UNIVERSITA' DEGLI STUDI DI MILANO
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Exploring non-covalent interactions in molecular crystals through the analysis of their experimental electron density distribution

Gabriele Saleh, Carlo Gatti, Leonardo Lo Presti

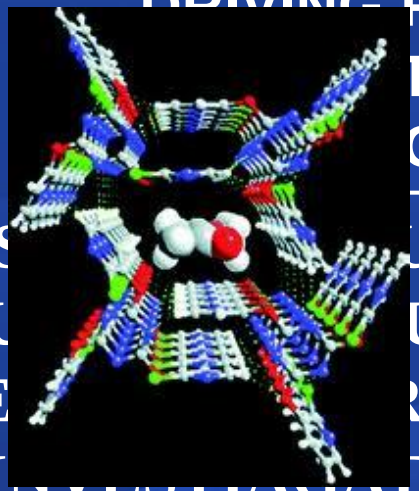
OUTLINE

- NCI DESCRIPTOR: brief introduction
- APPLICATION TO EXPERIMENTAL ELECTRON DENSITIES
- COMPARISON WITH THEORY
- OUR CODE TO IMPLEMENT NCI DESCRIPTOR (going beyond the original description?)

IMPORTANT IN MANY AREA OF CHEMISTRY

BIODISCIPLINES

CRYSTAL ENGINEERING



DRIVING FORCE

TAL

ON

CRYS UITABLE

SU ULAR

E R NCI

INVESTIGATION

NON-COVALENT INTERACTIONS

INVOLVE SMALL CHANGES IN ENERGY AND ρ DISTRIBUTION

DIFFICULT TO BE DESCRIBED

NON-COVALENT INTERACTIONS: A NEW DESCRIPTOR (NCI)

IN 2010 JOHNSON *et al.* PROPOSED A NEW DESCRIPTOR[1]

Based on Reduced Density Gradient, RDG

$$RDG = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla\rho|}{\rho^{4/3}} \propto \frac{|\nabla\rho|}{\rho^{4/3}}$$

Requires only the knowledge of ED distribution!

$$E[\rho(\vec{r})] = T_S[\rho(\vec{r})] + J[\rho(\vec{r})] + E_{XC}[\rho(\vec{r})]$$

[A. Zupan, K. Burke, M. Ernzerhof, J. P. Perdew, J. Chem. Phys. 1997, 106, 10184 –10193]

- Atoms to molecules
- Elongated to equilibrium bonds

LOW RDG VALUES ⟺ **CHEMICAL INTERACTIONS**

[1] E.R. Johnson, S. Keinan, P. Mori-Sanchez, J. Contreras-Garcia, A.J. Cohen, W.Yang. JACS (2010),132,6498-6506

THE NON COVALENT INTERACTIONS (NCI) DESCRIPTOR

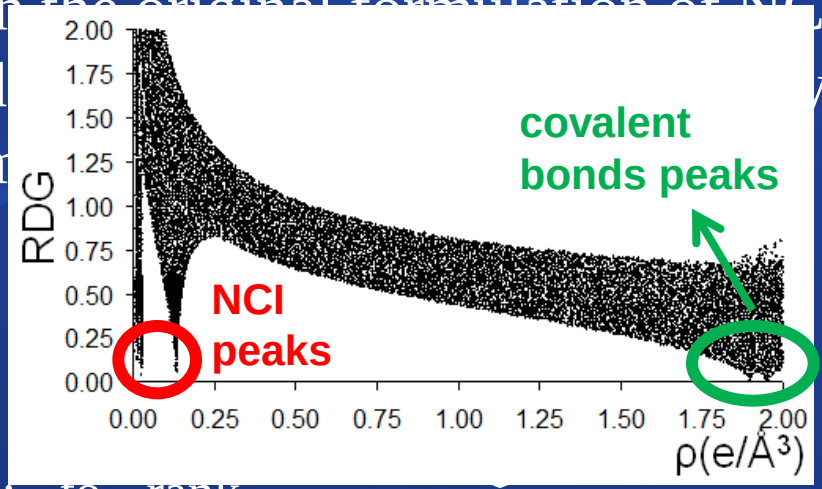
small RDG values in low-ED regions are the 'signature' of NCI

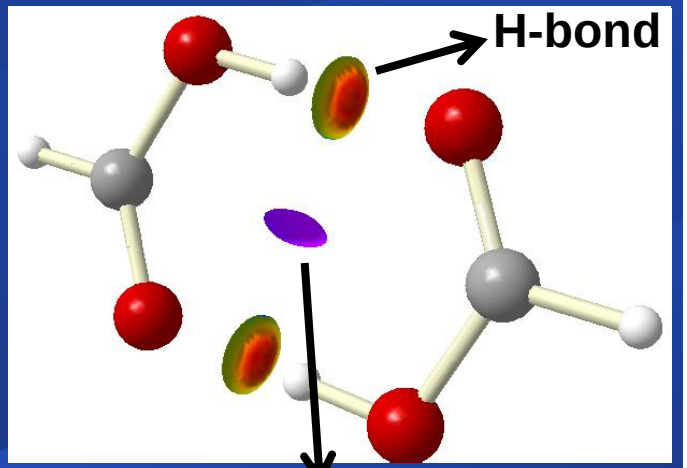
low-value RDG isosurfaces (low-ED regions*) detect NCI

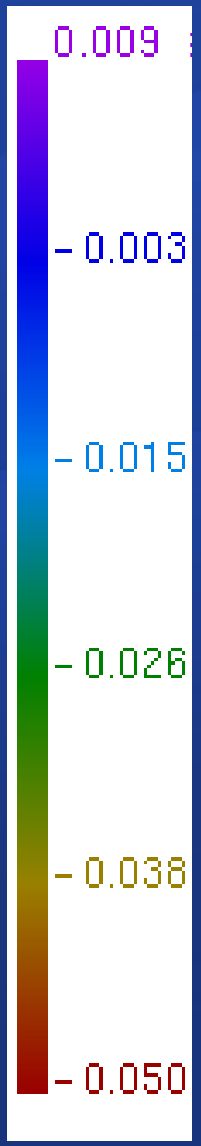
in the original formulation of NCI

d y is

m







ED: to rank the strength of interactions (the higher the stronger)

second eigenvalue of ED Hessian matrix: to distinguish between attractive interactions ($\lambda_2 < 0$) and non-bonded contacts ($\lambda_2 > 0$)

* A cutoff of 0.05 au (= 0.337e/Å^3) has been used throughout

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NCI DESCRIPTOR: application to experimentally derived ED

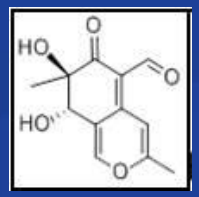
WE HAVE APPLIED *FOR THE FIRST TIME* THE RDG-BASED NCI DESCRIPTOR TO EXPERIMENTALLY DERIVED ELECTRON DENSITIES[2]

AIM OF THIS WORK:

- Apply NCI descirptor to experimental ED (data from literature[3-5]) by building an *ad-hoc* code
- Explore how this NCI descriptor characterizes the interactions present in various molecular crystals
- Compare the NCI picture with the one offered by QTAIM
- Compare the experimental picture with fully periodical calculations to explore the reliability of results

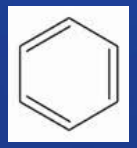
TEST CASES (molecular crystals):

AUSTDIOL[3]:



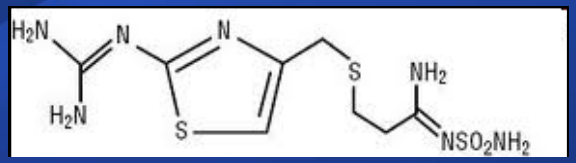
- many HBs (from weak C-H···O to strong O-H···O)
- vdW NCI play an important role

