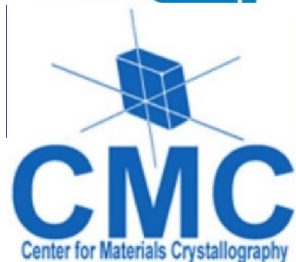




Giornate del CrisDi

The Role of Crystallography in Drug Science and Biology



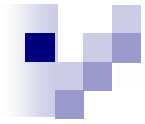
Gaining insights on chemistry from the analysis of the charge density

Torino, March 5th, 2018

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Outline

1. The **Quantum Theory of Atoms in Molecules**
2. Applications
 - 2.1 The problem of electron delocalization
 - 2.2 A tool for 'seeing' Non-Covalent Interactions in the real space



Outline

1. The **Quantum Theory of Atoms in Molecules**

2. Applications

2.1 The problem of electron delocalization

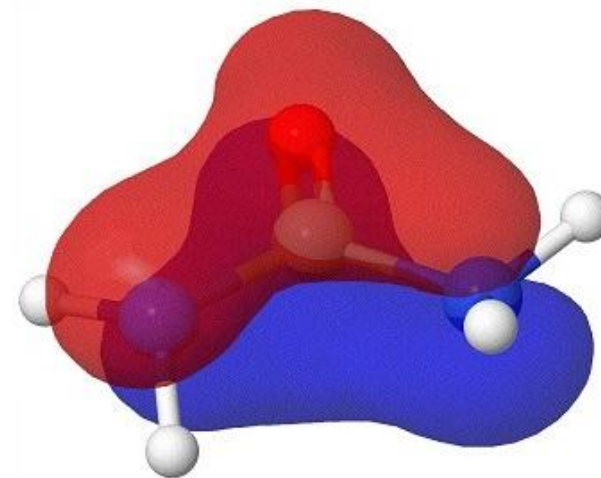
2.2 A tool for 'seeing' Non-Covalent Interactions in the real space

The quantum description

Quantum mechanics: the wavefunction $\psi(\mathbf{r},\mathbf{R})$ contains all the conceivable information of a given quantum system in a stationary state

But: molecular orbitals are usually **delocalized** over a significant part of the nuclear ensemble

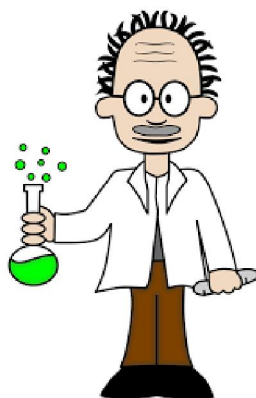
The quantum description, **despite being formally correct**, often lacks of interpretability from the viewpoint of the synthetic chemist





Do atoms in molecules even exist?

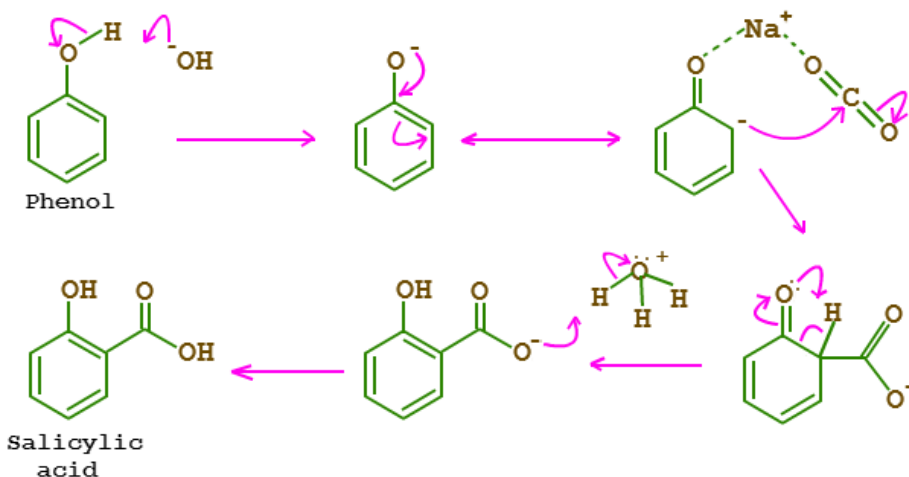
Synthetic chemist: **yes**



Physicist: **What really matters is the total wavefunction**

$$\Psi(\mathbf{r}, \mathbf{R})$$

Which, however, it is **NOT** an experimental observable

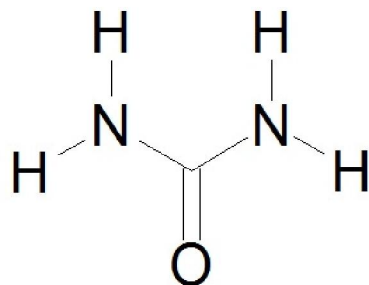
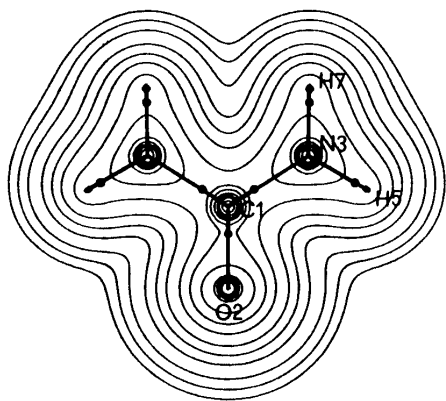


The central role of the electron density

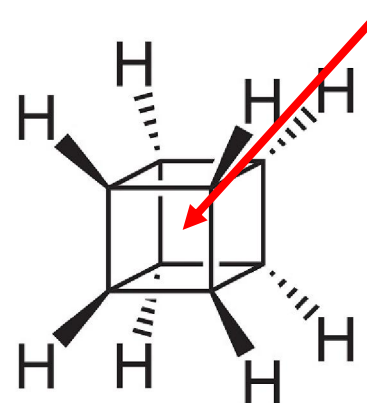
In the real space, chemistry is governed by the **electron density**:

$$\rho(\mathbf{r}) = N \int_{-\infty}^{+\infty} \psi^*(\mathbf{r}_1 \dots \mathbf{r}_N, \mathbf{R}_1 \dots \mathbf{R}_M) \psi(\mathbf{r}_1 \dots \mathbf{r}_N, \mathbf{R}_1 \dots \mathbf{R}_M) ds_1 d^4 \mathbf{r}_2 \dots d^4 \mathbf{r}_N d^4 \mathbf{R}_1 \dots d^4 \mathbf{R}_M$$

It expresses the **probability density** (per unit volume) of finding an electron at point \mathbf{r} , independent from its spin, and from spins and positions of all the other electrons and nuclei. By definition, it is always *positive*.



It is a continuous and differentiable scalar field in \mathbb{R}^3 , with maxima (usually) at nuclei and minima either at $r \rightarrow \infty$ or at the centre of closed *atom cages*



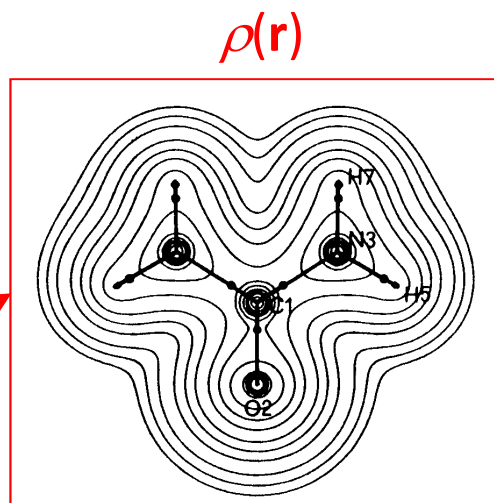
The central role of the charge density



Accessible from
the experiment

$$\rho(\mathbf{r}) = \frac{1}{V} \sum_{hkl=-\infty}^{\infty} F_{hkl} e^{-2\pi i(hx+ky+lz)}$$

$$F_{hkl} = \int_V \rho(\mathbf{r}) e^{2\pi i(hx+ky+lz)} d^3 \mathbf{r}$$



$$\rho(\mathbf{r}) = N \int_{-\infty}^{+\infty} \psi^* \psi d\mathbf{r}' d\mathbf{R}$$

$$-\frac{\hbar^2}{2m} \nabla^2 \psi + V(\mathbf{r}) \psi = E \psi$$

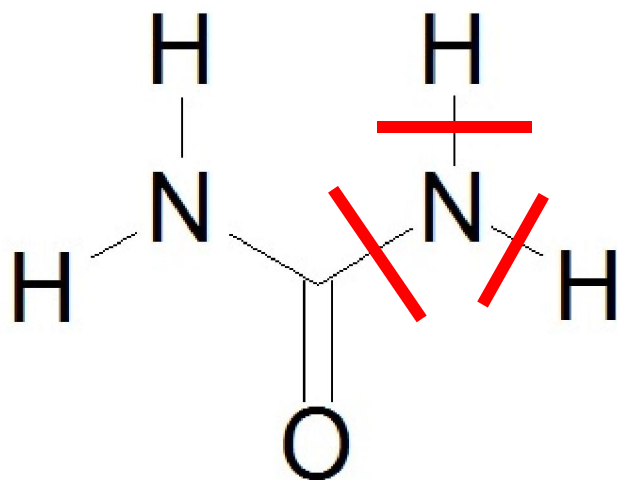
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quantum simulations



Chemical bond
Molecular properties
Non Covalent Interactions

Partitioning criteria

To define atoms in molecules, thus reconciling the quantum perspective with the chemist' one, choosing a partitioning criterion is mandatory





