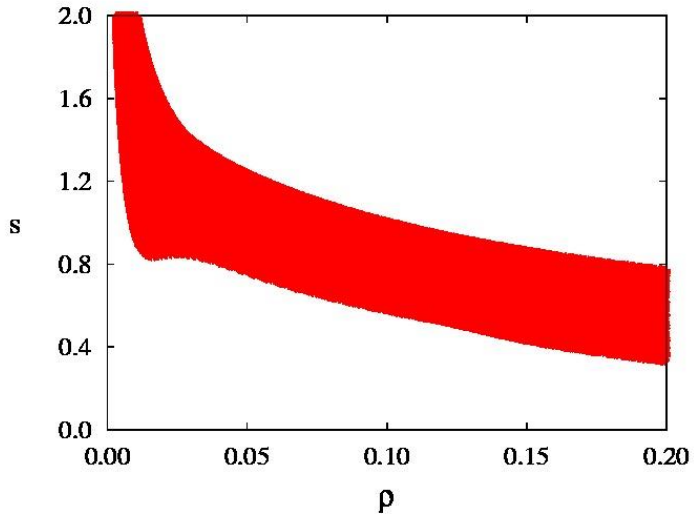
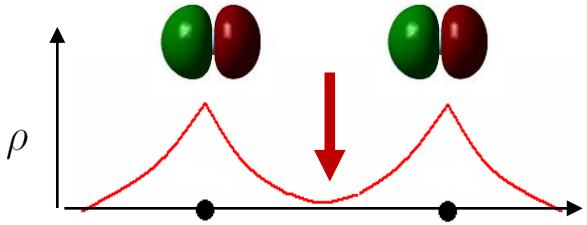
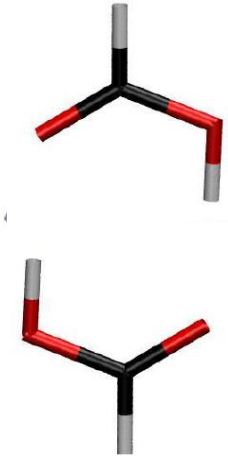


Interacting densities





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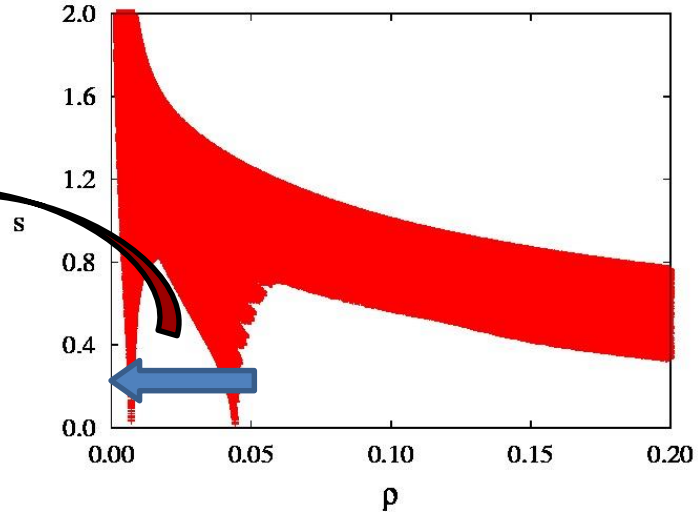
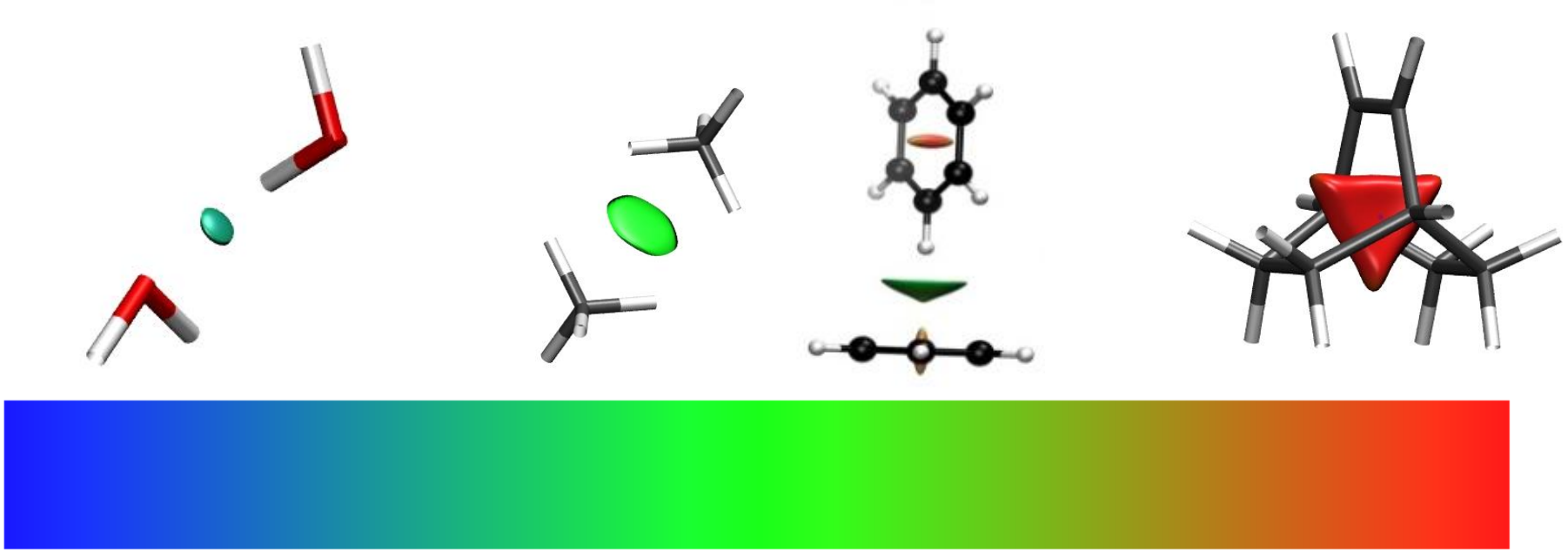


J. Am. Chem. Soc. 132 , 6498 (2010)

The reduced density gradient



Strong and attractive:

Hydrogen bonds

Very weak:

van der Waals

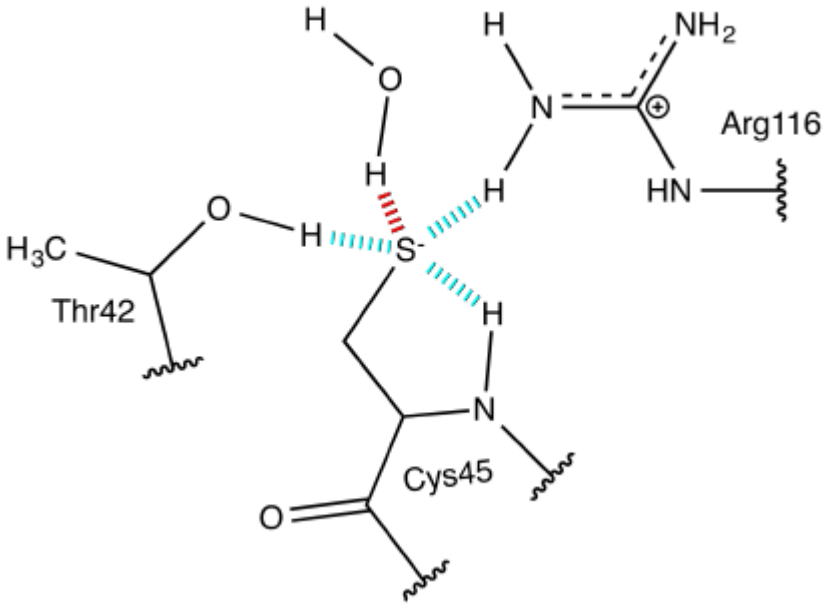
Strong and repulsive:

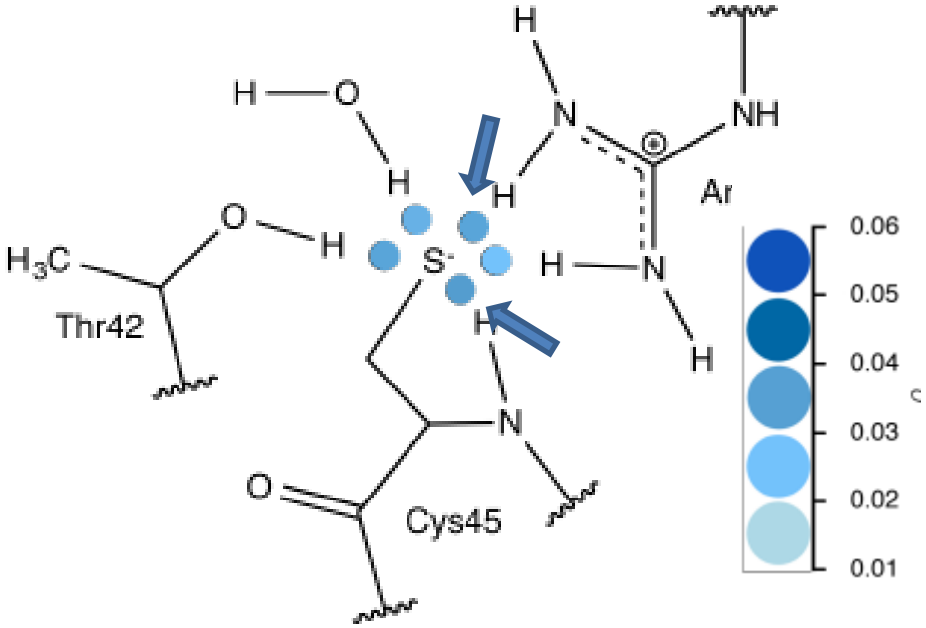
Steric clashes

J. Am. Chem. Soc. 132 , 6498 (2010)

Big systems

SO back to the beginning…are we doing any better???
The electron density does not need to think about distances and angles, it directly takes different atom types into account





The electron localization function

Bosonic system (iso-orbital)

If we are in a region that can be described by a solely orbital j:

$$\rho = \sum_i |\varphi_i|^2 = |\varphi_j|^2$$

$$\begin{cases} \varphi_j = \sqrt{\rho} \\ \nabla\varphi_j = \dfrac{\nabla\rho}{2\sqrt{\rho}} \end{cases}$$

Kinetic energy densities

$$t = \frac{1}{2}\sum_i \nabla\varphi_i^*\nabla\varphi_i \Rightarrow t_w = \frac{1}{2}\frac{\nabla\rho}{2\sqrt{\rho}}\frac{\nabla\rho}{2\sqrt{\rho}} = \frac{1}{8}\frac{(\nabla\rho)^2}{\rho}$$

$$t_{bose}(\mathbf{r}) = \frac{\tau_w(\mathbf{r})}{\tau_{TF}(\mathbf{r})}$$

Its a scaled reference

- with the same density
- Pauli principle has been turned off

NCI is directly related to t_{bose}

$$t_{bose} = \frac{\tau_w}{\tau_{TF}} = \frac{|\nabla\rho(\vec{r})|^2}{8c_F\rho(\vec{r})^{8/3}} = \frac{5}{3}\left(\frac{|\nabla\rho(\vec{r})|}{c_s\rho(\vec{r})^{4/3}}\right)^2$$

$$\boldsymbol{t_{bose} = \frac{5}{3}s^2}$$

NCI identifies regions of marked bosonic character, including covalent bonds, lone pairs, etc

How does this relate to the common NCI pic?

Critical points

$$\nabla t_{bose}(\mathbf{r}) = \frac{1}{4C_F} \frac{\nabla\rho(\mathbf{r})}{\rho(\mathbf{r})^{5/3}} \left[\frac{\nabla^2\rho(\mathbf{r})}{\rho(\mathbf{r})} - \frac{4}{3} \frac{(\nabla\rho(\mathbf{r}))^2}{\rho(\mathbf{r})^2} \right]$$

AIM-CPs:

$\nabla\rho = 0 \Rightarrow \nabla s = 0$ (AIM)

Critical points

$$\nabla t_{bose}(\mathbf{r}) = \frac{1}{4C_F} \frac{\nabla\rho(\mathbf{r})}{\rho(\mathbf{r})^{5/3}} \left[\frac{\nabla^2\rho(\mathbf{r})}{\rho(\mathbf{r})} - \frac{4}{3} \frac{(\nabla\rho(\mathbf{r}))^2}{\rho(\mathbf{r})^2} \right]$$

AIM-CPs:

$\nabla\rho = 0 \Rightarrow \nabla s = 0$ (AIM)

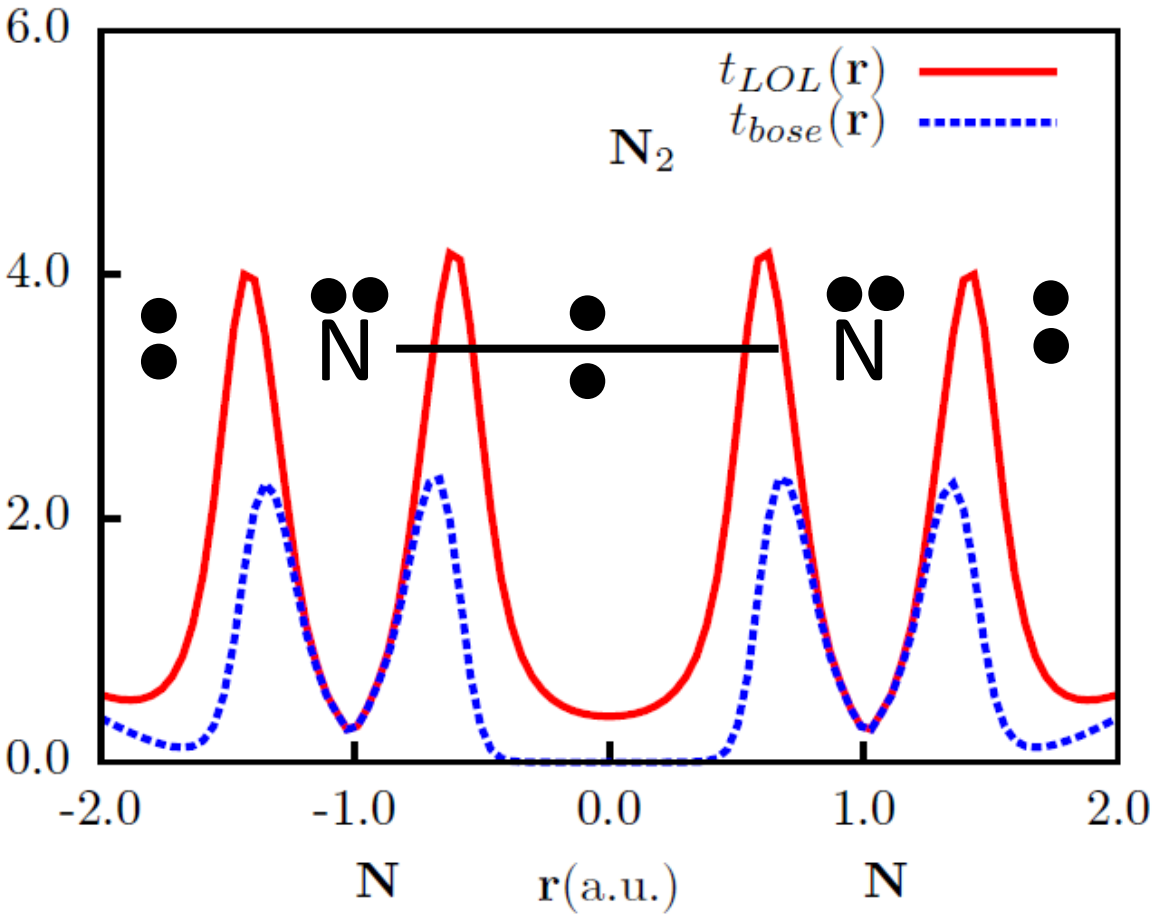
Bond critical points (BCPs)
RCPs, CCPs

$$t_{LOL}(\mathbf{r}) = \frac{\tau_I(\mathbf{r})}{\tau_{TF}(\mathbf{r})} \qquad t_{bose}(\mathbf{r}) = \frac{\tau_w(\mathbf{r})}{\tau_{TF}(\mathbf{r})}$$