BENZENE[4]:



- characterized by NCI involving π electrons

FAMOTIDINE[5]:



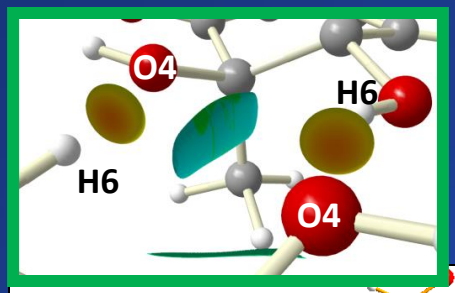
- heteroatoms-rich (many kinds of interaction)
- two polymorphs

[2] G. Saleh, C. Gatti, L. Lo Presti, J. Contreras-Garcia (2012) *Chem. Eur. J.*,18(48),15523

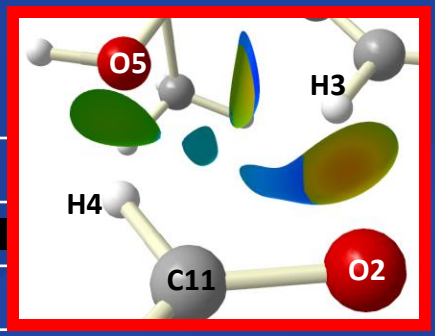
[3] L. Lo Presti *et al*. J.Phys.Chem.B(2006) 110, 6405-6514 [4] H.S. Börgi *et al*. Chem.Eur.J.(2002) 8,No.15,3512-3521 [5] J. Overgaard *et al*. Acta Cryst. (2004) A60, 480-487

NCI PICTURE ON AUSTDIOL: HBs

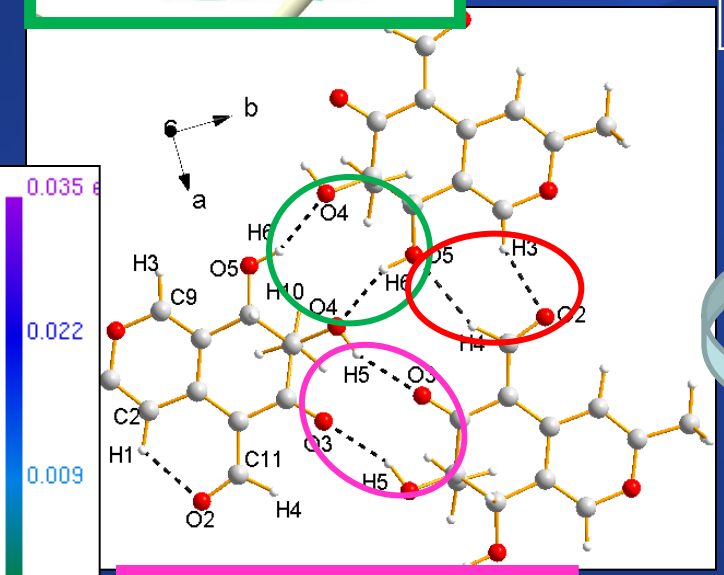
in the *a*,*b* plane of Austdiol crystal molecules are held together by HB network



	dH···O (Å)	ρ_{BCP}(e/Å^3)	λ1	λ2
H6···O4	2.023	0.14(4)	-0.75	-0.71



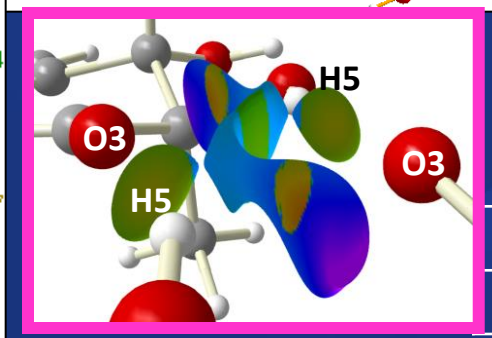
	dH···O (Å)	ρ_{BCP}(e/Å^3)	λ1	λ2
H4···O5	2.519	0.05(2)	-0.26	-0.18
H3···O2	2.174	0.13(3)	-0.68	-0.45



- HBs are described as disc-shaped isosurfaces (λ_2<0). Stronger HBs give rise to smaller isosurfaces

shrinking of isosurfaces mirrors the more localized character of stronger interactions (despite higher higher ρ_{BCP}): higher curvatures ($\nabla\rho$ grows faster)

$$RDG \propto \frac{|\nabla \rho|}{\rho^{4/3}}$$

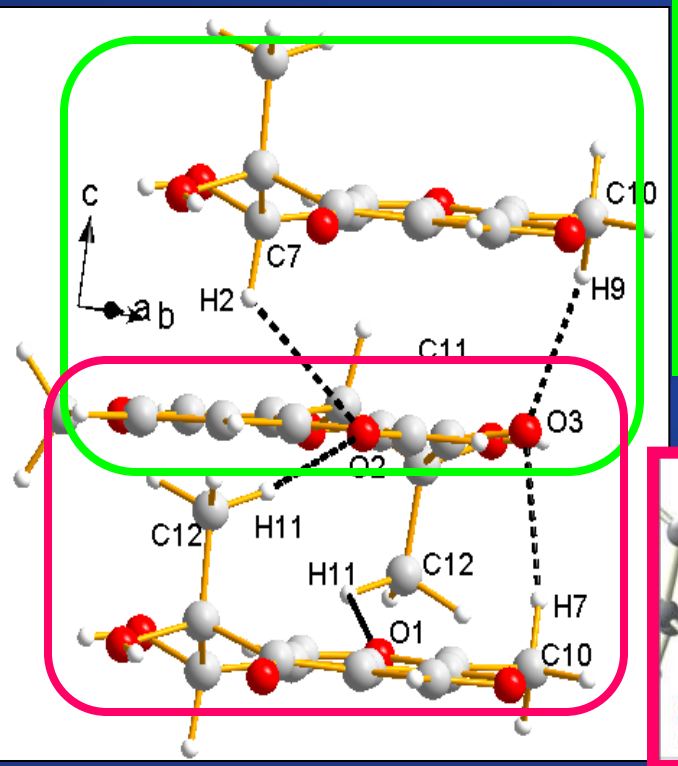


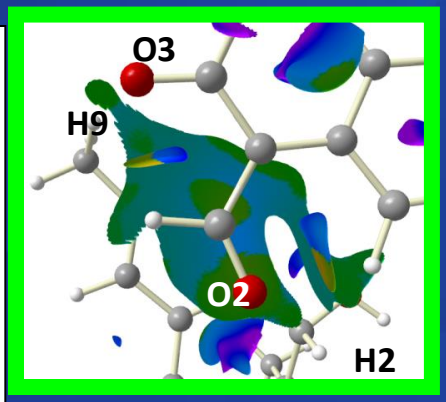
	dH···O (Å)	ρ_{BCP}(e/Å^3)	λ1	λ2
H5···O3	2.114	0.09(4)	-0.57	-0.39

RDGisoval.= **0.6**

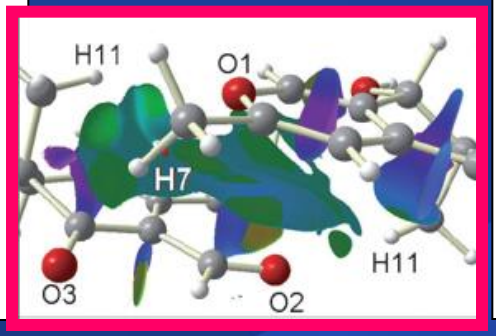
NCI PICTURE ON AUSTDIOL: vdW

In the *c* direction of Austdiol crystal there are no strong HB.
QM calculation showed that van der Waals interactions plays a significant role.