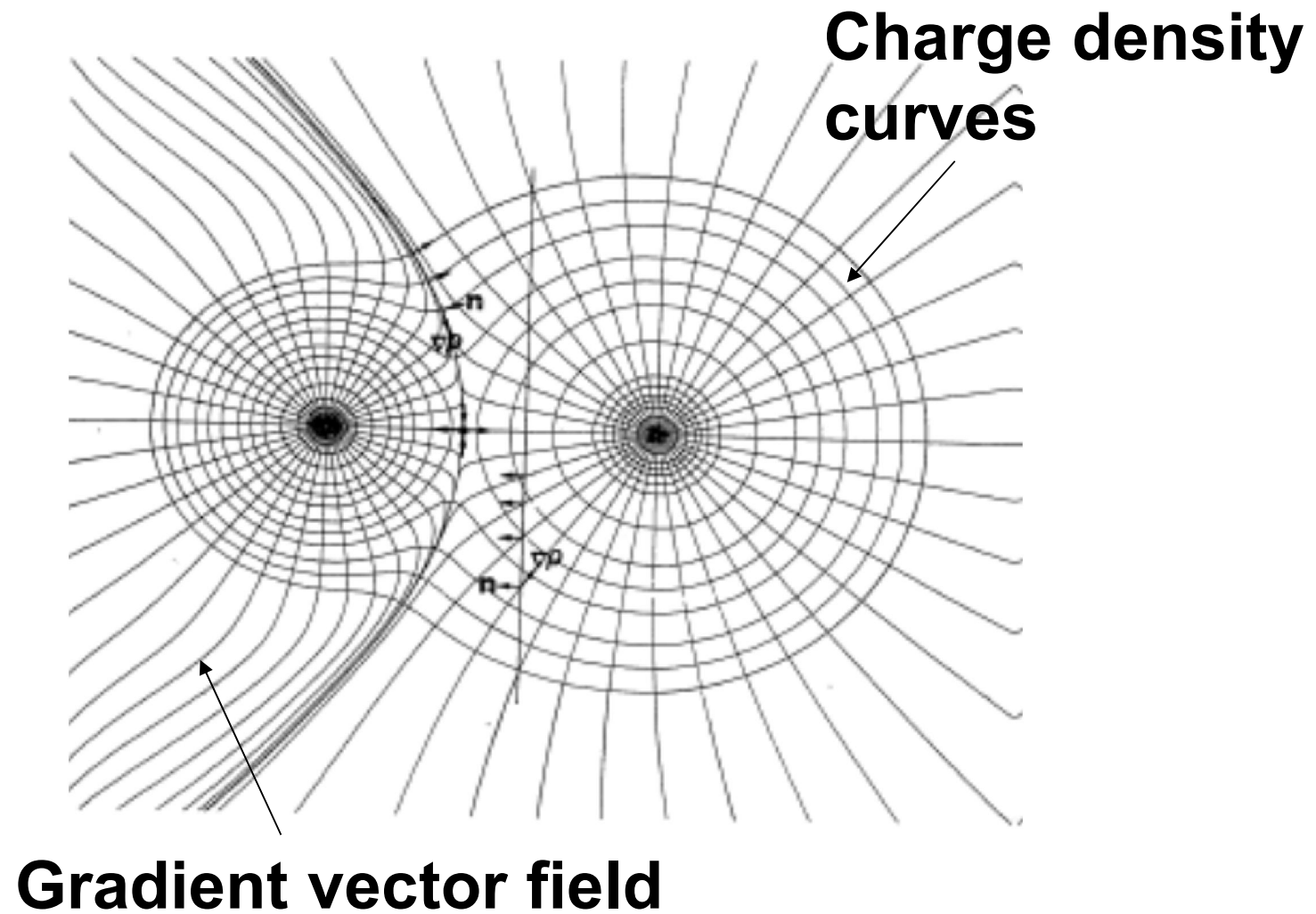
Quantum Theory of Atoms in Molecules

R. F. W. Bader defines an 'atom' through the topology of the $\rho(\mathbf{r})$ scalar field (*Atoms in Molecules, AIM, approach*)

Topological atom: a nucleus + the region of space enclosed by surfaces S which are never crossed by the gradient lines of $\rho(\mathbf{r})$, i.e.

$$\oint_S \nabla \rho(\mathbf{r}) \hat{\mathbf{n}} dS = 0$$

The topological atom

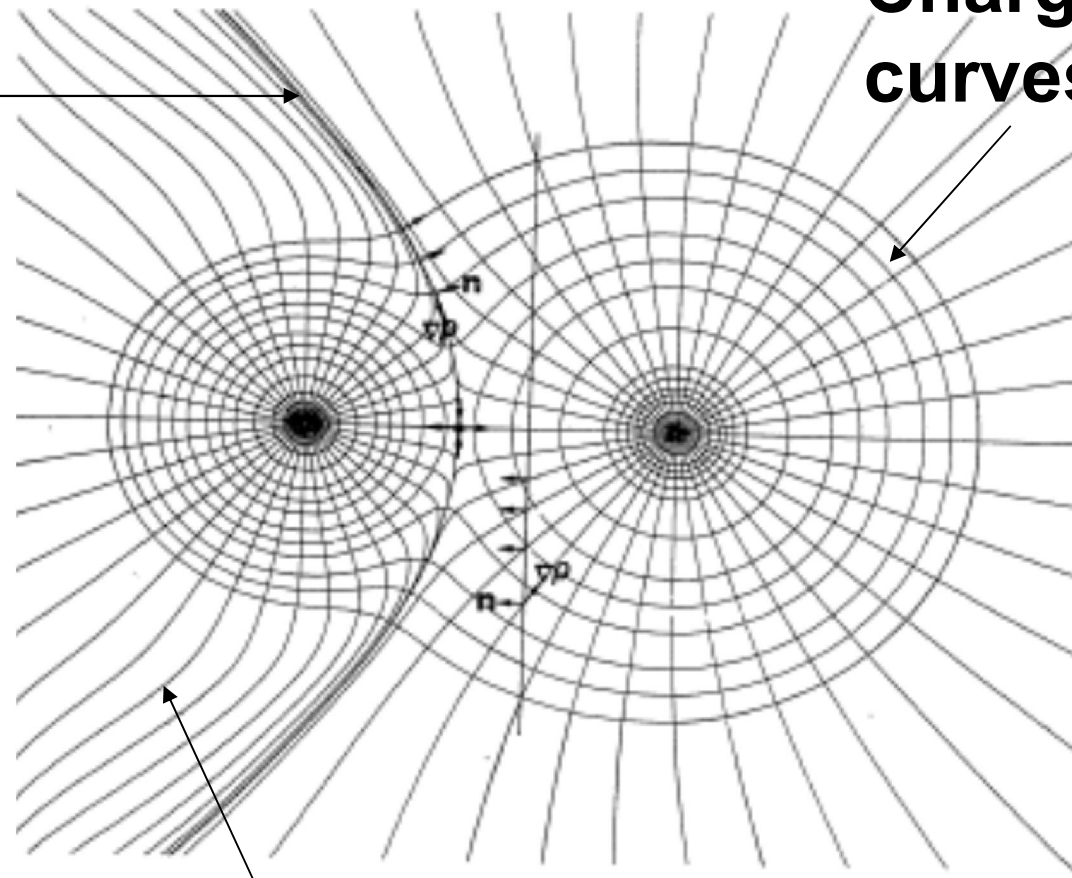


The topological atom

Zero-flux surface

$$\oint_S \nabla \rho(\mathbf{r}) \cdot \hat{\mathbf{n}} dS = 0$$

Charge density curves



Gradient vector field

The topological atom

Zero-flux
surface

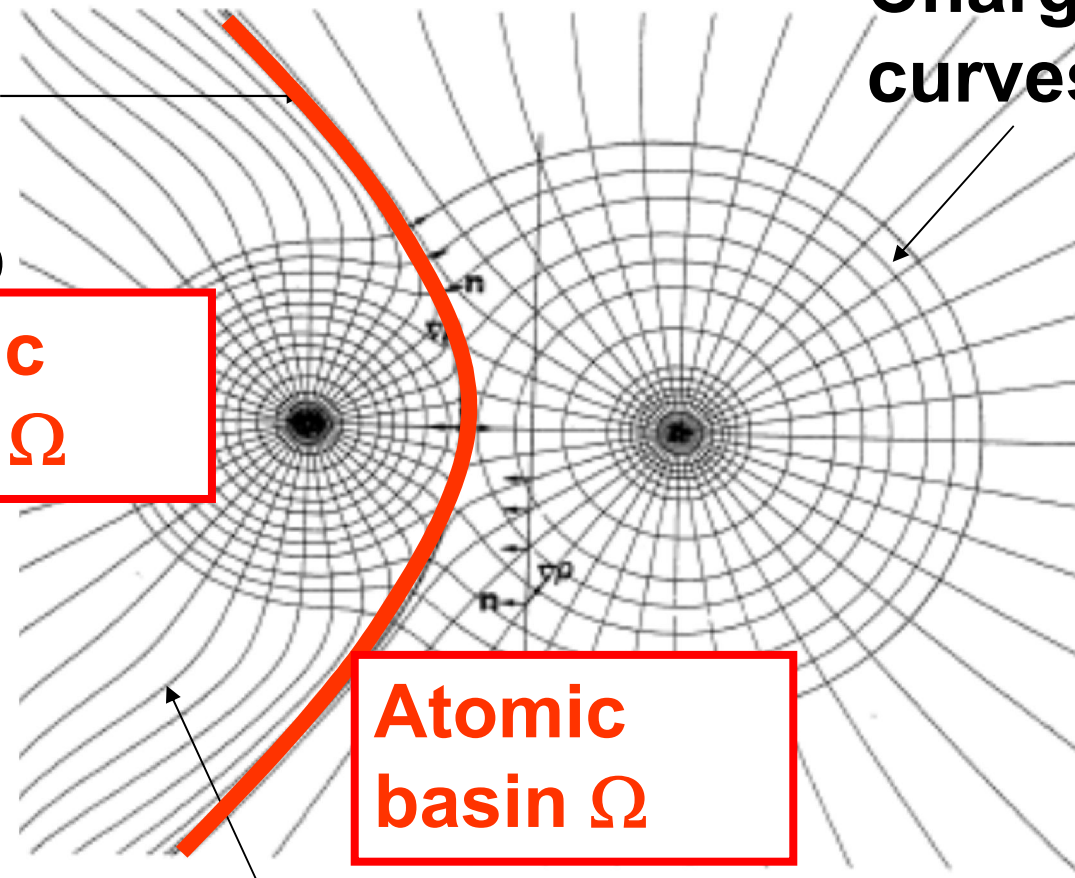
$$\oint_S \nabla \rho(\mathbf{r}) \cdot \hat{\mathbf{n}} dS = 0$$

Atomic
basin Ω

Atomic
basin Ω

Charge density
curves

Gradient vector field





Critical points

$\nabla \rho(\mathbf{r}_{cp}) = \mathbf{0}$ A point \mathbf{r}_{cp} is called a **critical point** if the gradient at that point is null

Different critical points are characterized by the eigenvalues of the **Hessian matrix**, which quantifies the **principal curvatures** λ_1 , λ_2 and λ_3 of ρ at that point.

$$\mathbf{H}[\rho(\mathbf{r}_{cp})] = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix},$$

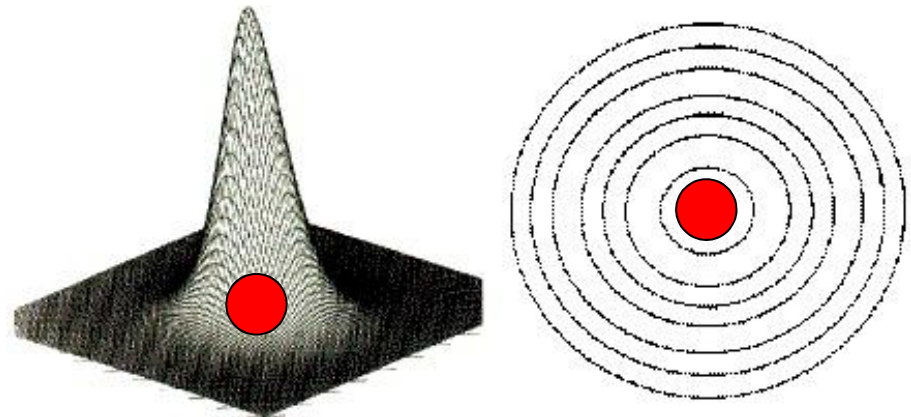
$$\lambda_1 = \frac{\partial^2 \rho(\mathbf{r}_{cp})}{\partial x^2}$$
$$\lambda_2 = \frac{\partial^2 \rho(\mathbf{r}_{cp})}{\partial y^2}$$
$$\lambda_3 = \frac{\partial^2 \rho(\mathbf{r}_{cp})}{\partial z^2}$$

By convention, $\lambda_1 < \lambda_2 < \lambda_3$

Critical points

Maximum (nuclear positions)