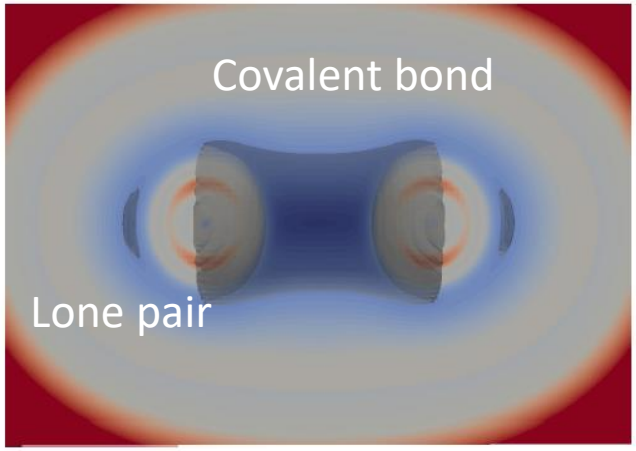
t_{bose} is a lower bound

$t_{LOL} \approx t_{bose}$ in perfectly localized orbitals

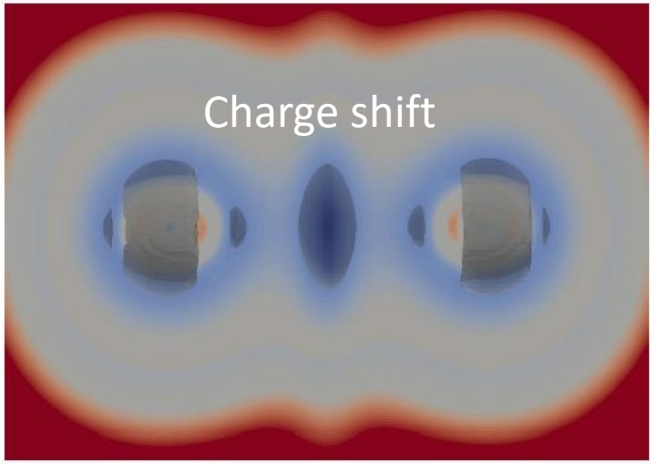
Electrons spread more due to their fermionic nature



Covalent bonds



N_2



F_2

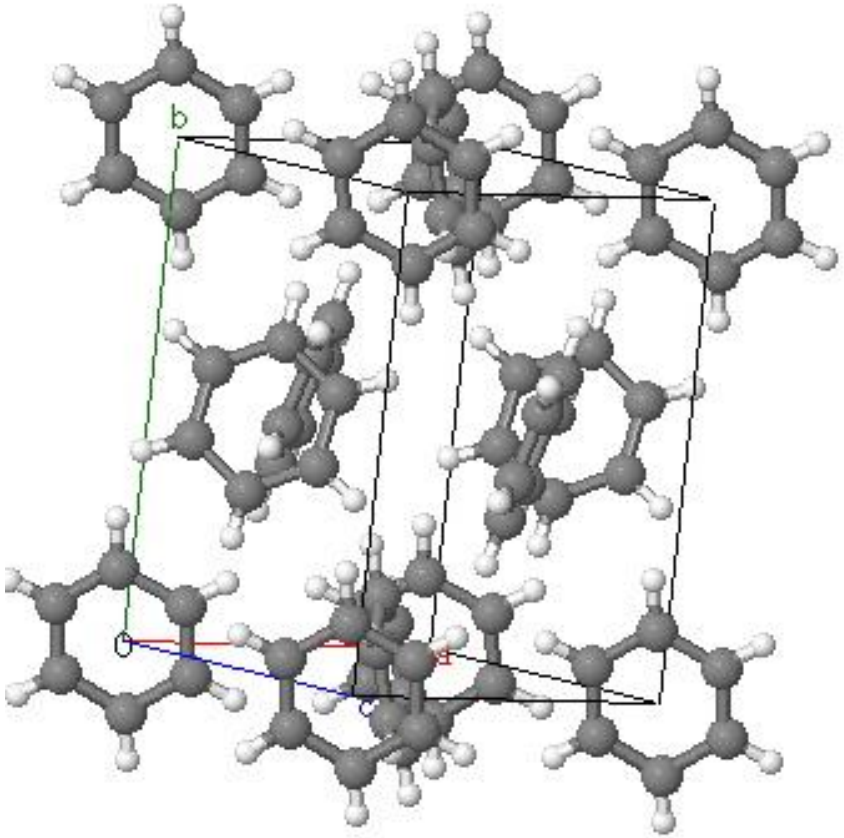
Localised electron pairs are also regions of Low Pauli repulsion

t_{bose} identifies regions of electron localization:

- Shell structure
- Covalent bonds
- Lone pairs

NCI vs AIM

Nevertheless, thanks to the shape of the isosurface we can visually collect more information…



Benzene packing maximizes the number of C-H···π and C-H···C contacts.

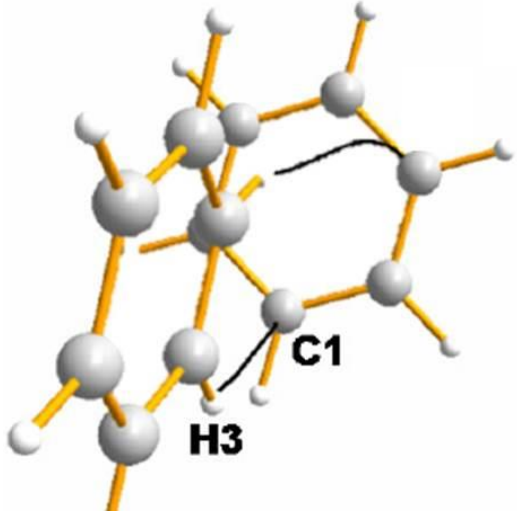
NCI vs AIM

Delocalized interactions

AIM

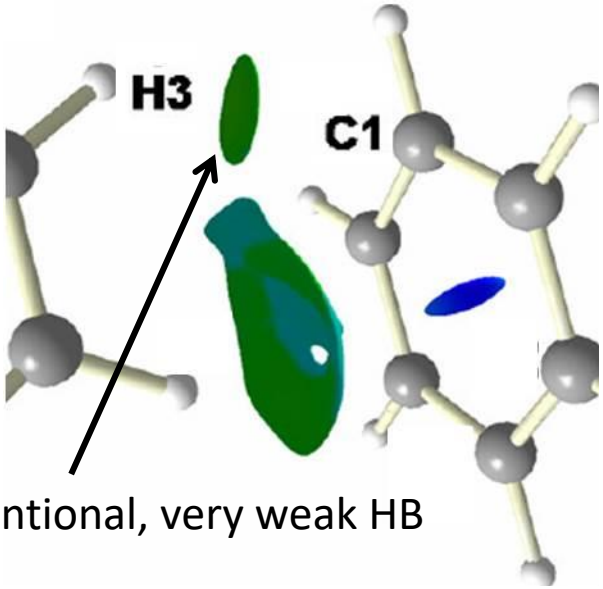
Largely oriented location of H3

Straight BP privileges the interaction of the H with just one single atom of the ring