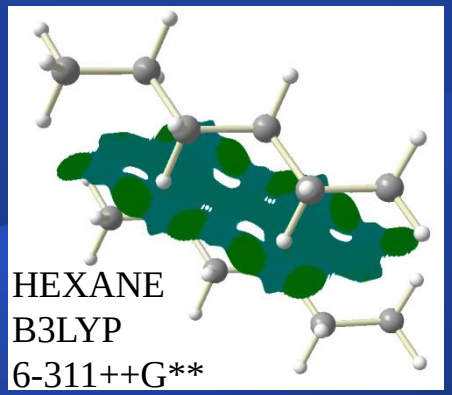


RDGisoval.= **0.6**



vdW interactions are descibed as large isosurfaces with very low ED

isosurfaces similar to the ones found in hydrocarbons



DISPERSIVE INTERACTIONS:

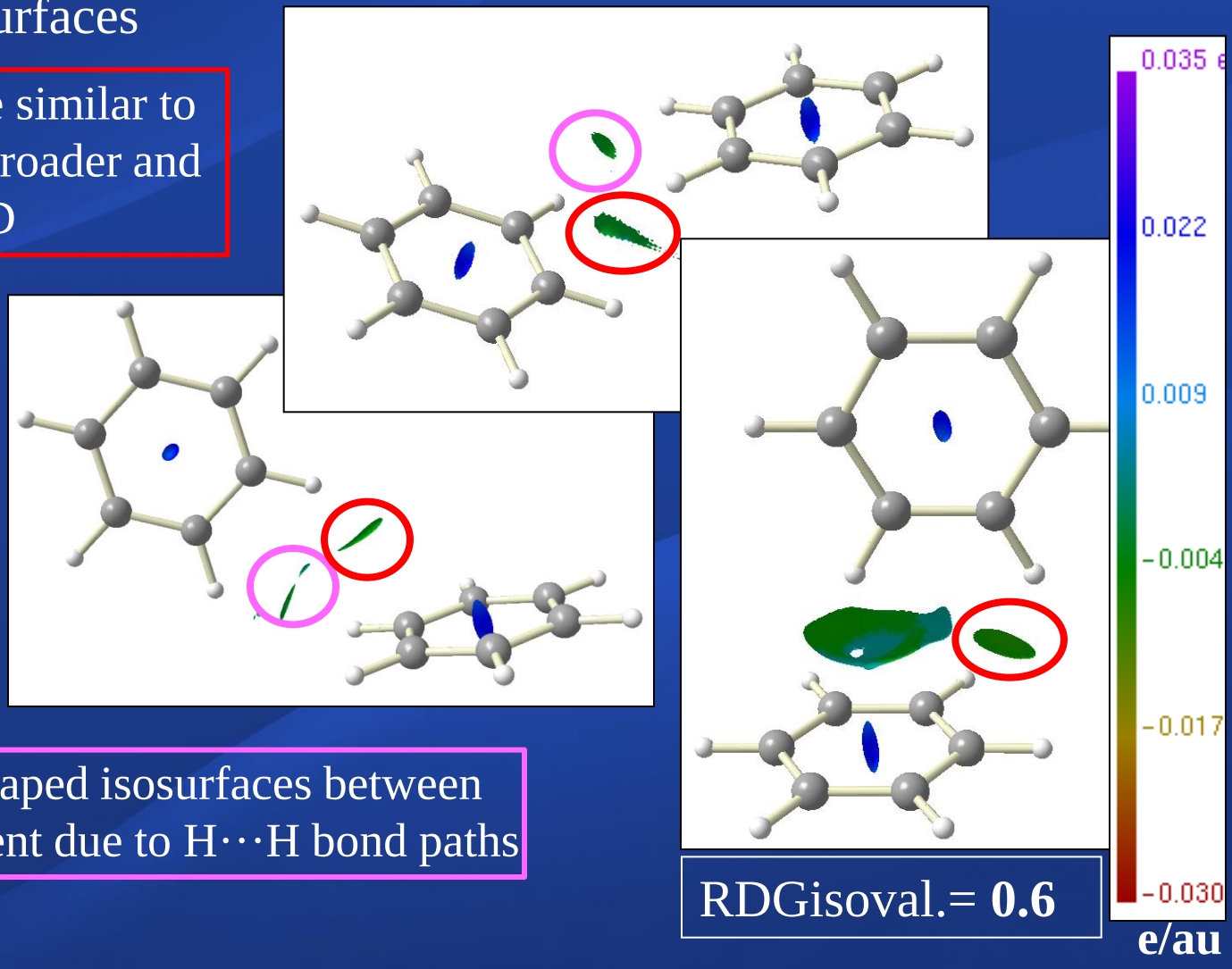
- are inherently non-local
- always present
- do not significantly affect ED
- are not described by 'common' DFT methods

THESE KIND OF ISOSURFACES SIMPLY HIGHLIGHT AN ED DISTRIBUTION IN WHICH vdW (DISPERSIVE) INTERACTIONS PLAY A SIGNIFICANT ROLE (no strong interactions)

BENZENE: crystal packing

Benzene packing motifs has been classified as ‘herringbone’. Such motifs maximize the number of C-H···π and C-H···C contacts [6]. Such behavior is mirrored by NCI isosurfaces

C-H···C isosurfaces are similar to HB but the former are broader and have lower ED



additional disc-shaped isosurfaces between hydrogens are present due to H···H bond paths

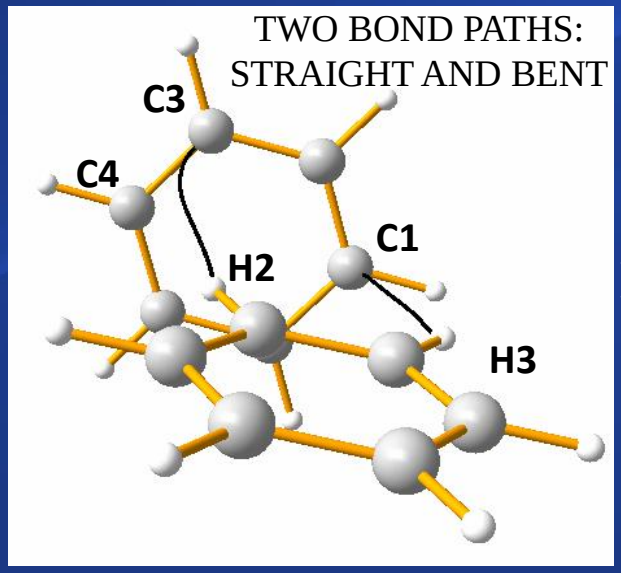
RDGisoval.= **0.6**

[6] G. R. Desiraju, A. Gavezzotti, Acta Crystallogr. Sect. B 1989, 45, 473 – 482

COMPARISON WITH QTAIM: benzene

- Quantum Theory of Atoms In Molecules (QTAIM) is able to provide *quantitative* estimation of interactions (and it is rooted in quantum mechanics).
- QTAIM picture is discontinuous: presence or absence of Bond Paths (yes/no)
- Bond Paths join two atoms: delocalized interactions are often not recovered