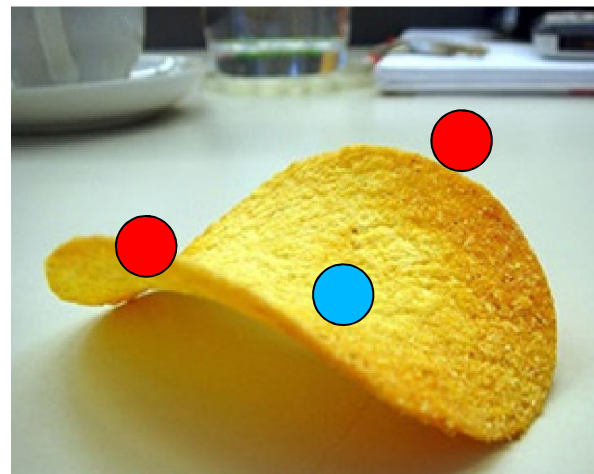
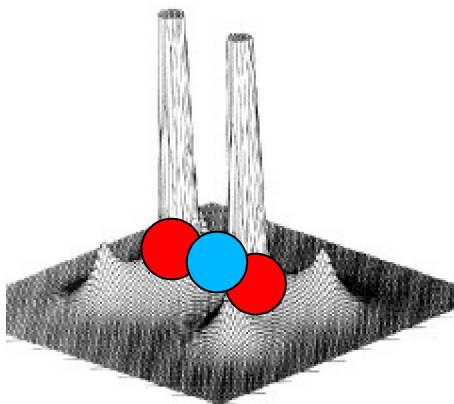
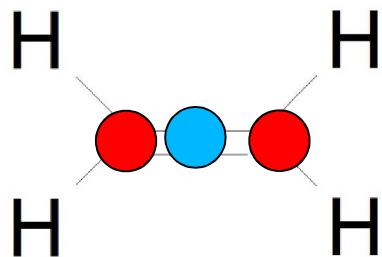
$$\lambda_1 < \lambda_2 < \lambda_3 < 0$$



Critical points

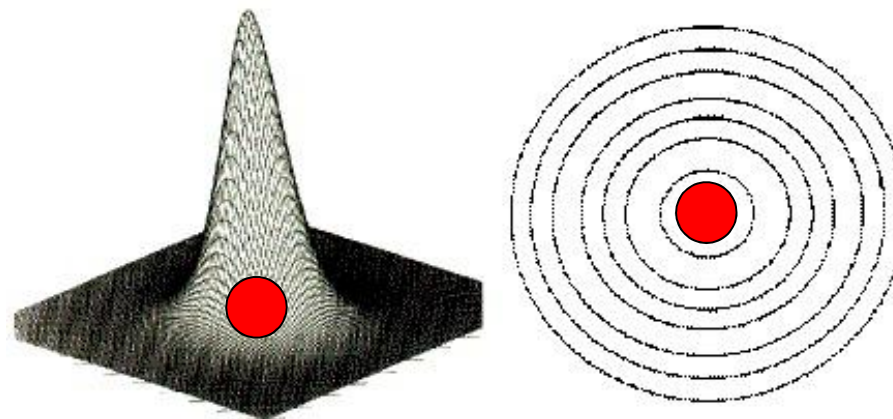
$$\lambda_1 < \lambda_2 < 0 < \lambda_3$$

Bond critical point (saddle): representative of chemical interactions



Maximum (nuclear positions)

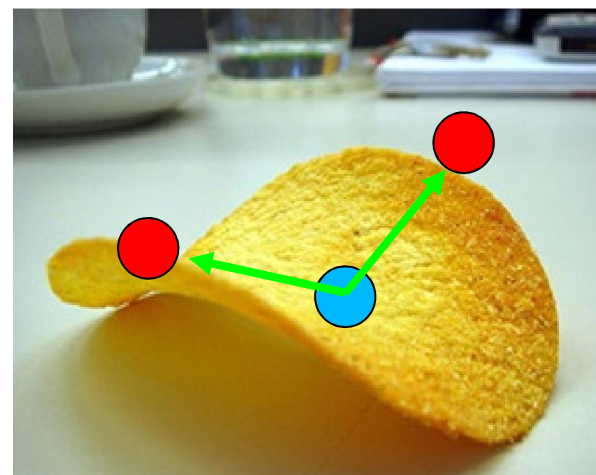
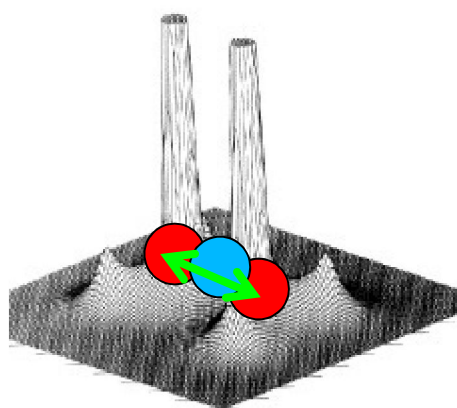
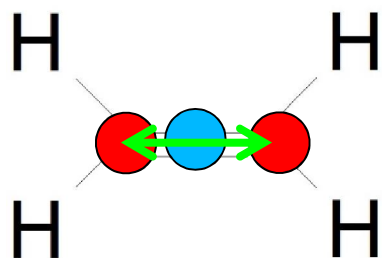
$$\lambda_1 < \lambda_2 < \lambda_3 < 0$$



Critical points

$$\lambda_1 < \lambda_2 < 0 < \lambda_3$$

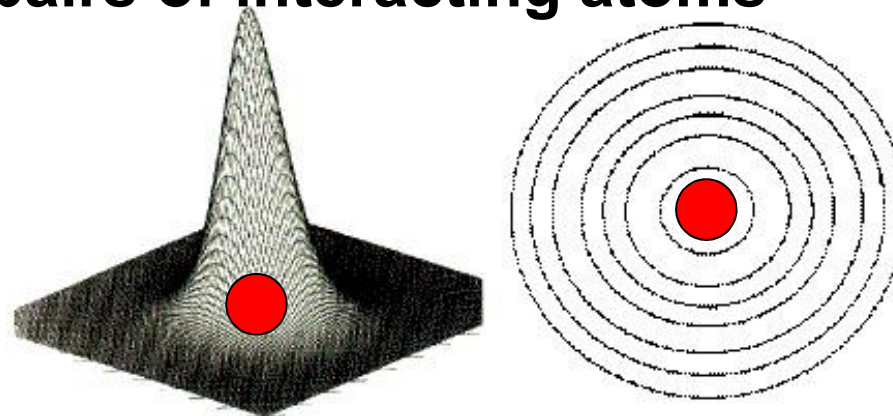
Bond critical point (saddle): **representative of chemical interactions**



A bond critical point is always associated to an **atomic interaction line**, i.e. it marks pairs of interacting atoms

Maximum (nuclear positions)

$$\lambda_1 < \lambda_2 < \lambda_3 < 0$$



The topological atom

Zero-flux
surface

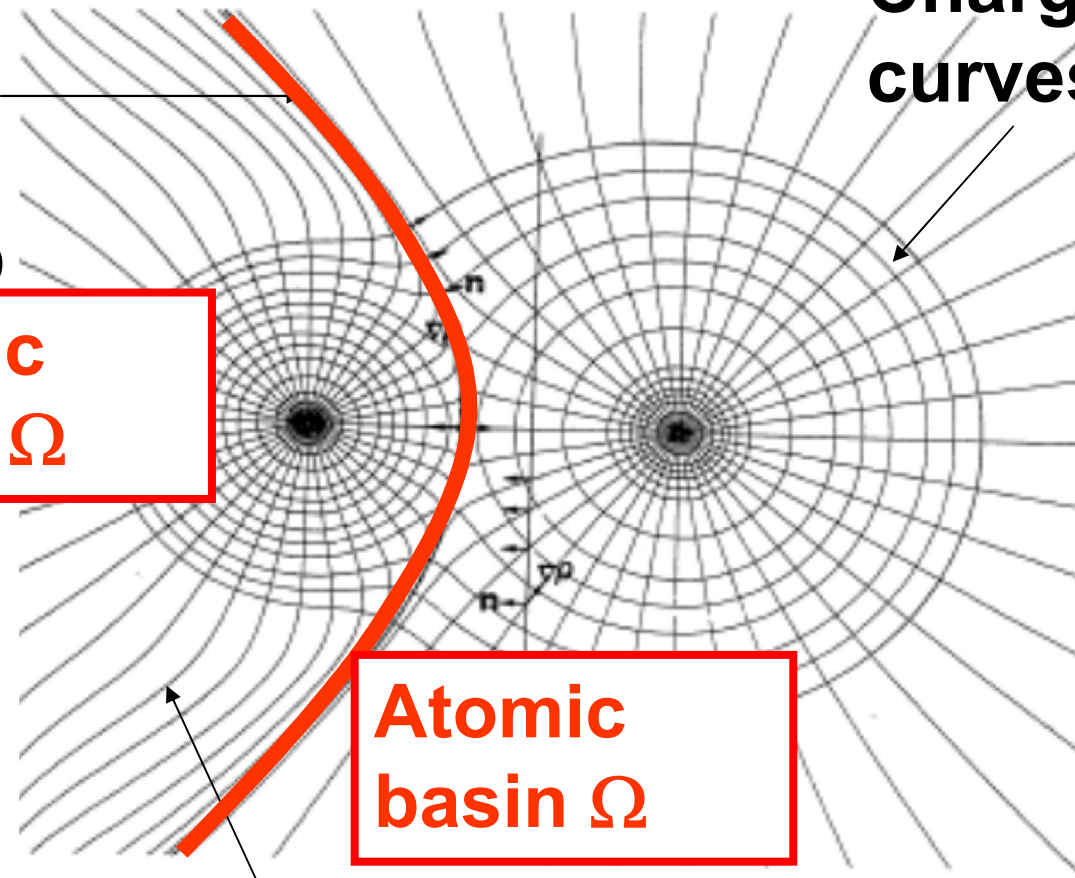
$$\oint_S \nabla \rho(\mathbf{r}) \cdot \hat{\mathbf{n}} dS = 0$$