NCI

Disc-shaped and localized



conventional, very weak HB

NCI and BP pictures nicely match

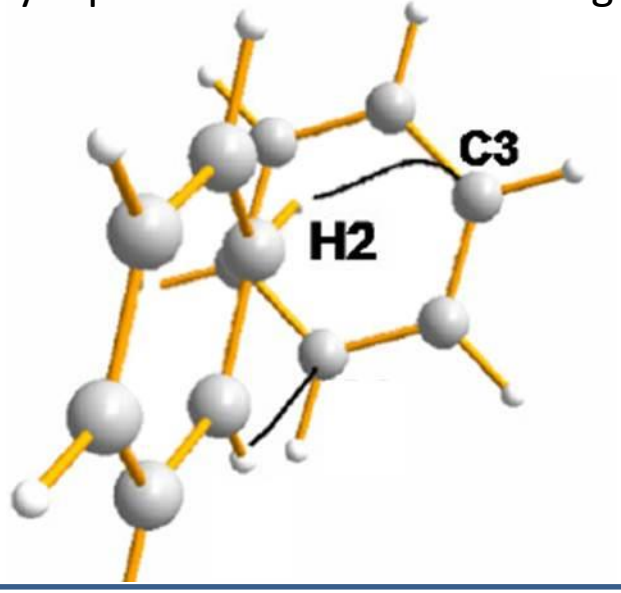
NCI vs AIM

Delocalized interactions

AIM

CH···C interaction significantly bent

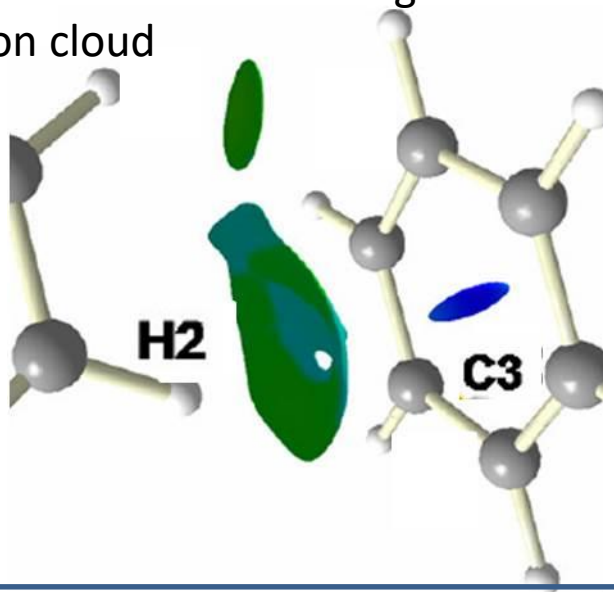
H roughly equidistant to the whole ring



NCI

Large isosurface that covers the ring

C-H···π interaction involving the whole π electron cloud



BP analysis privileges the interaction of the H with just one single atom of the ring

NCI provides a delocalized interaction

Critical points

$$\nabla t_{bose}(\mathbf{r}) = \frac{1}{4C_F}\frac{\nabla\rho(\mathbf{r})}{\rho(\mathbf{r})^{5/3}}\left[\frac{\nabla^2\rho(\mathbf{r})}{\rho(\mathbf{r})} - \frac{4}{3}\frac{(\nabla\rho(\mathbf{r}))^2}{\rho(\mathbf{r})^2}\right]$$

AIM-CPs:

$\nabla\rho = 0 \Rightarrow \nabla s = 0$ (AIM)

Bond critical points (BCPs)
RCPs, CCPs

Non-AIM-CPs:

$\nabla\rho \neq 0$ and $\nabla s = 0$

$$\frac{\nabla^2\rho(\mathbf{r})}{\rho(\mathbf{r})} - \frac{4}{3}\frac{(\nabla\rho(\mathbf{r}))^2}{\rho^2(\mathbf{r})} = 0$$

Shells, lone pairs

Critical points

$$\nabla t_{bose}(\mathbf{r}) = \frac{1}{4C_F}\frac{\nabla\rho(\mathbf{r})}{\rho(\mathbf{r})^{5/3}}\left[\frac{\nabla^2\rho(\mathbf{r})}{\rho(\mathbf{r})} - \frac{4}{3}\frac{(\nabla\rho(\mathbf{r}))^2}{\rho(\mathbf{r})^2}\right]$$

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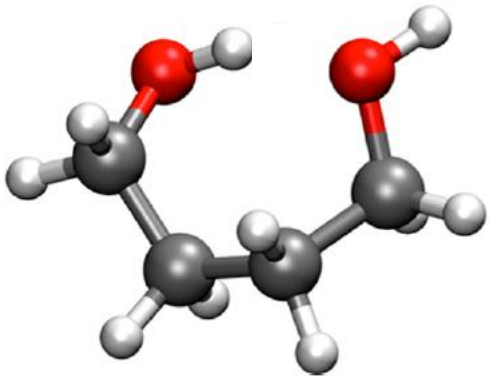
$$\frac{\nabla^2\rho(\mathbf{r})}{\rho(\mathbf{r})} - \frac{4}{3}\frac{(\nabla\rho(\mathbf{r}))^2}{\rho^2(\mathbf{r})} = 0$$

Shells, lone pairs
Closed shell interactions not identified by AIM

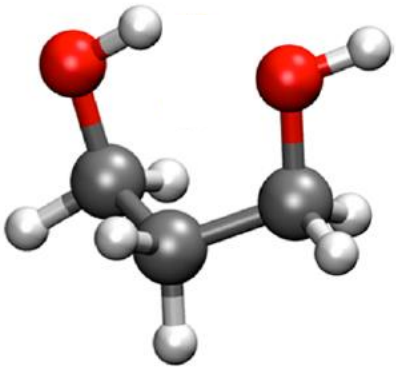
Non-AIM CPs

Progressive OH-O interaction

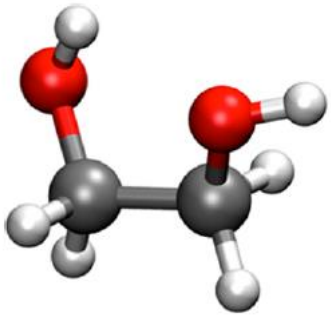
Strong → Moderate → Weak



BD
1,4-butendiol



PD
1,3-propanediol



ED
1,2-ethanediol

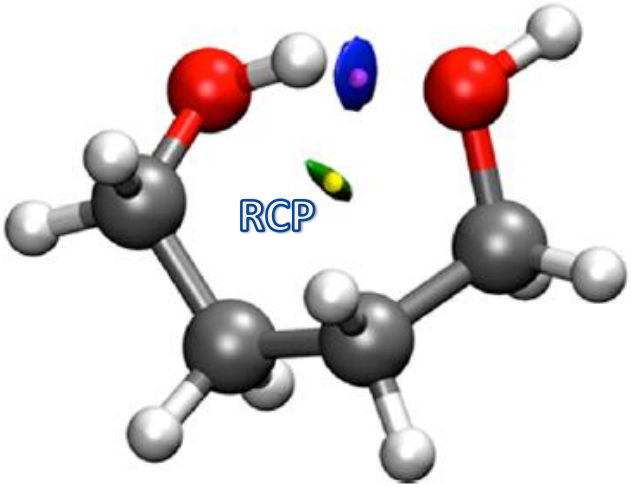
Experimental evidence:

OH-stretching vibrational mode of the hydroxyl group becomes progressively less red-shifted in the fundamental and overtone regions

Non-AIM CPs

AIM-CPs:

$\nabla\rho = 0 \Rightarrow \nabla s = 0$ (AIM), s=0



1,4-butendiol

J. Chem. Theory Comp. 9, 3263 (2013) **[Most read in JCTC]**

Non-AIM CPs

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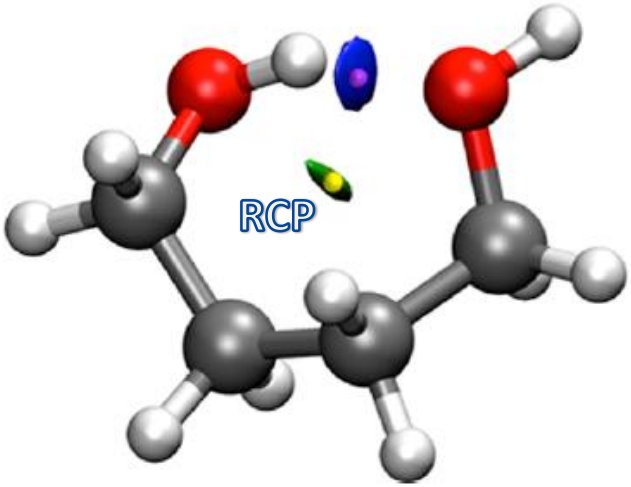
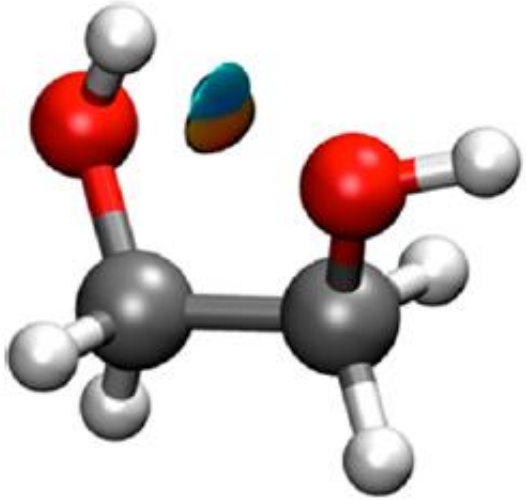
Non-AIM-CPs:

$\nabla\rho \neq 0$ and $\nabla s = 0, s \neq 0$

$$\nabla^2\rho(\boldsymbol{r}) = \frac{4}{3}\frac{(\nabla^2\rho(\boldsymbol{r}))^2}{\rho(\boldsymbol{r})} > 0$$



1,4-butendiol



1,2-ethanediol

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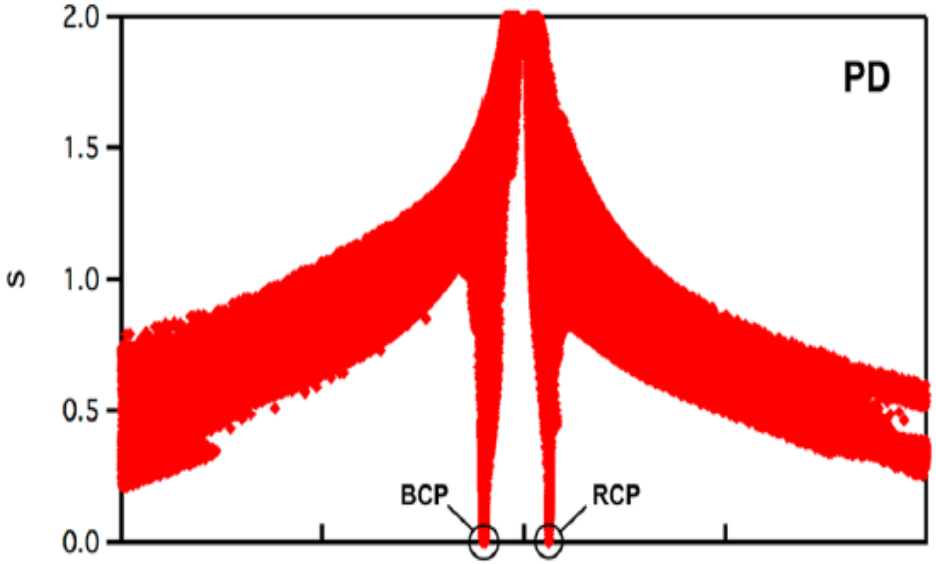
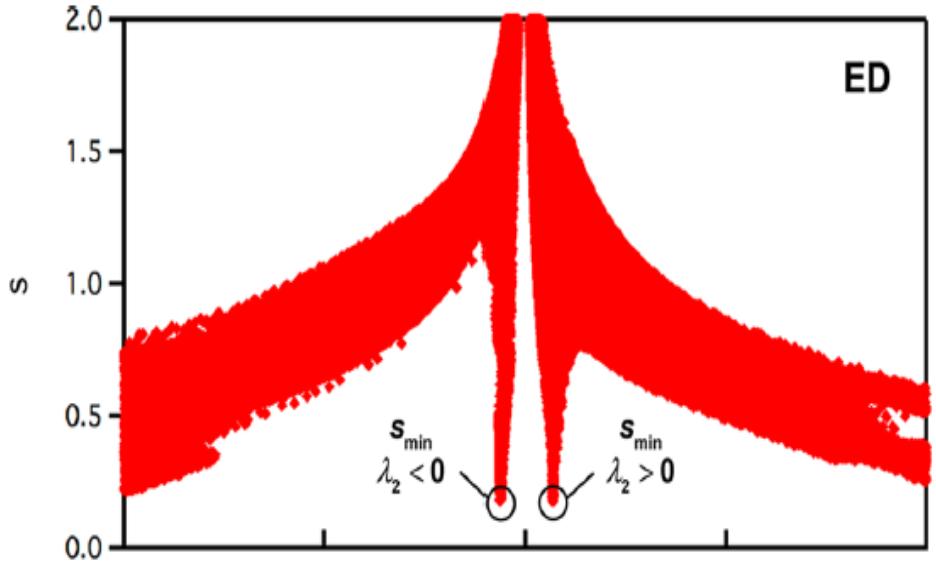


1,4-butendiol

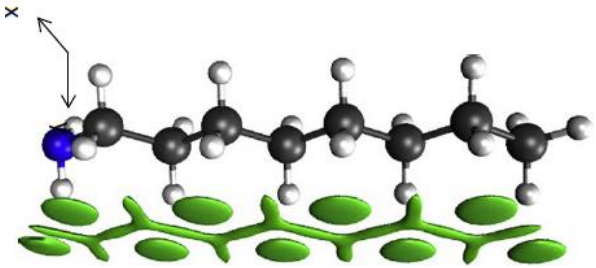


1,2-ethanediol

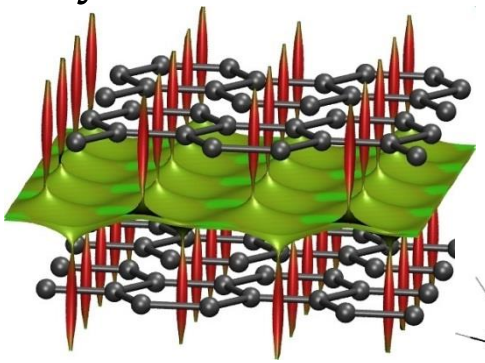
J. Chem. Theory Comp. 9, 3263 (2013)

The reduced density gradient

Dispersion interactions are critical for:

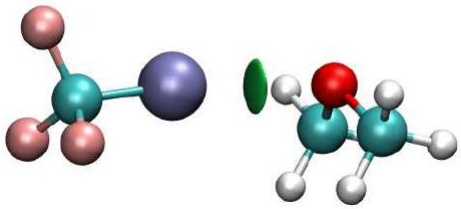


- surface chemistry,
- nano-scale and materials chemistry,

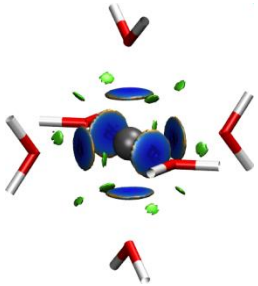


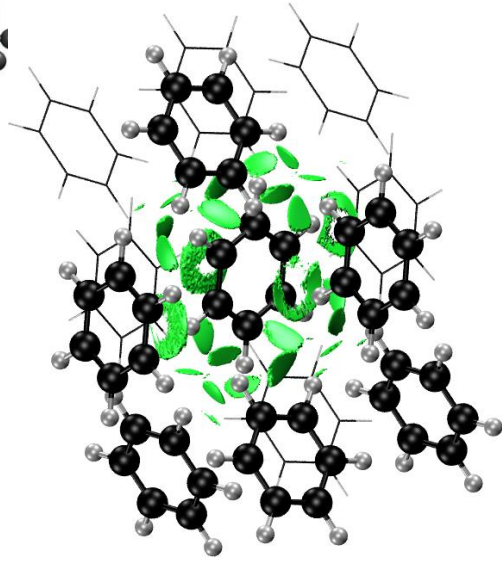
- biological chemistry
  - protein folding,
  - ligand-receptor binding,