QTAIM description

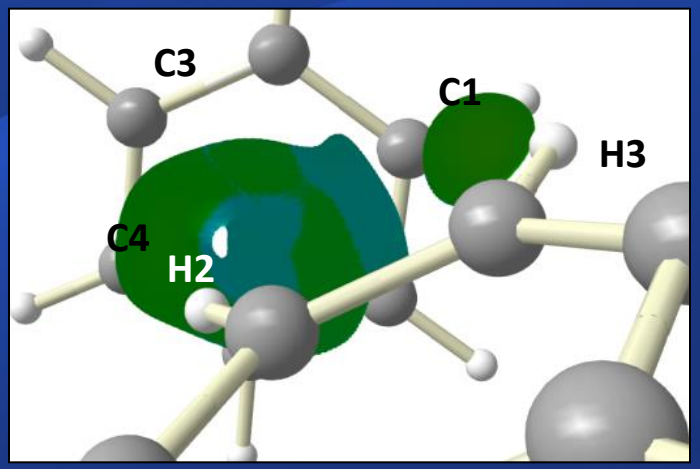


molecular pair from benzene crystal

H2 is above the centre of the benzene ring

($d_{C\cdots H}$ min= 3.065 Å ; $d_{C\cdots H}$ max=3.109 Å)

In such cases H interacts with the whole π cloud [7]



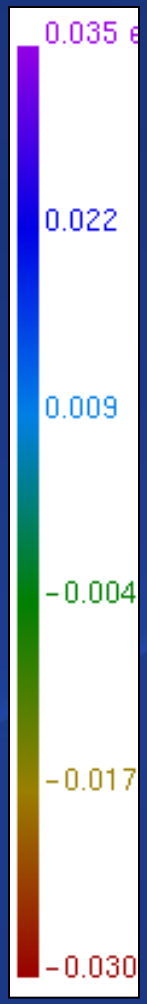
RDG-based description

(isovalue=0.6)

RDG-based NCI descriptor is able to recover the delocalized character of interactions also when QTAIM is not

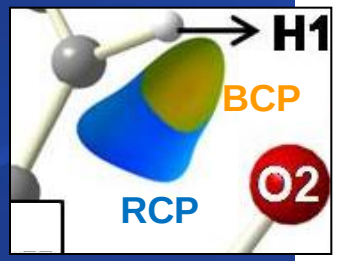
[7] Nishio, M. *Phys. Chem. Chem. Phys.*, **2011**, 13,13873-13900

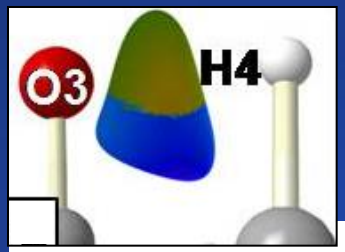
COMPARISON WITH QTAIM: austdiol

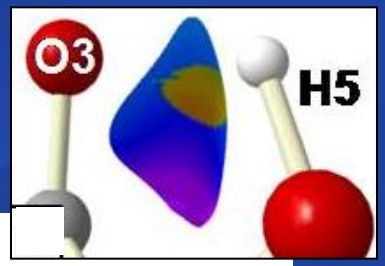


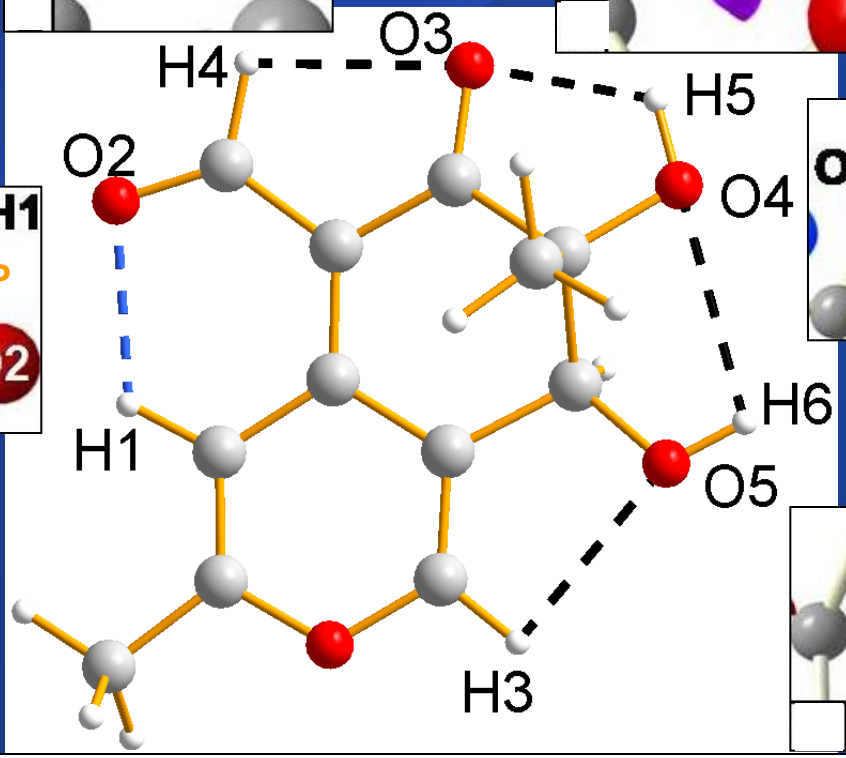
e/au

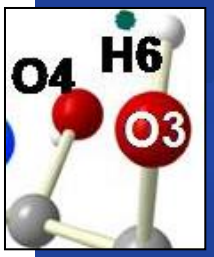
(isovalue=0.6)

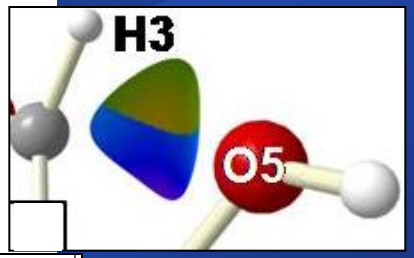












Bond	ρ_{BCP}(e/Å^3)	$\nabla^2\rho_{BCP}$(e/Å^5)	$d_{H\cdots O}$(Å)	angle XHO(deg)
C(2)-H(1)···O(2)	0.11(3)	2.00(3)	2.145	121.8
C(11)-H(4)···O(3)	no BCP	no BCP	2.359	100.5
O(4)-H(5)···O(3)	no BCP	no BCP	2.052	116.9
O(5)-H(6)···O(4)	no BCP	no BCP	2.589	102.2
C(9)-H(3)···O(5)	no BCP	no BCP	2.461	92.1

NCI is a more 'continuous' descriptor with respect to QTAIM

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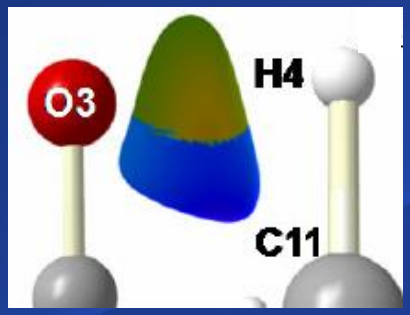
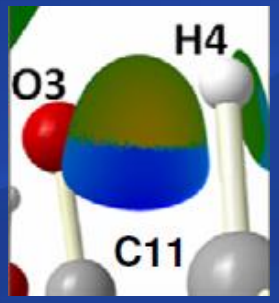
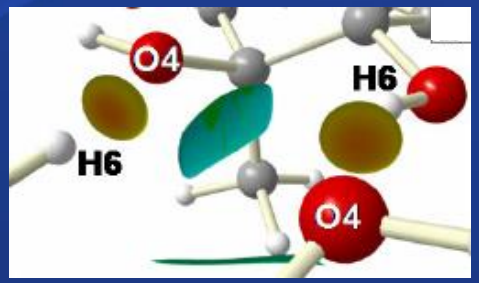
COMPARISON WITH THEORY
(periodical B3LYP/6-311G**)

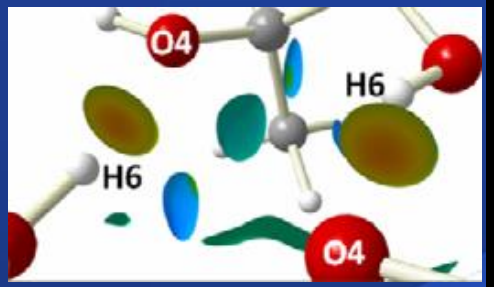
EXPTL (RDG=0.6)