Atomic
basin Ω

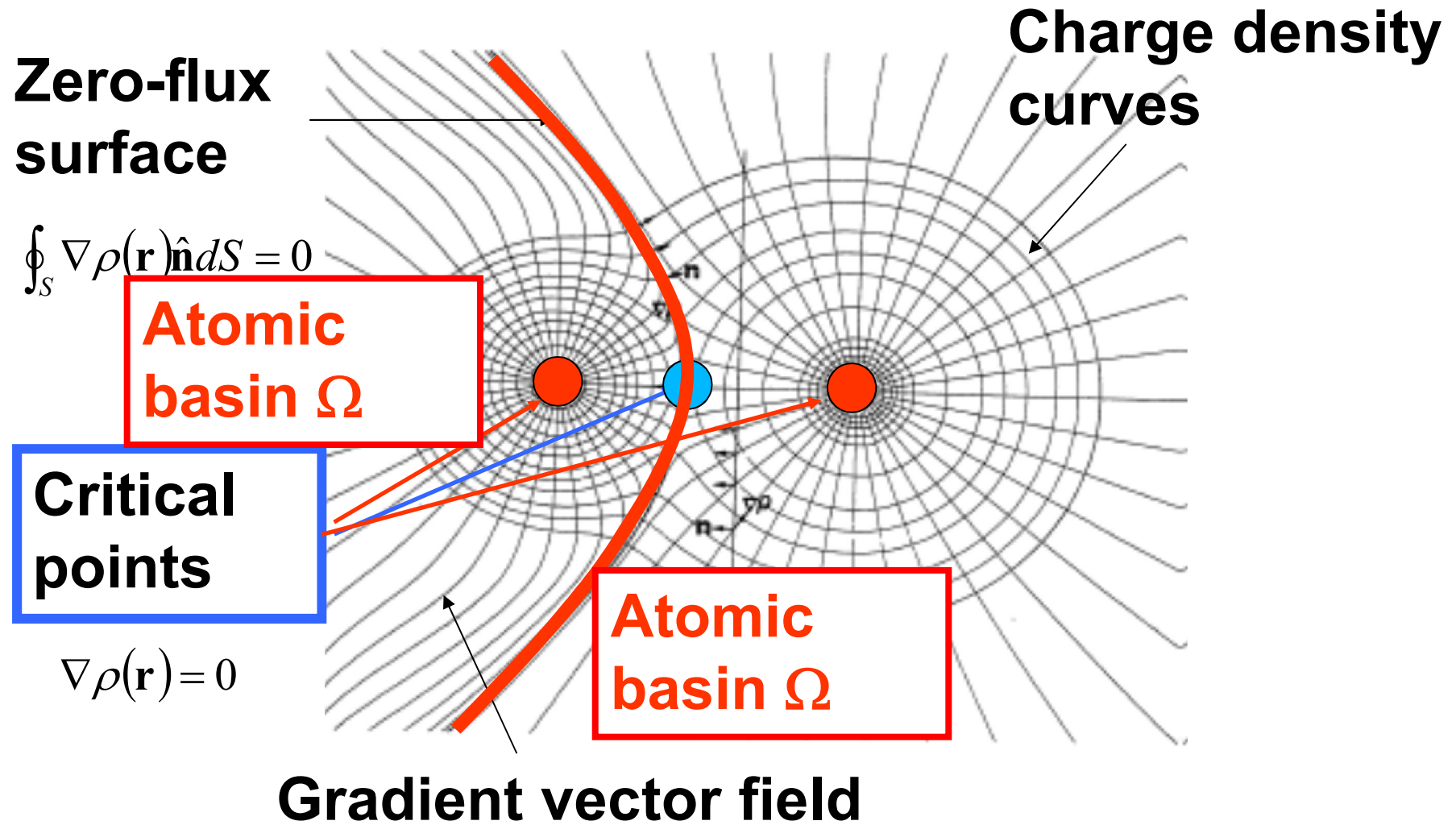
Atomic
basin Ω

Charge density
curves

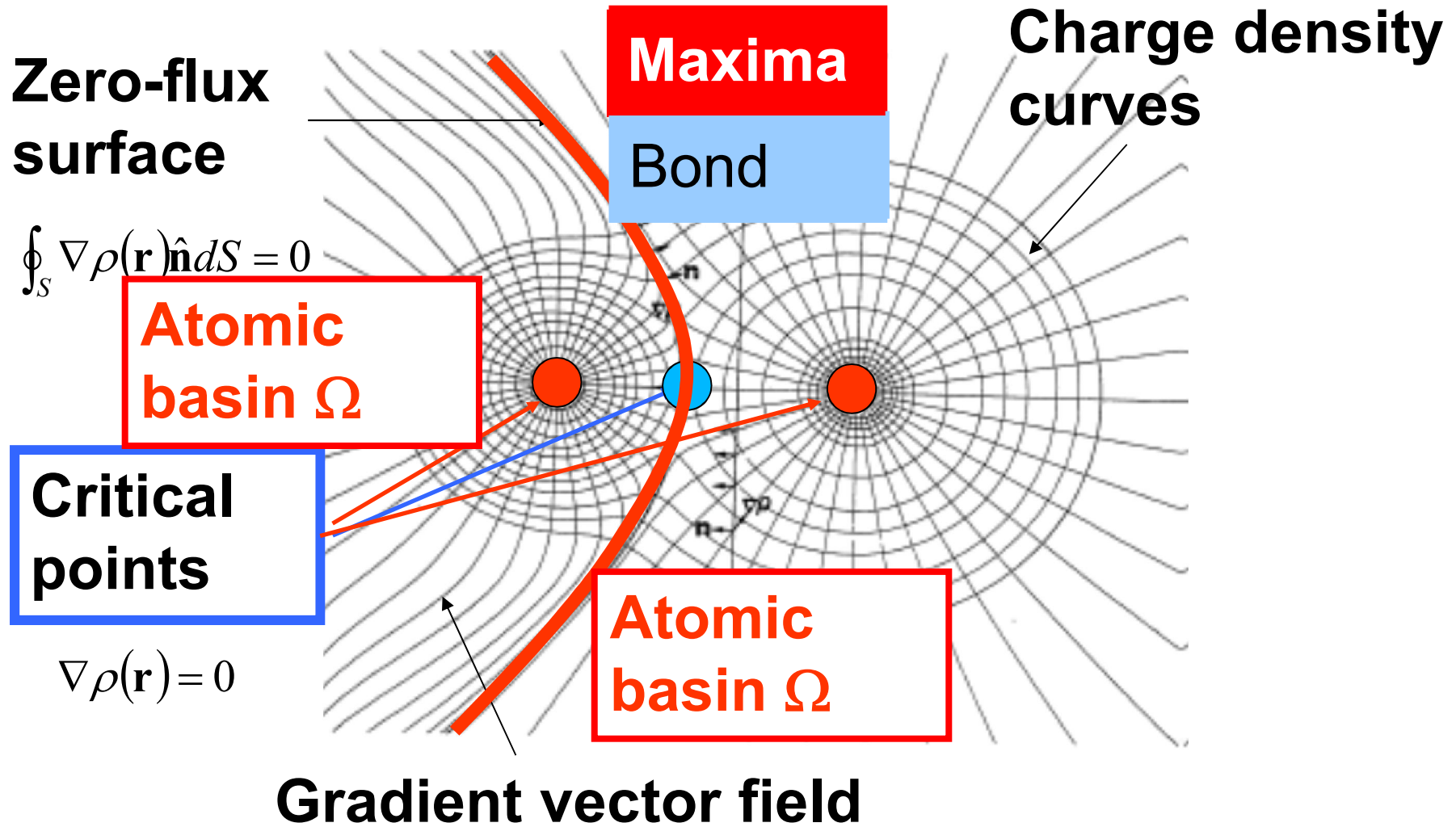
Gradient vector field



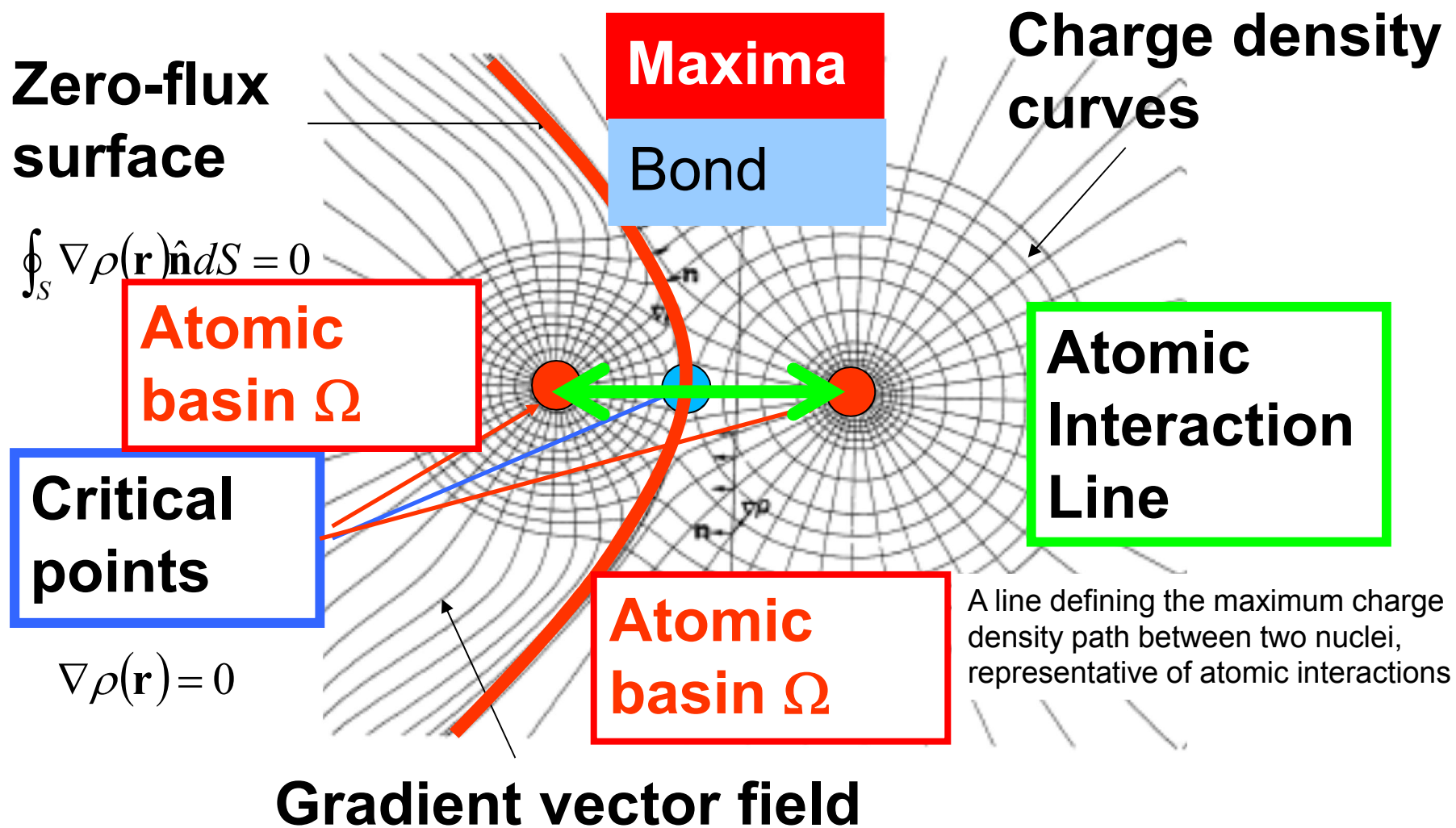
The topological atom



The topological atom



The topological atom





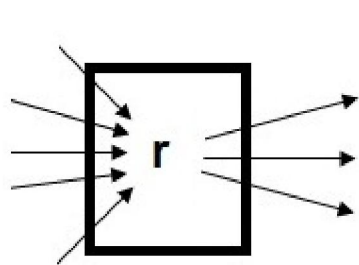
Laplacian of the charge density

$$\nabla^2 \rho(\mathbf{r}) = \lambda_1 + \lambda_2 + \lambda_3$$

Laplacian of the charge density

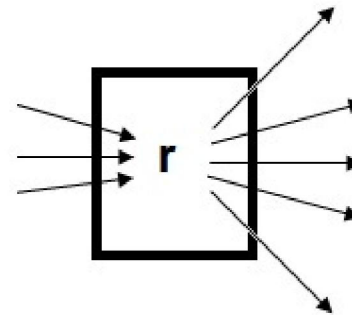
Following the Gauss theorem:

$$\int_V \nabla^2 \rho(\mathbf{r}) d\mathbf{r} = \oint_S \hat{\mathbf{n}} \nabla \rho(\mathbf{r}) dS$$



$$\nabla^2 \rho(\mathbf{r}) < 0$$

More gradient lines enter the volume than the exiting ones: **charge is being accumulated** in the neighborhood of the critical point