Halogen bonds



Coordination, solvation





The reduced density gradient

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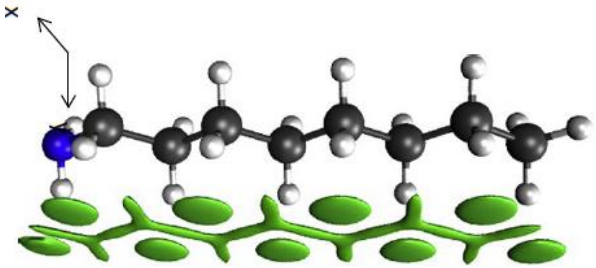

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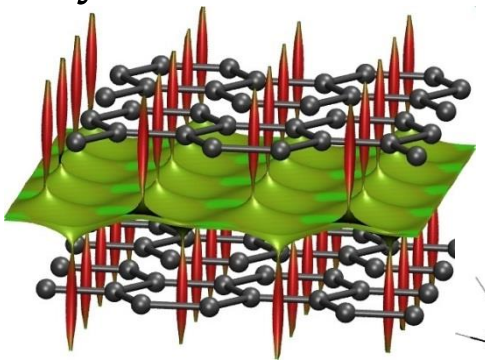

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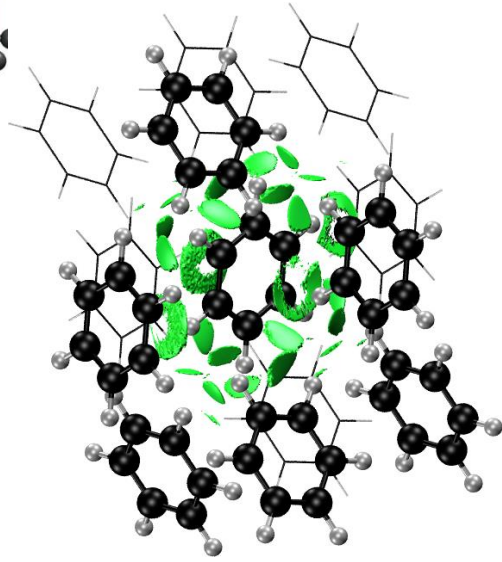
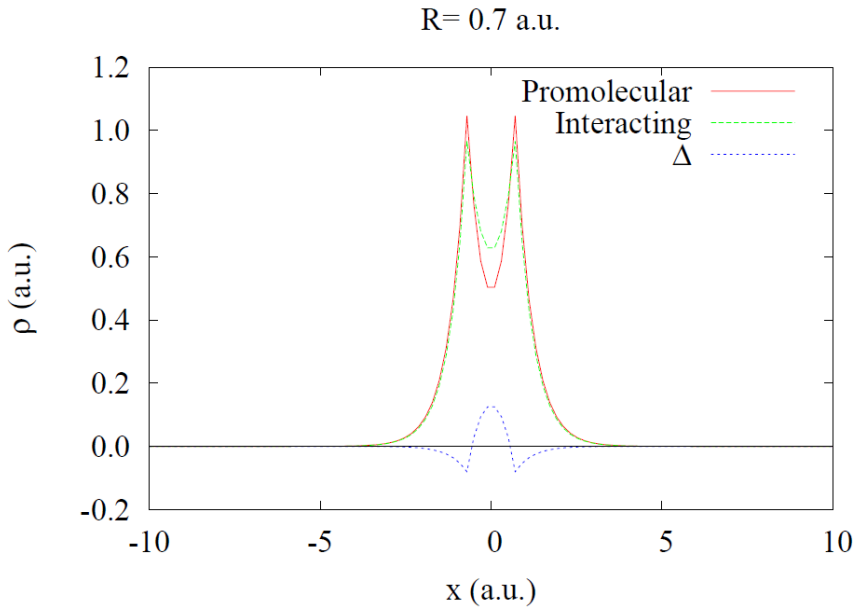


We don’t have a wavefunction!!!

Big systems

Non covalent interactions are crucial in supramolecular systems…can we apply NCI to them ?

- **YES: density approximated from atomic densities (NCI=very little perturbation)**



Big systems

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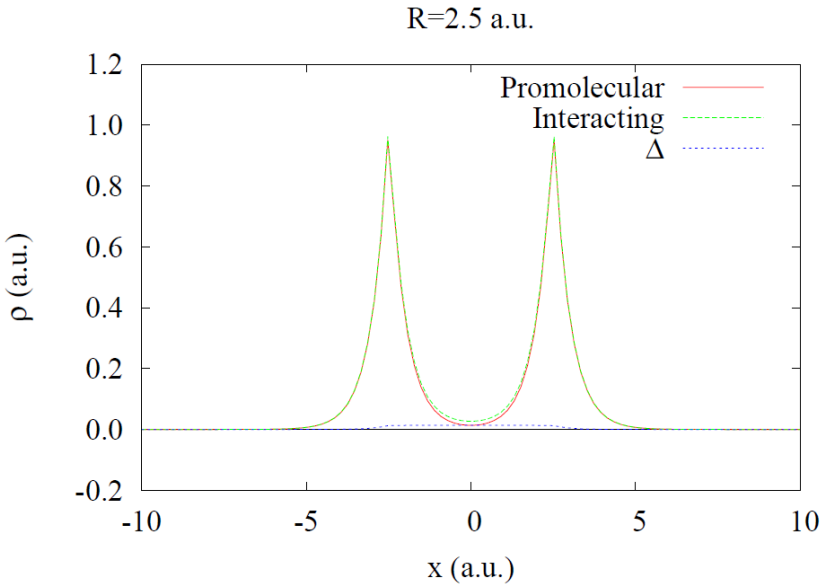


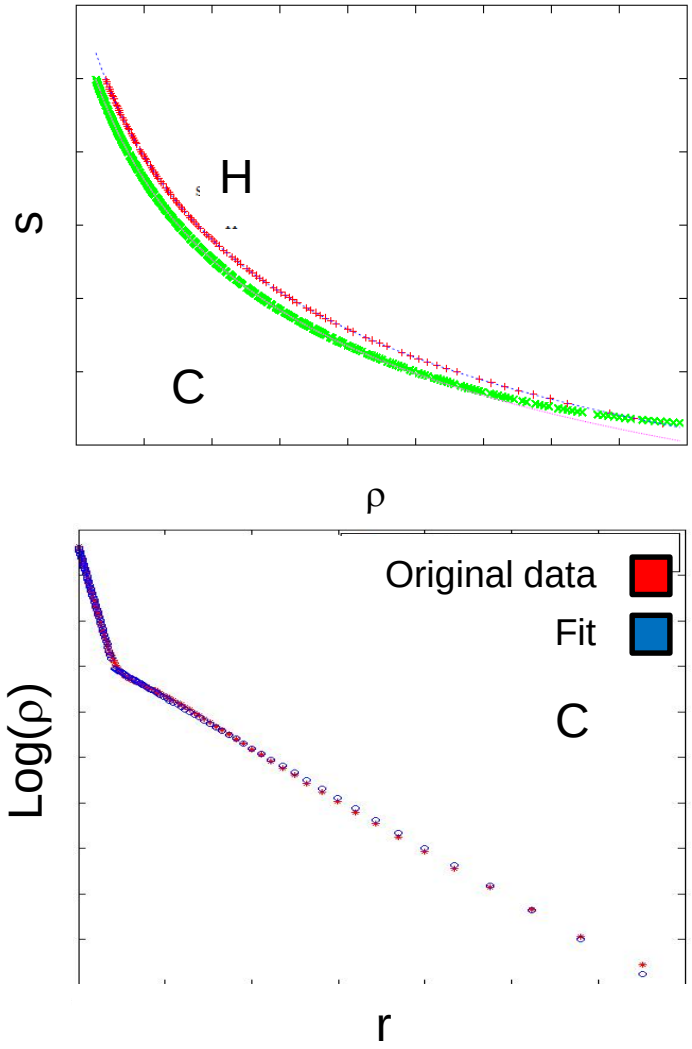
Big systems

Non covalent interactions are crucial in supramolecular systems…can we apply NCI to them ?

- **YES: density approximated from atomic densities (NCI=very little perturbation)**
- **Only atomic coordinates are required as input**

  (x,y,z of atoms, crystallographic coordinates)
- **Very fast calculation; applicable to large systems**

•What are promolecular densities?