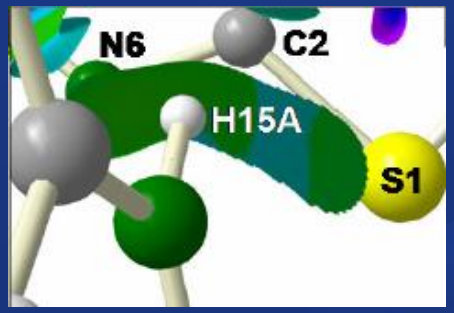


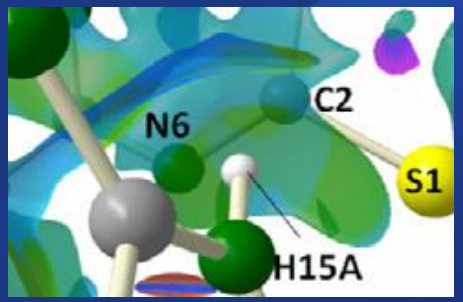
THEO (RDG=0.6)



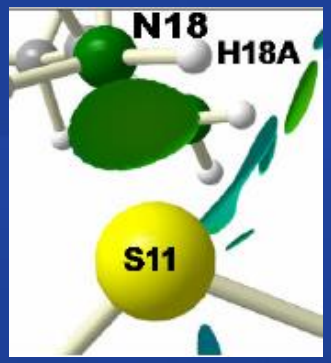




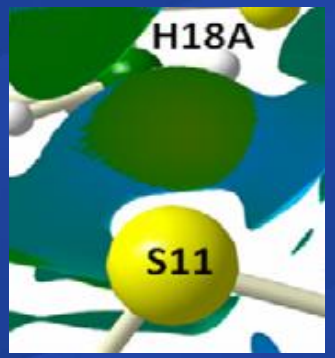


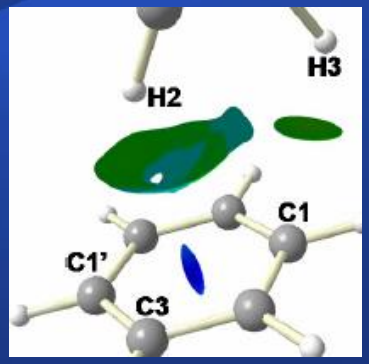


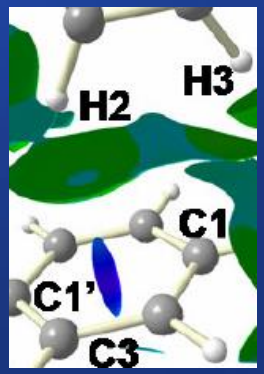
EXPTL (RDG=0.6)



THEO (RDG=0.6)



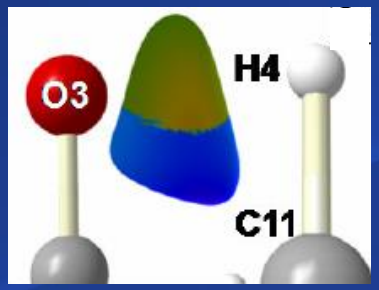


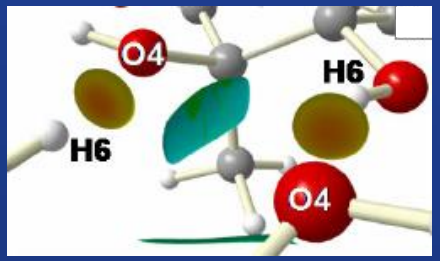


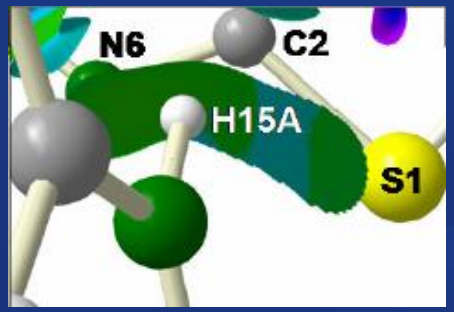
bad agreement for weak interactions

COMPARISON WITH THEORY
(periodical B3LYP/6-311G**)

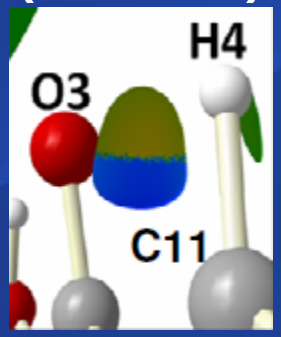
EXPTL (RDG=0.6)

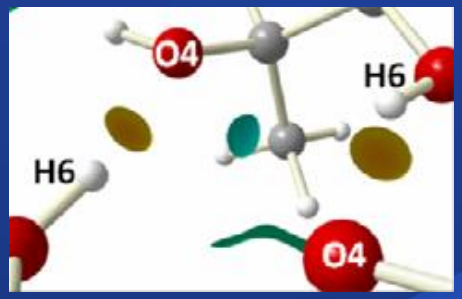


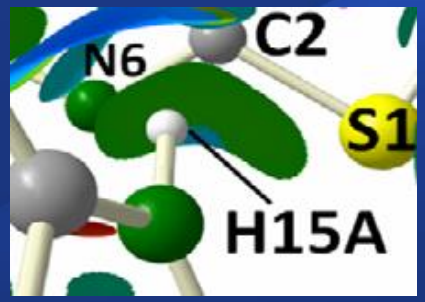


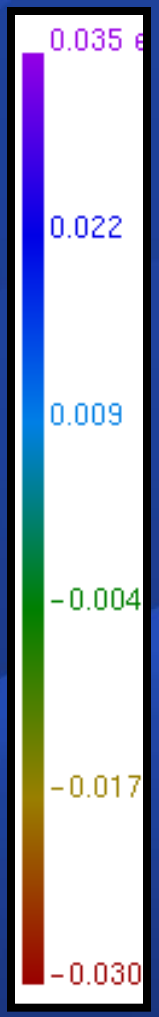


THEO (RDG=0.4)

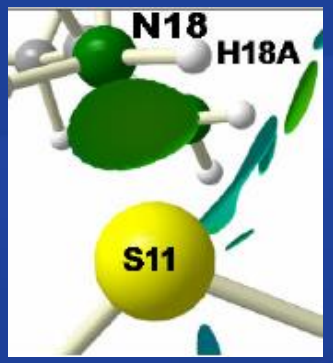


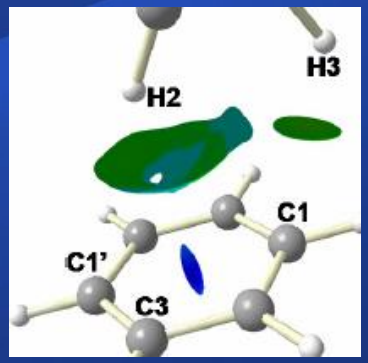




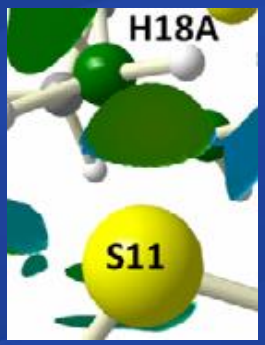


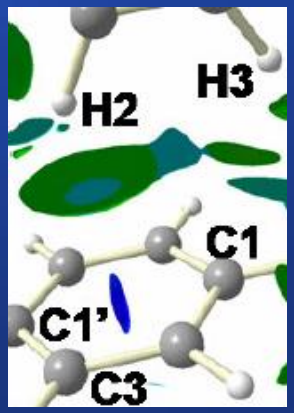
EXPTL (RDG=0.6)





THEO (RDG=0.4)



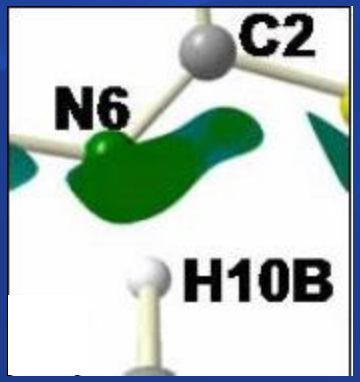


GOOD GENERAL AGREEMENT!