$$\nabla^2 \rho(\mathbf{r}) > 0$$

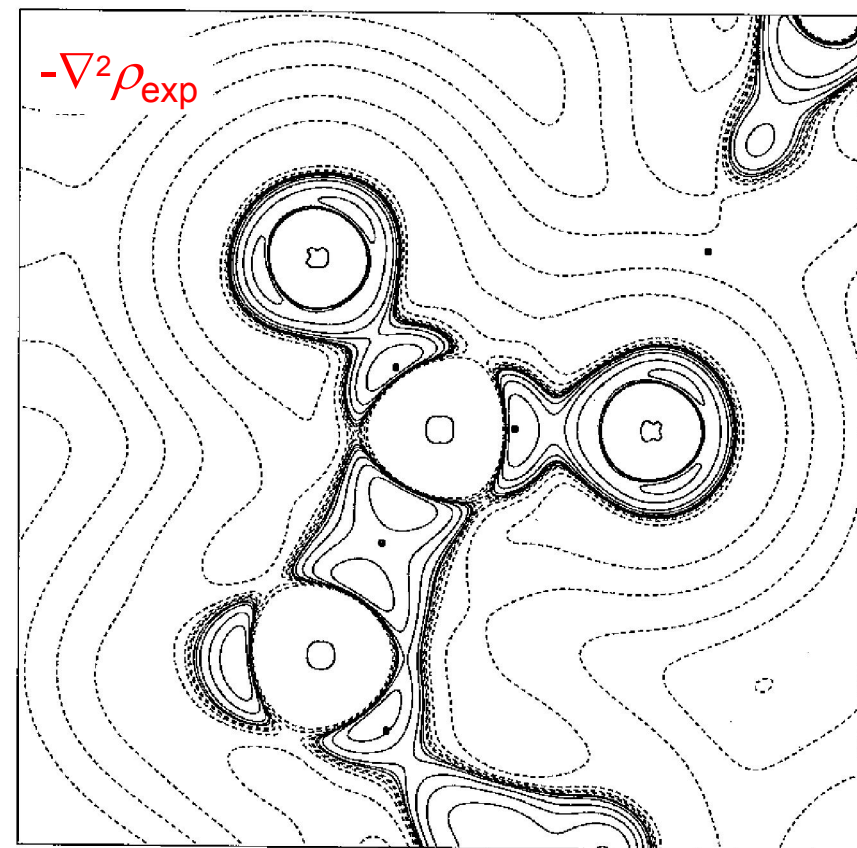
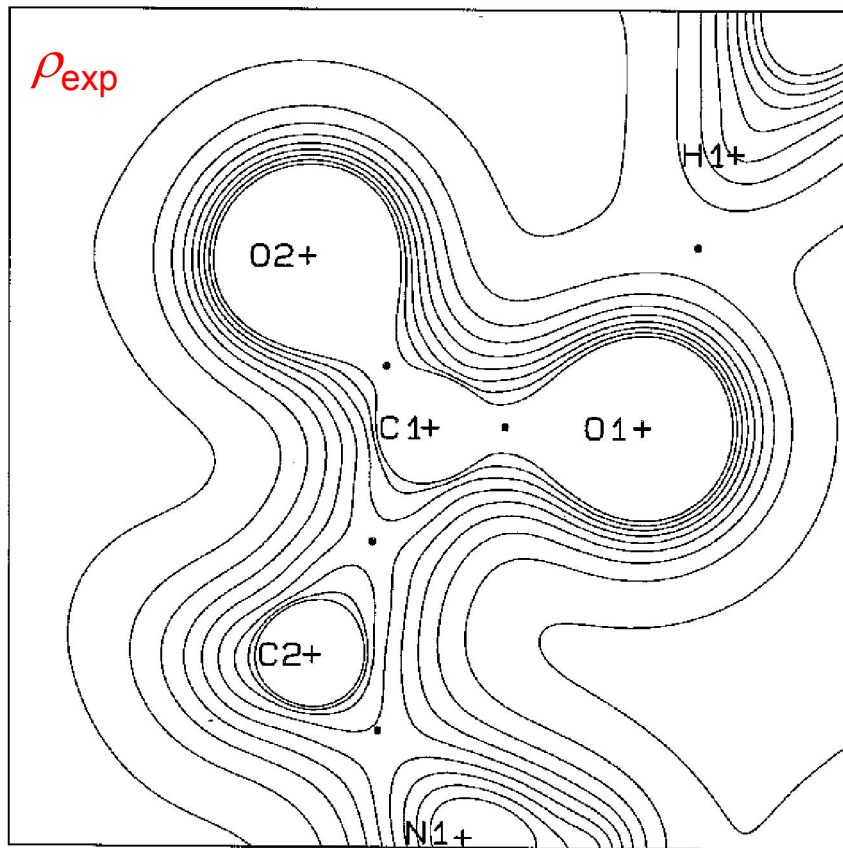
Less gradient lines enter the volume than the exiting ones: **charge is being depleted** in the neighborhood of the critical point

Laplacian of ED

$$\nabla^2 \rho(\mathbf{r}_{cp}) = \lambda_1 + \lambda_2 + \lambda_3$$

$\nabla^2 \rho(\mathbf{r}) > 0$ (dashed lines): **electron-poor** regions

$\nabla^2 \rho(\mathbf{r}) < 0$ (full lines): **electron-rich** regions



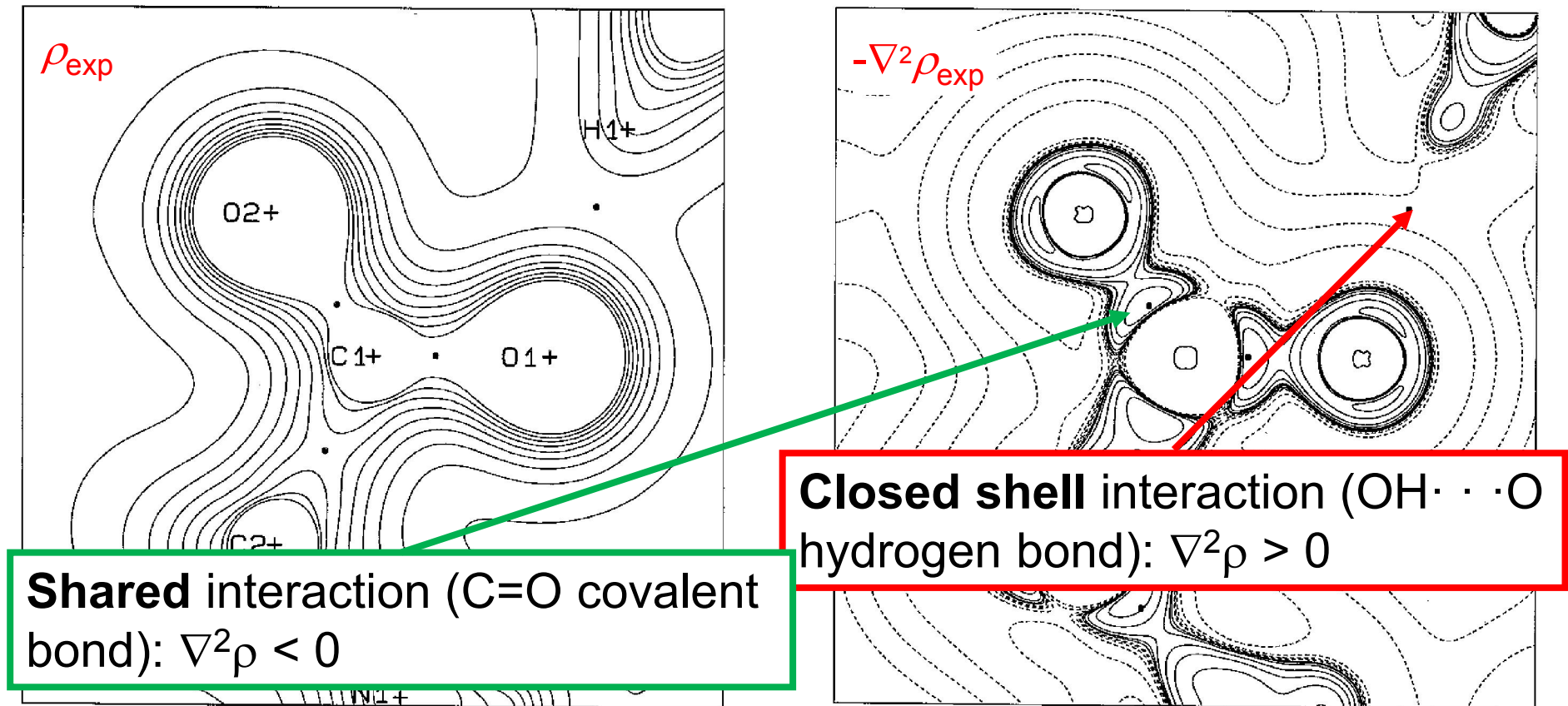
GLYCINE: 10835 measured intensities at T = 23 K

Laplacian of ED

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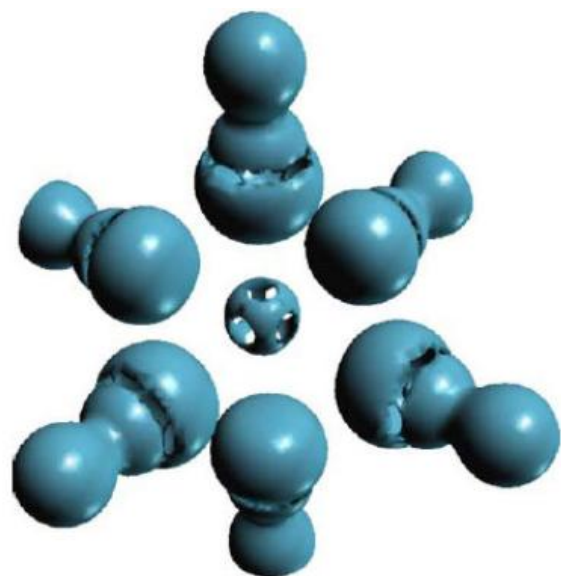
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GLYCINE: 10835 measured intensities at T = 23 K

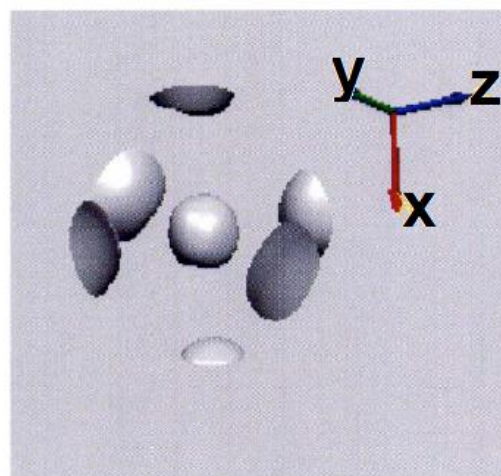
Laplacian of ED

$\nabla^2\rho=0$ isosurfaces enclose regions of **charge concentration**

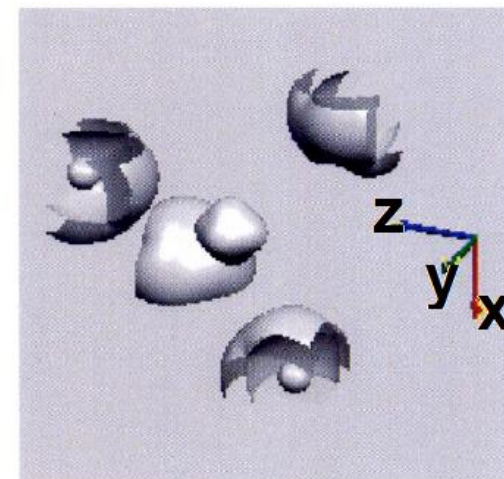


Co(CO)₆

Cortes-Guzman & Bader Coord. Chem.
Rev. 2005, 249, 633



Cr



Fe

FeCr₂S₄

6741 measured intensities at T = 23 K

Lo Presti & Destro, J. Chem. Phys. 2008, 044710

Areas of charge concentration match areas of charge depletion



Laplacian of ED

$$\frac{\hbar^2}{4m} \nabla^2 \rho(\mathbf{r}) = V(\mathbf{r}) + 2G(\mathbf{r})$$