•Densities can be mimicked like a sum of N^shell exponentials

$$\rho^{prom} = \sum_{i}^{N} \rho_i^{prom} \qquad \rho_{at}^{prom} = \sum_{n} c_n e^{\zeta_n r}$$

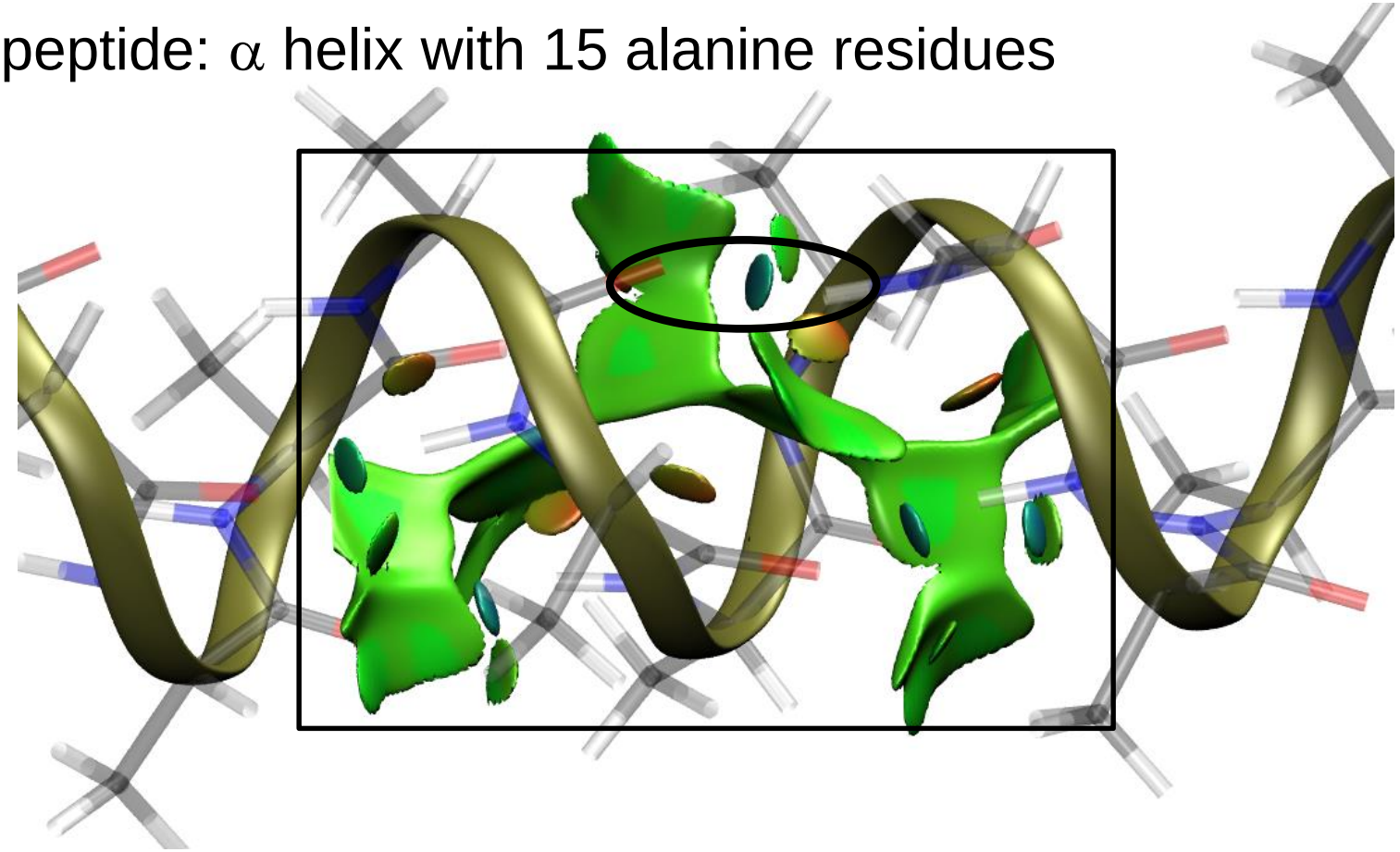
•So that when we plot *log* ρ *vs r*, a line is obtained for every shell that can be easily parameterized

•These parameters are internally stored in NCIPLOT

• Only depends on grid size: very fast calculation; applicable to large systems

Big systems

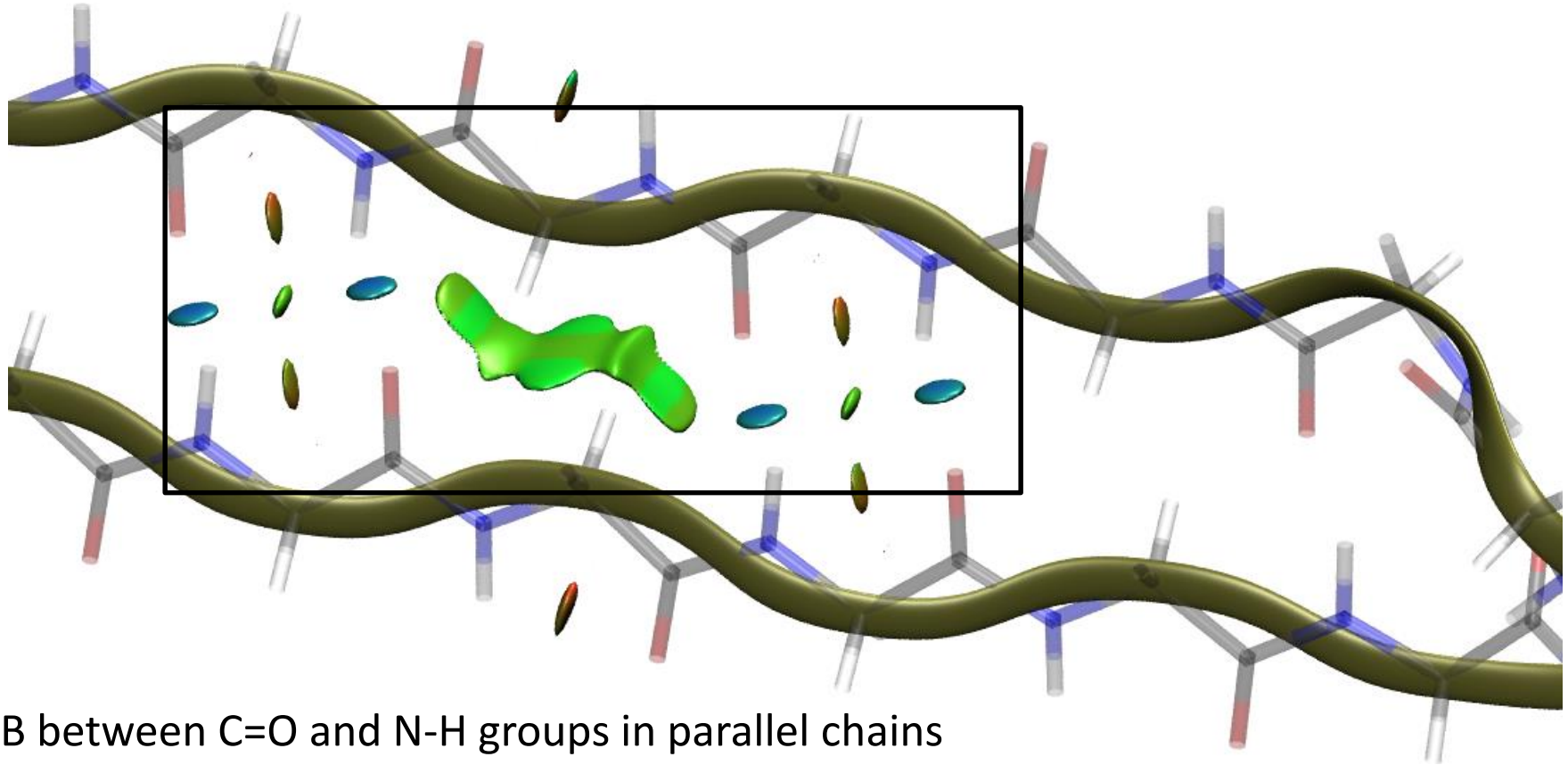
Polipeptide: α helix with 15 alanine residues