COMPARISON WITH THEORY
(periodical B3LYP/6-311G**)

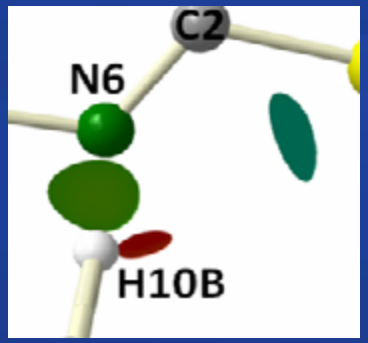
Among all the investigated interactions, only in one case we found a qualitatively different NCI picture between experiment and theory:

EXPTL (RDG=0.6)

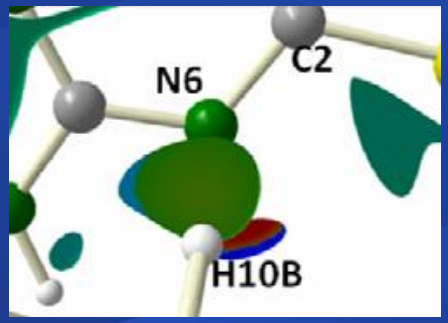


C-H···π

THEO (RDG=0.4)



THEO (RDG=0.6)



H-bond (C-H···N)

(likely to be caused by bad decription of hydrogen thermal motion in Famotidine)

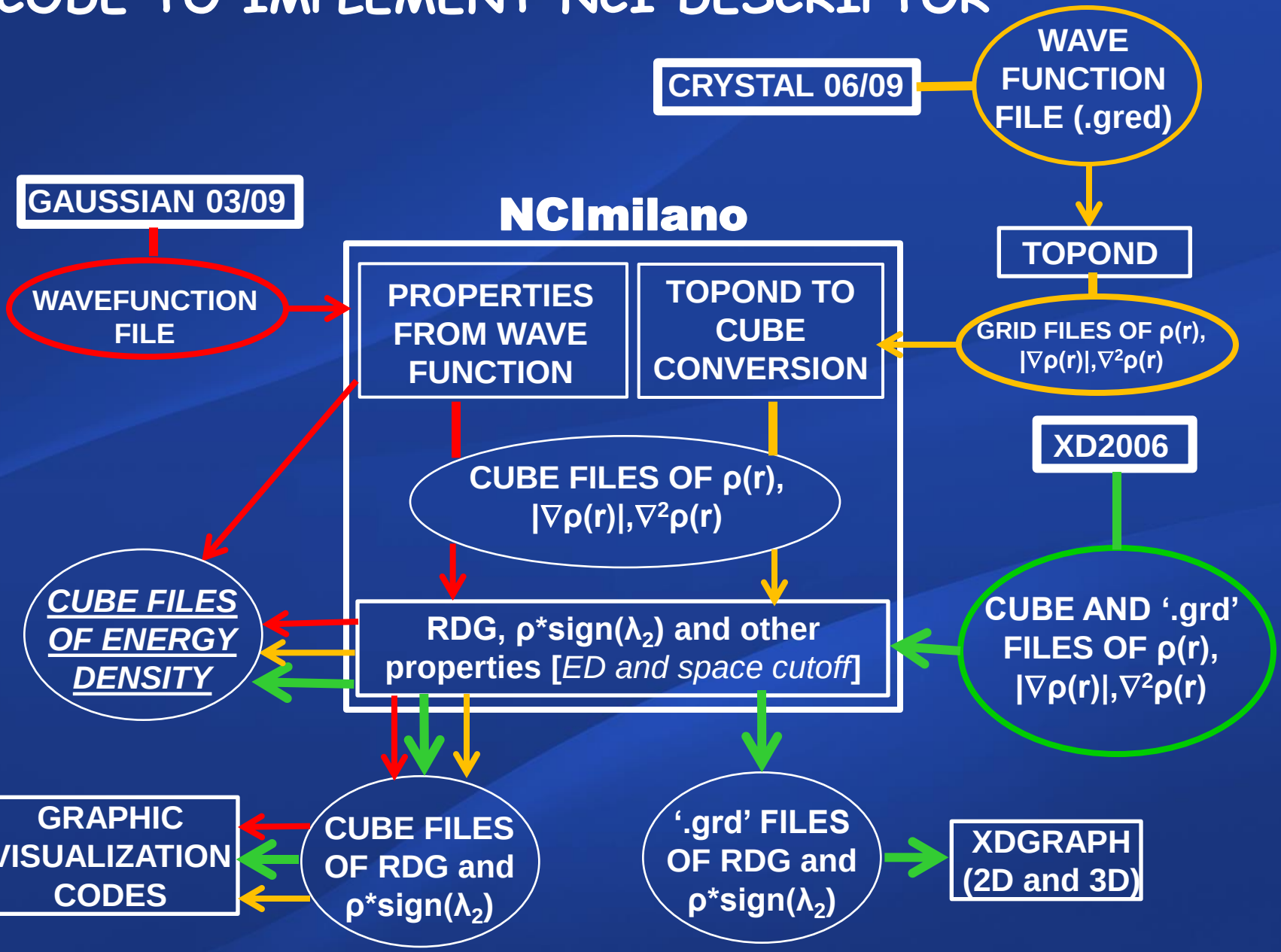
COMPARISON WITH THEORY: RDG isovalue

A scaling of RDG is necessary to obtain a good agreement between experiment and theory

RDG is also a measure of inhomogenity:
for the investigated cases, experimental ED distribution in intermolecular regions is less (too little?) homogeneous with respect to the theoretical ED distribution

- NCI DESCRIPTOR: brief introduction
- APPLICATION TO EXPERIMENTAL ELECTRON DENSITIES
- COMPARISON WITH THEORY
- OUR CODE TO IMPLEMENT NCI DESCRIPTOR (going beyond the original description?)

OUR CODE TO IMPLEMENT NCI DESCRIPTOR*



* G. Saleh, C. Gatti, L. Lo Presti, D. Ceresoli. **J. Appl. Cryst.**, *accepted*

ENERGY DENSITY

THE USE OF THE TOTAL ENERGY DENSITY $H(\mathbf{r})$ AS A QUANTITY TO BE MAPPED ONTO RDG ISOSURFACES BRINGS SEVERAL ADVANTAGES:

- It is a quantum-mechanical rooted quantity (integration over the whole system gives the total energy)
- The (arbitrary) distinction between attractive and repulsive interactions ($\text{sign}(\lambda_2)$) is avoided
- The decomposition into kinetic and potential contributions ($H(\mathbf{r})=G(\mathbf{r})+V(\mathbf{r})$) might give a better understanding of interaction type