Local form of the virial theorem

It relates the kinetic energy density, $G(\mathbf{r})$ (always >0), to the potential energy density $V(\mathbf{r})$ (always <0) at \mathbf{r} by means of the Laplacian of the charge density

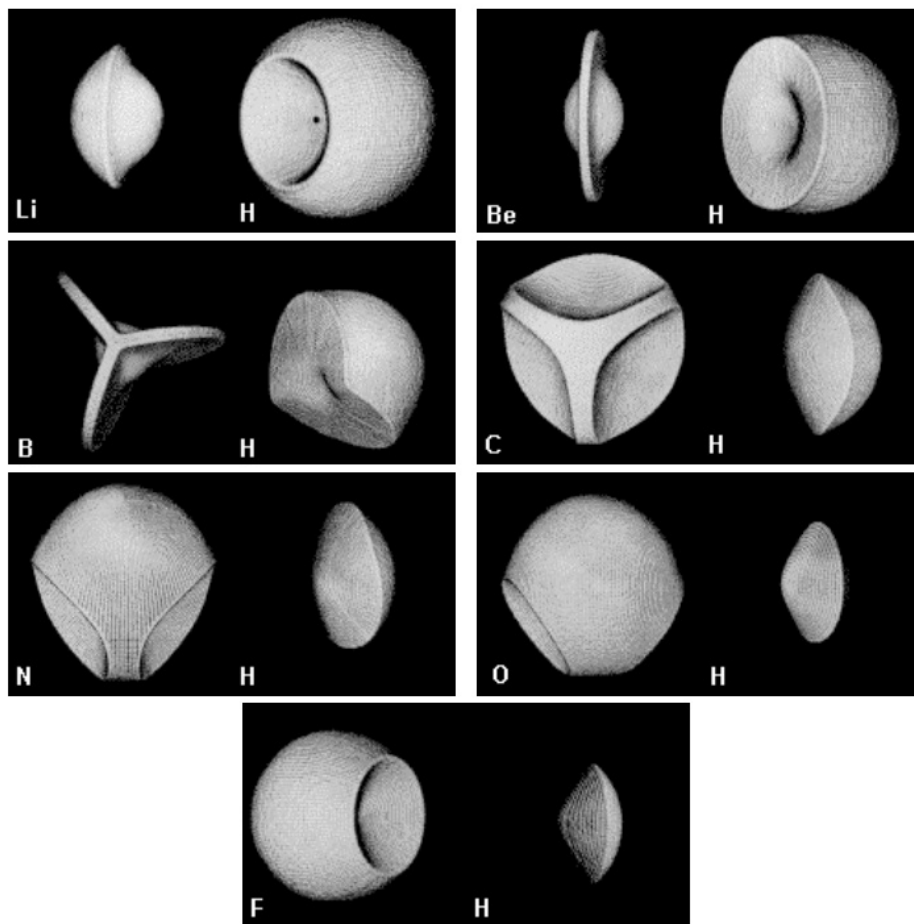
$$\nabla^2 \rho(\mathbf{r}) < 0 \quad \text{Prevailing } V(\mathbf{r}), \text{ bound state}$$

$$\nabla^2 \rho(\mathbf{r}) > 0 \quad \text{Prevailing } G(\mathbf{r}), \text{ unbound state}$$

If $G(\mathbf{r})$ is known, for example by means of the Abramov's functional or quantum calculations, $V(\mathbf{r})$ can be deduced from $\nabla^2 \rho$

→ **The strength of a given interaction can be estimated**

Atomic properties



3D representation of **atomic basins**, each bounded by its zero-flux surface, for the AH series, A being any 2nd-period element from Li to F

Topological atoms are (quite well) transferable among different chemical systems

Relative electronegativity determines the relative volumes



Atomic properties

Atomic volume: $V(\Omega) = \int_{\Omega} d\underline{r}$

Atomic charge: $q_{\Omega} = Z - \int_{\Omega} \rho(\underline{r}) d\underline{r}$

Atomic energy: $E(\Omega) = -T(\Omega)$

$$\mu_{x,\Omega} = \int_{V=\Omega} \rho(\mathbf{r}) \cdot r_x \cdot d\mathbf{r}$$

Atomic dipole
moments:

$$\mu_{y,\Omega} = \int_{V=\Omega} \rho(\mathbf{r}) \cdot r_y \cdot d\mathbf{r}$$

$$\mu_{z,\Omega} = \int_{V=\Omega} \rho(\mathbf{r}) \cdot r_z \cdot d\mathbf{r}$$

Molecular properties

Molecular volume: $V_{Mol} = \sum_{\Omega} V(\Omega)$

Molecular charge: $q_{Mol} = \sum_{\Omega} q_{\Omega}$

Molecular energy: $E_{Mol} = \sum_{\Omega} E(\Omega)$

Molecular dipole moments:

$$\mu_x = \sum_{\Omega} [\mu_{\Omega,x} + x_{\Omega} q_{\Omega}]$$

$$\mu_y = \sum_{\Omega} [\mu_{\Omega,y} + y_{\Omega} q_{\Omega}]$$

$$\mu_z = \sum_{\Omega} [\mu_{\Omega,z} + z_{\Omega} q_{\Omega}]$$

Intrinsic atomic polarization

Charge transfer



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2.1 The problem of electron delocalization

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The Source Function

Bader & Gatti, C. Chem. Phys. Lett. 287, 233, 1998

$$\rho(\mathbf{r}) = \int_{all\ space} LS(\mathbf{r}, \mathbf{r}') \cdot d\mathbf{r}'$$



The Source Function

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$$\rho(\mathbf{r}) = \int_{all\ space} \text{LS}(\mathbf{r}, \mathbf{r}') \cdot d\mathbf{r}'$$

$$\text{LS}(\mathbf{r}, \mathbf{r}') = -\frac{1}{4\pi} \frac{1}{|\mathbf{r} - \mathbf{r}'|} \nabla^2 \rho(\mathbf{r}')$$

Local Source



The Source Function

Bader & Gatti, C. Chem. Phys. Lett. 287, 233, 1998

$$\rho(\mathbf{r}) = \int_{all\ space} \text{LS}(\mathbf{r}, \mathbf{r}') \cdot d\mathbf{r}'$$

$$\text{LS}(\mathbf{r}, \mathbf{r}') = -\frac{1}{4\pi} \frac{1}{|\mathbf{r} - \mathbf{r}'|} \nabla^2 \rho(\mathbf{r}') \quad \text{Local Source}$$

Green function (*influence function*). It represents the effectiveness of how the **cause** ($\nabla^2 \rho(\mathbf{r}')$) contributes to the **effect** $\rho(\mathbf{r})$



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$$\rho(\mathbf{r}) = \int_{all\ space} \text{LS}(\mathbf{r}, \mathbf{r}') \cdot d\mathbf{r}' = \sum_{\Omega} \int_{\Omega} \text{LS}(\mathbf{r}, \mathbf{r}') \cdot d\mathbf{r}' \equiv \sum_{\Omega} S(\mathbf{r}, \Omega)$$

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$S(\mathbf{r}, \Omega)$ **Source Function** from the basin Ω to the point \mathbf{r}

$$\text{LS}(\mathbf{r}, \mathbf{r}') = -\frac{1}{4\pi} \frac{1}{|\mathbf{r} - \mathbf{r}'|} \nabla^2 \rho(\mathbf{r}') \quad \text{Local Source}$$

Green function (*influence function*). It represents the effectiveness of how the **cause** ($\nabla^2 \rho(\mathbf{r}')$) contributes to the **effect** $\rho(\mathbf{r})$



The Source Function

Bader & Gatti, C. Chem. Phys. Lett. 287, 233, 1998

The charge density $\rho(\mathbf{r})$ at any point \mathbf{r} is *intrinsically* influenced by all the atomic basins in the system: this is well-known in DFT theory, as $\rho(\mathbf{r})$ is an unique function of the exchange-correlation potential

$$\rho(\mathbf{r}) = \sum_{\Omega} S(\mathbf{r}, \Omega)$$

The Source Function accounts for this non-locality, allowing one to investigate which is the **relative influence** of an atom, or a group of atoms, in determining the **local properties** of the electron distribution at distant points

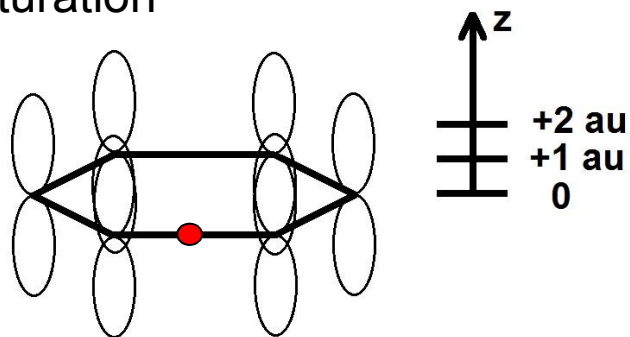


The Source Function as a descriptor of conjugation

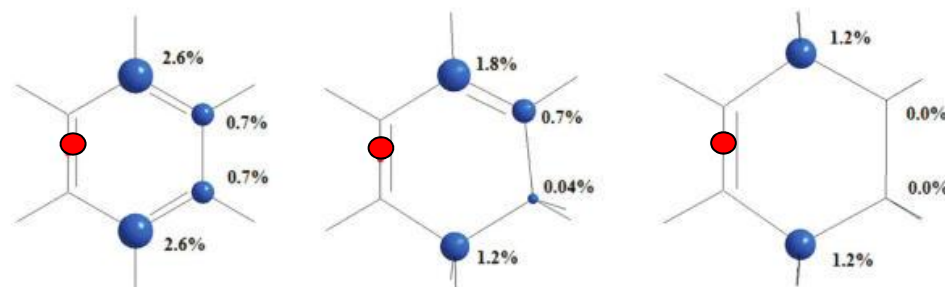
The Source Function (SF) can be used to study **electron conjugation** (and **aromaticity**) in the *real space*

These concepts **lack rigorous definitions**, as they are not directly associated to quantum-mechanical observables

The SF **focuses on the charge density observable**. It quantifies the different influence that distant atoms provide to a given **reference point** as a function of (i) the distance from the π nodal plane and (ii) the kind of the insaturation



Monza, Gatti & Lo Presti J. Phys. Chem. A 2011, 115, 12864
 $z = 0 \text{ a.u.}$



Bigger spheres = larger % SF contribution to the **red point**.
Yellow spheres mark negative SF contributions