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

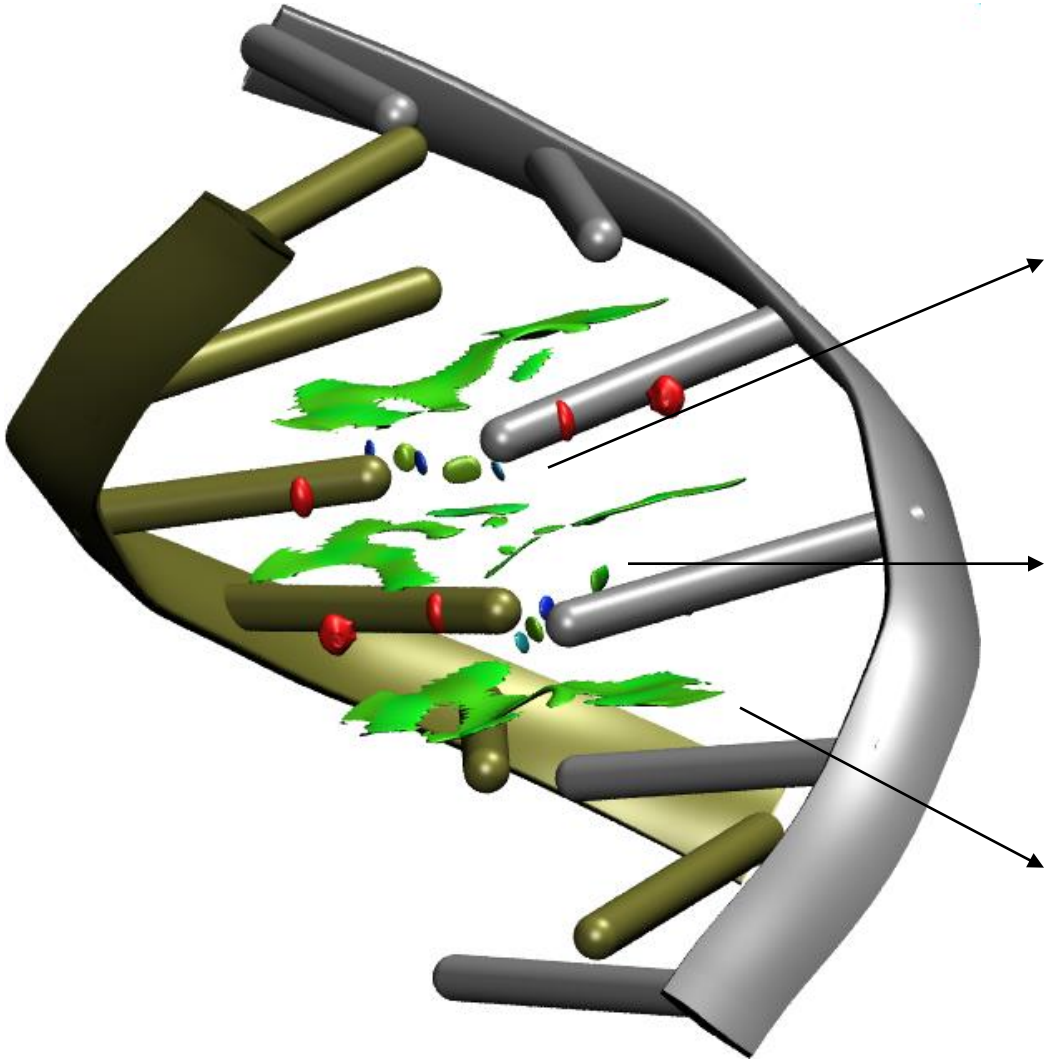
Big systems

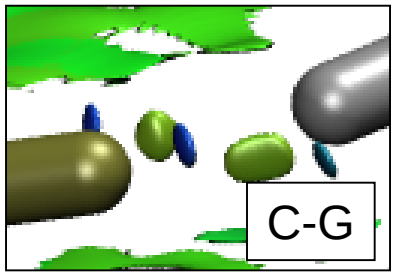
polypeptide: anti-parallel β-sheet consisting of 17 glycine residues

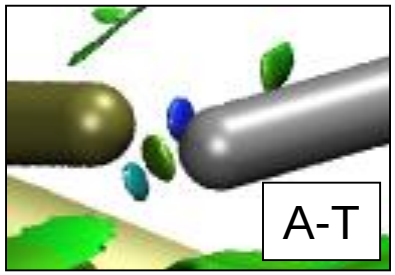


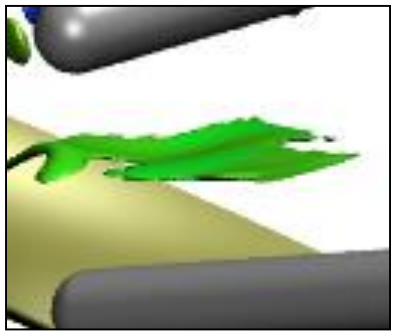
- HB between C=O and N-H groups in parallel chains
- Van der Waals interactions between CH_2 groups

Big systems









H-bonds between bases

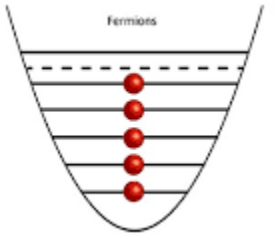
π-stacking

Summary

- We can locate convalent bonds from the electron density (QTAIM)
- We can locate non-covalent interactions from the reduced density gradient (NCI)
  - It enables to identify delocalized interactions
  - It gives insight into QTAIM blind weak interactions
  - It can be approximated for very big systems with promolecular densities

Physical meaning

- Historically, the reduced density gradient comes from the Thomas-Fermi model



- Properties of the system are relates to the Fermi wavevector:

$$\rho = \frac{N}{V} = \frac{k_F^3}{3\pi^2}$$

Fermi wavevector

$$p_F = \hbar k_F$$

Fermi wavelength

$$\lambda_F = \frac{h}{p_F} = \frac{2\pi}{k_F}$$

Physical meaning

- If we apply TF to a real system, the electron density will vary from one small volume element to the next.
- This inhomogeneity is accounted by the spatial derivative of λ_F :

$$|\nabla\lambda_F| = -\frac{h|\nabla p_F|}{p_F^2} = \frac{2\pi\rho^{-\frac{2}{3}}|\nabla\rho|}{3(3\pi^2)^{\frac{1}{3}}\rho^{\frac{2}{3}}} = \frac{4\pi}{3}\frac{|\nabla\rho|}{2(3\pi^2)^{\frac{1}{3}}\rho^{\frac{4}{3}}} = \frac{4\pi}{3}\,s$$

$$s = \frac{3}{4\pi}|\nabla\lambda_F|$$

A measure of inhomogeneity within the HEG model

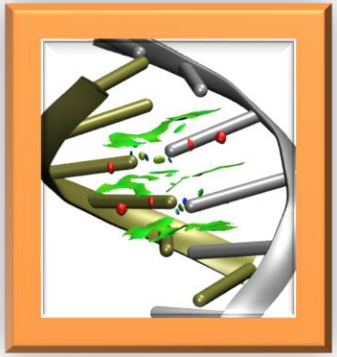
- Reduced density gradient looks at inhomogeneity for regions well approximated by the TF model (low densities!)

The programs

NCIPLOT

NCI for molecules and biomolecules

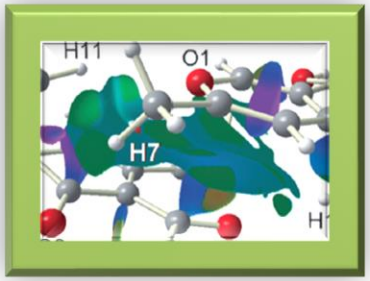
JCTC 7, 625 (2011)



NCIMILANO

NCI for experimental densities

Chem. Eur. J. 18, 15523 (2012)



CRITIC

NCI for solid calculations

PCCP 14, 12165 (2012)