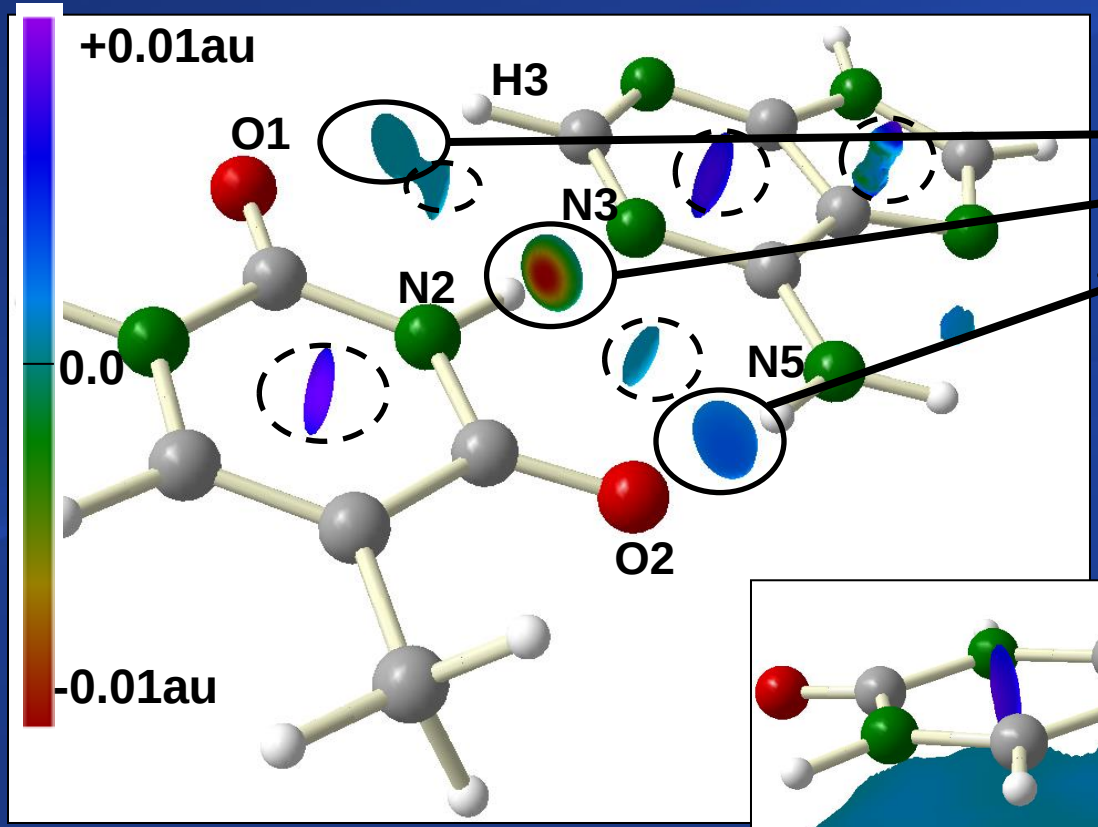
BUT: $H(\mathbf{r})$ requires the wavefunction to be evaluated

Abramov's functional[8] allows to obtain reliable estimation of H(r) IN LOW ED REGIONS using ED DISTRIBUTION ONLY

IT IS POSSIBLE TO OBTAIN H(r) DIRECTLY FROM ED
(NCI RDG isosurfaces appears in low ED regions)

[8] Y.A. Abramov. (1997) *Acta Cryst.* A53, 264-272

TOTAL ENERGY DENSITY H(r): adenine-thymine (B3LYP/6-311++G**)



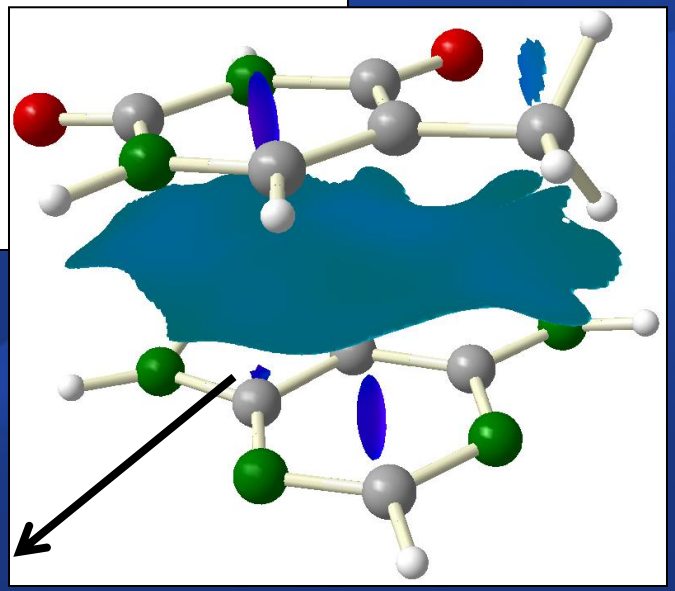
H-BONDS:

	$d_{H\cdots X}$ (Å)	angle
C3-H3···O1	2.830	132.8
N2-H2···N3	1.819	179.1
N5-H5···O2	1.929	173.6

Very weak: almost zero

Moderate: positive

Strong: negative



RCP: positive. Close to zero for 'non-covalent' RCP surfaces

Van der Waals: H is very close to zero

adenine-thymine: POTENTIAL AND KINETIC CONTRIBTUION

	$d_{H\cdots X}$ (Å)	angle
C3-H3···O1	2.830	132.8
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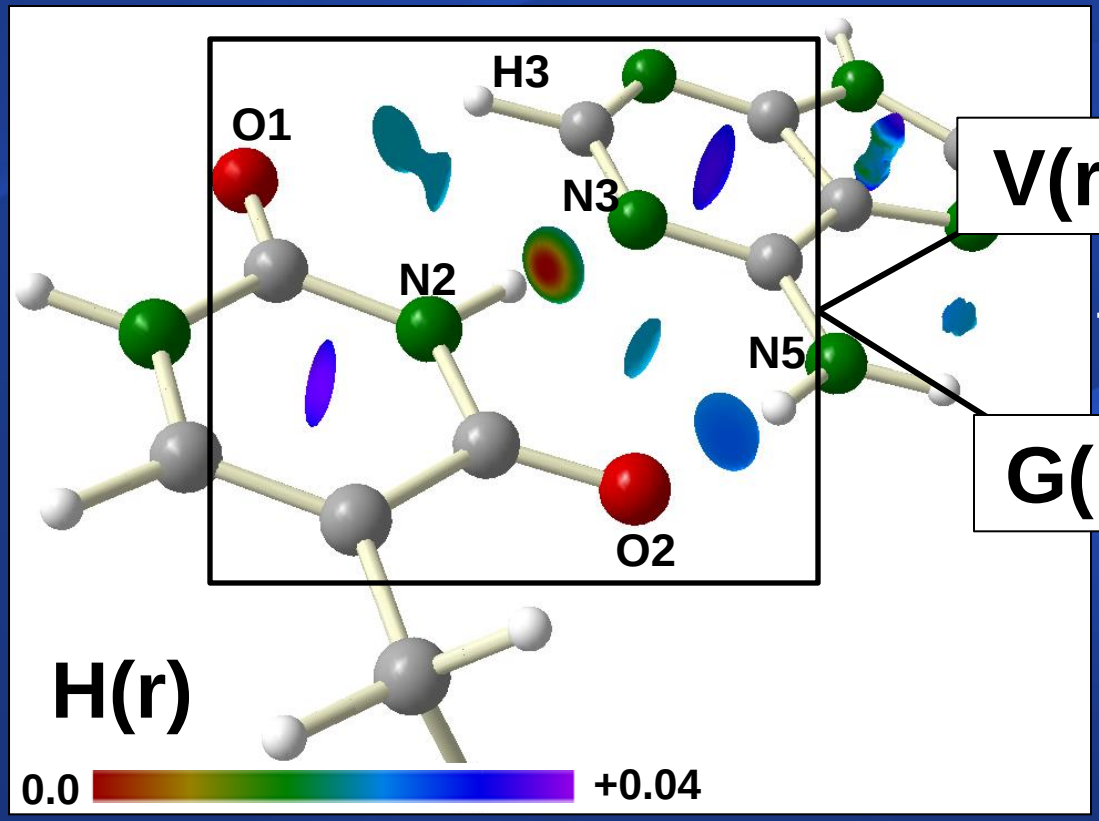
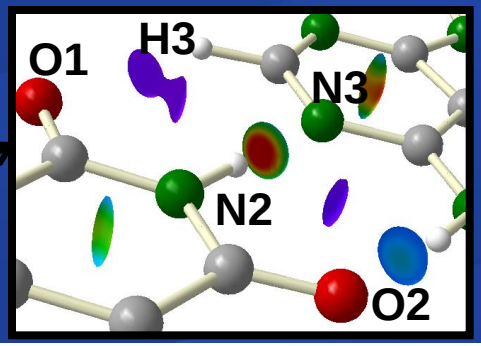