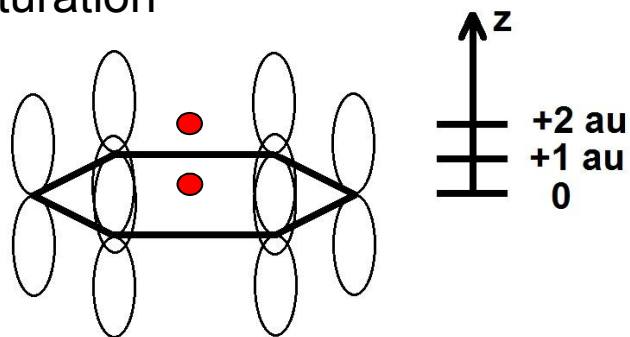


The Source Function as a descriptor of conjugation

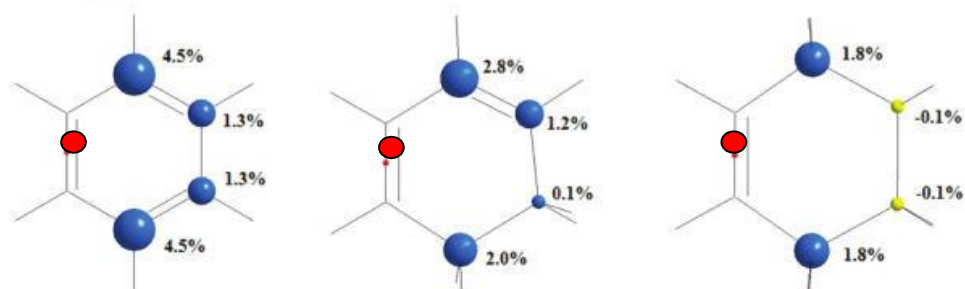
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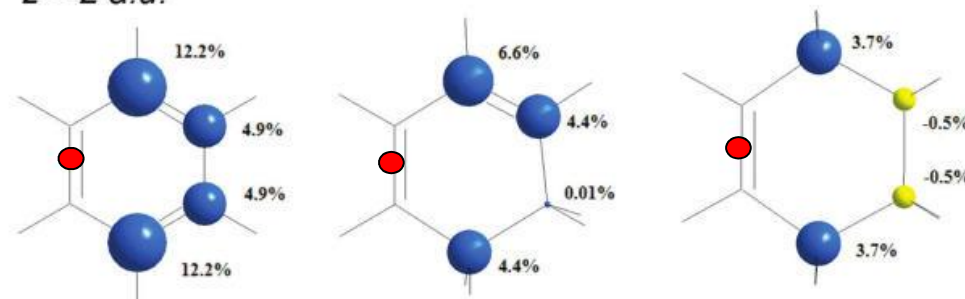
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Monza, Gatti & Lo Presti J. Phys. Chem. A 2011, 115, 12864
 $z = 0 \text{ a.u.}$



$z = 2 \text{ a.u.}$

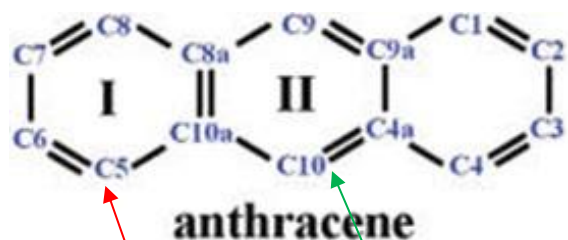


Bigger spheres = larger % SF contribution to the **red point**.
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The Source Function as a descriptor of local aromaticity

Monza, Gatti & Lo Presti J. Phys. Chem. A 2011, 115, 12864
 Matta & Hernandez-Trujillo, J. Phys. Chem. A 2003, 107, 7496

Source Function Local Aromaticity Index (SFLAI)



More
benzene-like

Less
benzene-like

Ring I

Ring II

SFLAI

0.712

0.678

$$\text{SFLAI} = 1 - \frac{c}{6} \sqrt{\sum_{\Omega=1}^6 (k - \sum_{b=1}^6 \text{SF}_{\Omega b} \%)^2}$$

Normalization constant,
to have SFLAI = 0 in
cyclohexane

SF % contributions to the
 b^{th} C-C bond critical point in
the polycyclic hydrocarbon

SF % contributions to
any C-C bond critical
point in the benzene

The SFLAI results **agree well** with the outcomes of other quantum local aromaticity descriptors and also with the **chemical sense**, as **positions 9 and 10** are known to be **reactive** in anthracene



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Reduced density gradient

In DFT theory, the **Reduced Density Gradient (RDG)** is defined as

$$s(\mathbf{r}) = \frac{|\nabla\rho(\mathbf{r})|}{2(3\pi^2)^{1/3}\rho(\mathbf{r})^{4/3}}$$

RDG describes *local deviations of the electron density (ED) from a homogeneous electron gas*, that has $s(\mathbf{r})=0$ everywhere.

$s(\mathbf{r})$ is **large** in regions **far from the nuclei**, where the total $\rho \rightarrow 0$ exponentially and the denominator approaches zero faster than the numerator.

Its lowest bound is 0, which is achieved every time $\nabla\rho(\mathbf{r}) = 0$

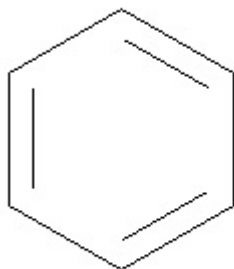
RDG properties

$$s(\mathbf{r}) = \frac{|\nabla\rho(\mathbf{r})|}{2(3\pi^2)^{1/3}\rho(\mathbf{r})^{4/3}}$$

Generalizing...

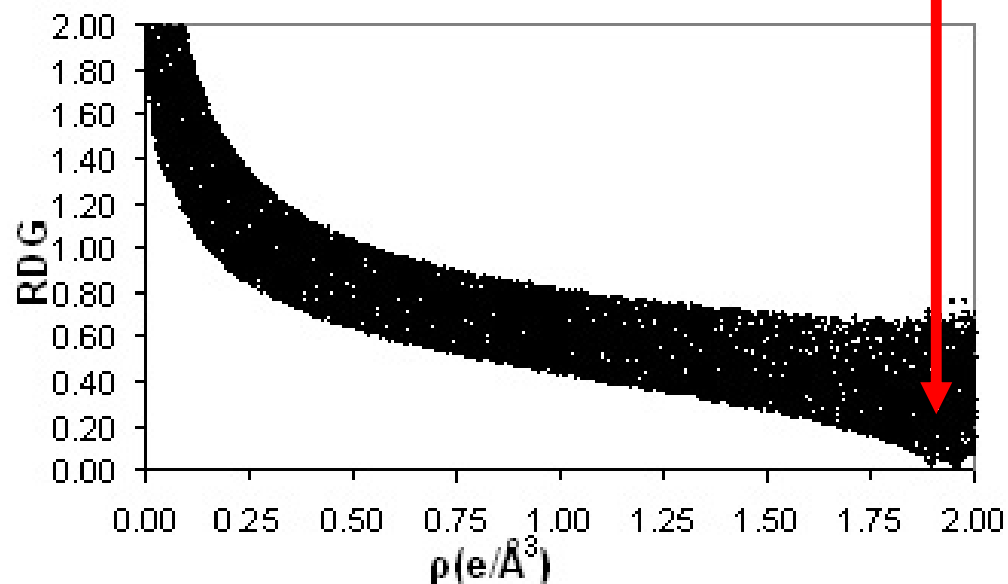
$$\nabla\rho(\mathbf{r} \rightarrow \mathbf{r}_{cp}) \approx 0 \quad \rightarrow \quad s(\mathbf{r} \rightarrow \mathbf{r}_{cp}) \approx 0$$

Low RDG values might be related to atom-atom interactions



Saleh, Gatti, Lo Presti, Contreras-Garcia, *Chem. Eur. J.* 2012, 18, 15523 – 15536

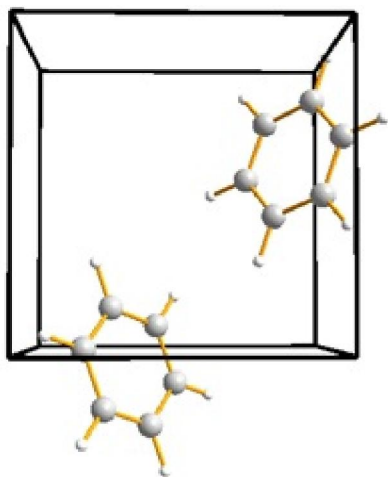
Johnson, Keinan, Mori-Sanchez, Contreras-Garcia, Cohen, *ang, J. Am. Chem. Soc.* 2010, 132, 6498 – 6506.



RDG properties

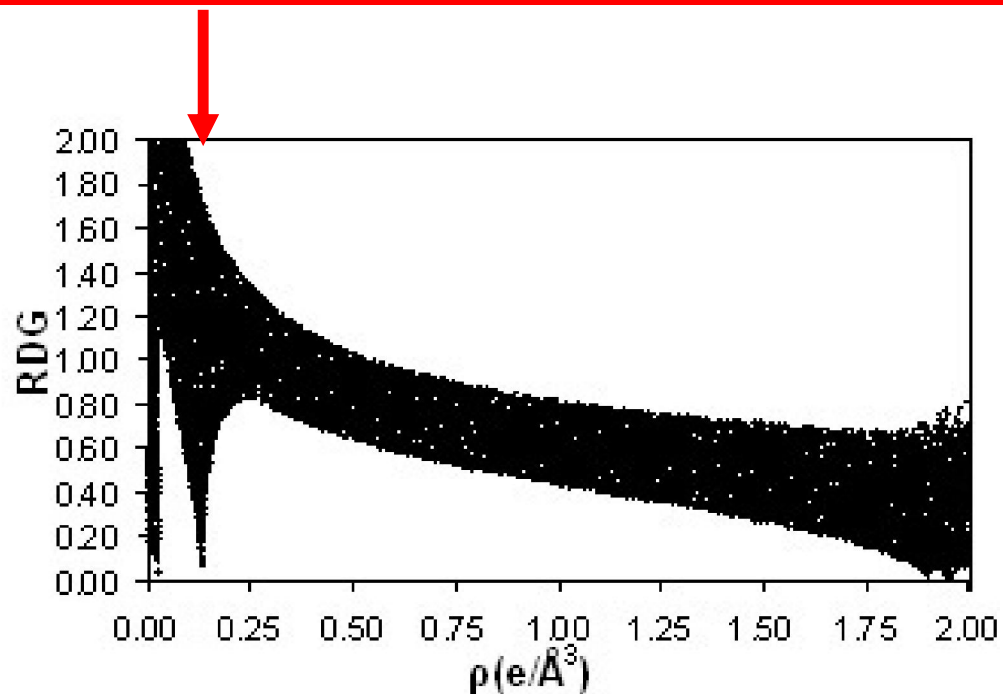
$$s(\mathbf{r}) = \frac{|\nabla\rho(\mathbf{r})|}{2(3\pi^2)^{1/3}\rho(\mathbf{r})^{4/3}}$$

If molecules in the solid state are analyzed, sharp spikes in the RDG vs ED plot appear in the low ED region → These are the signature of non-covalent interactions



Saleh, Gatti, Lo Presti, Contreras-Garcia, *Chem. Eur. J.* 2012, 18, 15523 – 15536

Johnson, Keinan, Mori-Sanchez, Contreras-Garcia, Cohen, *ang, J. Am. Chem. Soc.* 2010, 132, 6498 – 6506.