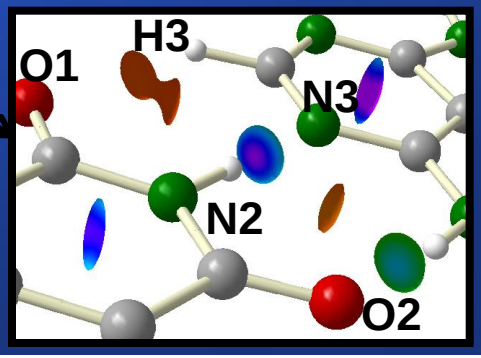
V(r)



-0.04 0.0

Hartree

G(r)

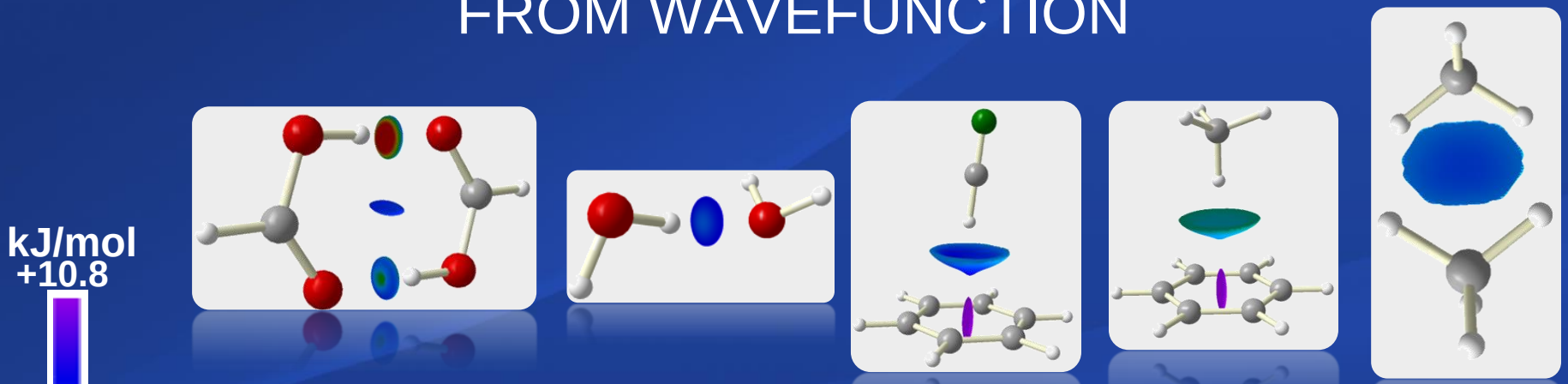


0.0 +0.04

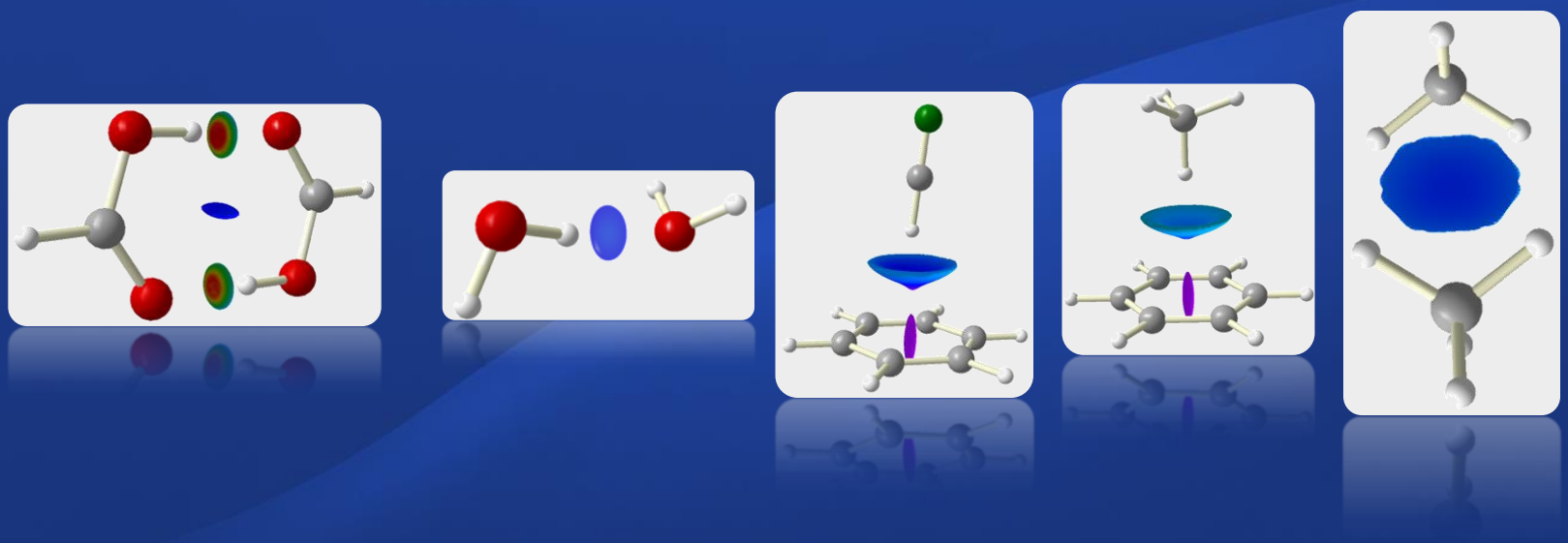
Hartree

ENERGY DENSITY FROM ED DISTRIBUTION

FROM WAVEFUNCTION



FROM ABRAMOV'S FUNCTIONAL



CONCLUSIONS

• RDG-based NCI descriptor has been applied to experimentally derived (X-ray diffraction) ED distribution of molecular crystals

• It has been shown how such descriptor mirrors the intermolecular interactions which give rise to the observed crystal packing

• The comparison with QTAIM confirmed that RDG-based NCI descriptor is able to go beyond the discontinuous description given by bond paths analysis (hence to recover the delocalized character of certain interactions)

• In general, QTAIM and NCI descriptor can be fruitfully complemented each other to gain insights into the various NCI present in a system

• The reliability of results has been demonstrated through a comparison with periodical calculation, although a scaling of isovalue is necessary to fully match the two pictures

• A code to apply NCI descriptor to experimental as well as theoretical (both periodic and *in vacuo*) ED distribution has been implemented (THE PROGRAM IS AVAILABLE UPON REQUEST: JUST CONTACT ME!)

• The use of energy density as a quantity to be mapped onto RDG isosurfaces might help to obtain a better description of the various NCI

THANKS TO:

- The organizers of this conference
- Dr. Carlo Gatti and Dr. Leonardo Lo Presti
- The Center for Materials Crystallography (Aarhus, Denmark)

YOU ALL FOR THE ATTENTION

(grazie per l'attenzione)