RDG properties

The idea of Johnson et al.: plotting $\text{sign}(\lambda_2) \cdot \rho(\mathbf{r})$ onto low-values RDG isosurfaces

$$\nabla^2 \rho(\mathbf{r}_{cp}) = \lambda_1 + \lambda_2 + \lambda_3$$

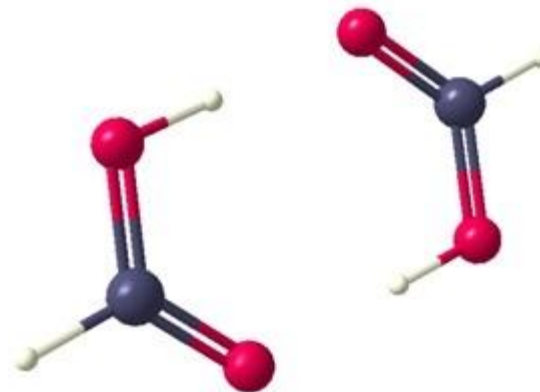
$\lambda_1 < \lambda_2 < 0 < \lambda_3$ Bonding regions (usually negative Laplacian)

$\lambda_1 < 0 < \lambda_2 < \lambda_3$ Non-Bonding regions (usually positive Laplacian)

As ED is always positive, $\text{sign}(\lambda_2)\rho(\mathbf{r}) > 0$ values should be related to allegedly repulsive interactions, while $\text{sign}(\lambda_2)\rho(\mathbf{r}) < 0$ ones should highlight zones of ED buildup associated to specific NCI patterns

RDG surfaces

The idea of Johnson et al.:
plotting $\text{sign}(\lambda_2) \cdot \rho(\mathbf{r})$ onto low-
values RDG isosurfaces



Formic acid cyclic dimer

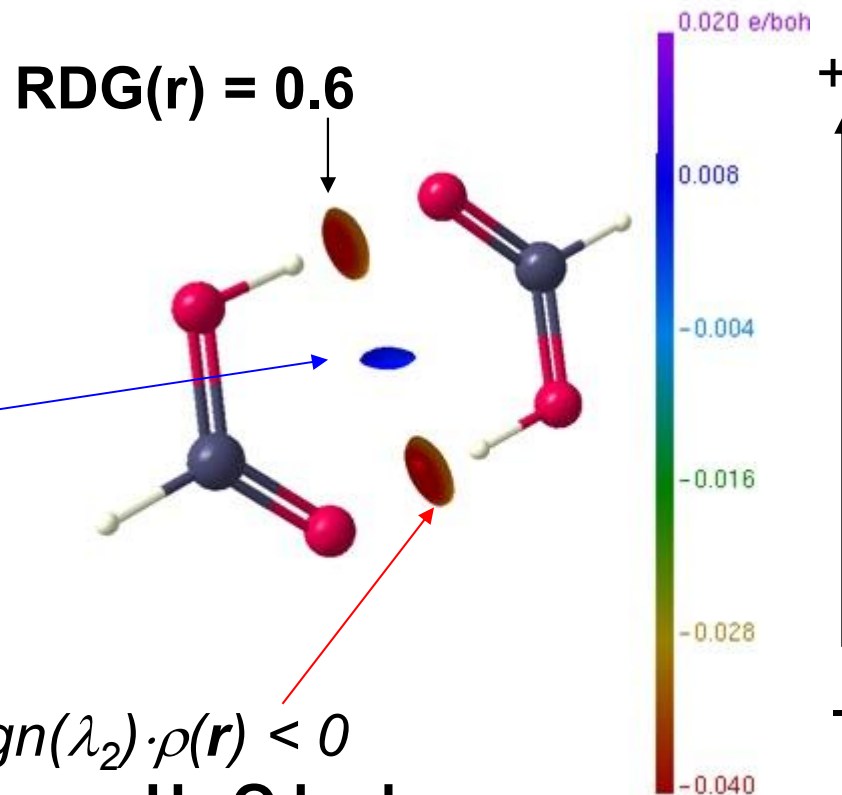
RDG surfaces

The idea of Johnson et al.:
plotting $\text{sign}(\lambda_2) \cdot \rho(\mathbf{r})$ onto low-
values RDG isosurfaces

$\text{sign}(\lambda_2) \cdot \rho(\mathbf{r}) > 0$
**O...O, C...C nonbonded
contacts**

Formic acid cyclic dimer

$\text{sign}(\lambda_2) \cdot \rho(\mathbf{r}) < 0$
**Strong H...O hydrogen
bonds**



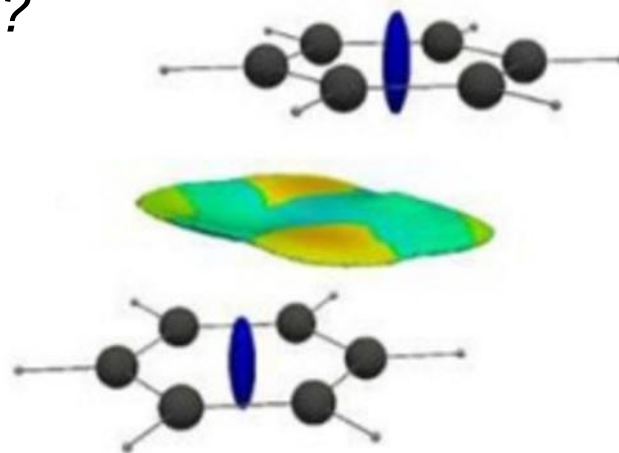
The color bar is related to the strength of the interaction: red →
strongly attractive; blue → strongly repulsive

RDG surfaces: physical meaning

On the other hand, flat and unstructured RDG surfaces, associated to $\text{sign}(\lambda_2) \cdot \rho(\mathbf{r})$ values close to 0, appear among facing aromatic rings

Is this a tool to 'see' dispersive interactions?

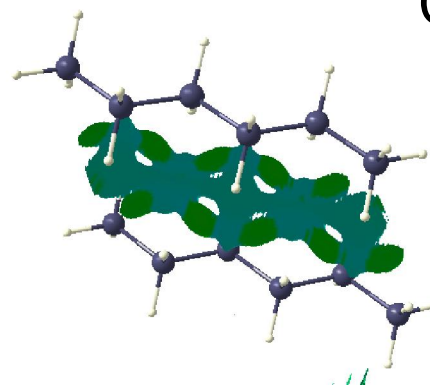
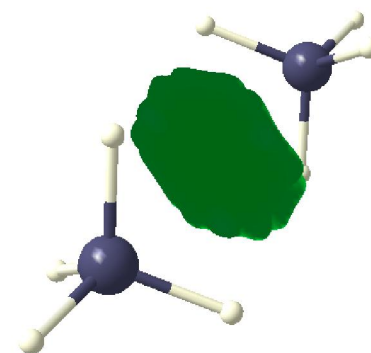
No! Dispersive interactions are always present among interacting charge distributions; flat RDG surfaces mean that the ratio between the gradient vector module and the charge density is rather constant in space



RDG surfaces: physical meaning

At the same time, they are colored green as the ED in region not dominated by directional interactions is low and the $\text{sign}(\lambda_2)$ factor is rather indeterminate

Such surfaces mark zones of ED where no directional strong(er) interactions are present (steric clashes, hydrogen bonds...), being therefore dominated by dispersive/repulsive contributions



Crystalline
hexane



Conclusions

The **topological analysis** of the $\rho(\mathbf{r})$ scalar field according to the Quantum Theory of Atoms in Molecules allows one to **unequivocally** partition any molecule into disjoint atomic basins connected by atomic interaction lines. Though the Bader's partitioning scheme is by itself **as much arbitrary as any other one**, it is **rooted in quantum mechanics** and allows to **naturally recover the concept of atomicity** from the charge density observable

The **Laplacian** is related to the **charge concentration** and **depletion** regions of the charge density. Through the virial theorem in its local form, it provides information on the relative balance between potential and kinetic energy densities in a given region of space



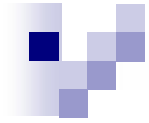
Conclusions

The Source Function provides insights on the properties of delocalization patterns and aromaticity

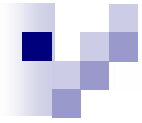
The RDG-based NCI descriptor allows to distinguish regions dominated by different networks of non-covalent interactions

All the topological descriptors are based on the charge density observable, amenable to experimental determination.

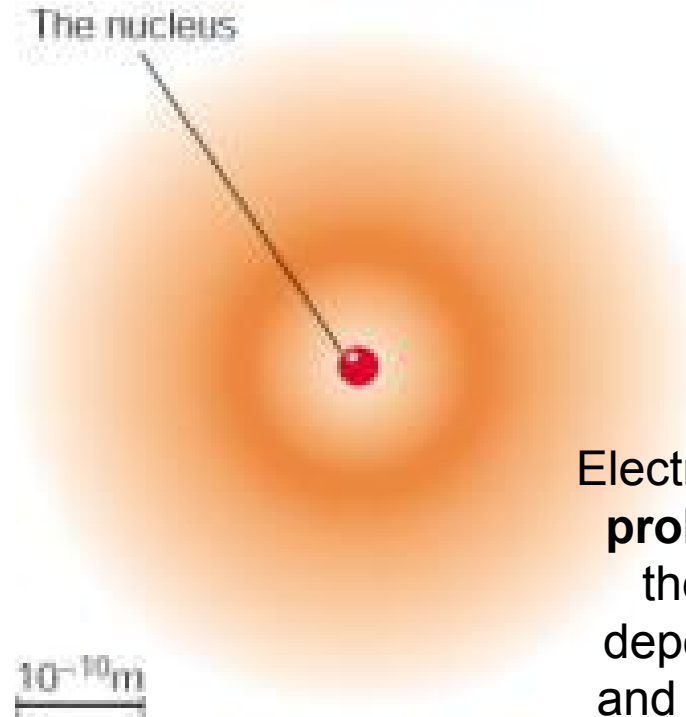
Single-crystal X-ray diffraction is much more than a tool to investigate the molecular structure. It can be used to **experimentally** grant access to a wealth of chemical information, including **intermolecular interaction energies**, nature and strength of **weak intermolecular bonds**, **chemical correlations** among distant atoms, **nucleophilic or electrophilic hot-spots** on the molecular surface, **electrostatic moments** and so on.



Thank you for your kind attention



The quantum description



Any sensible description of the matter at the molecular and sub-molecular level **must** rely on **quantum mechanics**

Electrons and nuclei should be described in terms of the **probability amplitudes** (wavefunctions, Ψ) of finding them in a certain region of the spacetime. The Ψ 's depend on the coordinates of electrons (\mathbf{r}), nuclei (\mathbf{R}), and possibly on time (t), if the system is not stationary.

Ψ must satisfy the **Schrödinger equation**

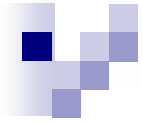
$$\hat{H}\Psi(\mathbf{r}, \mathbf{R}, t) = ih \frac{\partial \Psi(\mathbf{r}, \mathbf{R}, t)}{\partial t}$$

Quantum Theory of Atoms in Molecules

$$\oint_{S(\Omega)} \nabla \rho(\mathbf{r}) \hat{\mathbf{n}} dS = 0$$

This choice avoids ambiguities in the definition of the electronic kinetic energy

$$\begin{aligned} T(\Omega) &= -\frac{\hbar^2}{4m} N \int_{\Omega} d\mathbf{r} \int (\Psi^* \nabla^2 \Psi + \Psi \nabla^2 \Psi^*) d\tau' = \\ &= \frac{\hbar^2}{2m} N \int_{\Omega} d\mathbf{r} \int (\nabla \Psi \cdot \nabla \Psi^*) d\tau' - \frac{\hbar^2}{4m} \oint_{S(\Omega)} \hat{\mathbf{n}} \cdot \nabla \rho(\mathbf{r}) dS \end{aligned}$$



Analysis of X-ray diffracted intensities

$$I_{\text{meas}}(\underline{H}) \div |F_{\text{obs}}(\underline{H})|^2$$

$$F_{\text{obs}}(\underline{H}) = \int \rho(\underline{r}) \exp(2\pi i \underline{H} \cdot \underline{r}) d\underline{r}$$

1. Conventional analysis of $\rho(\underline{r})$

$$\rho(\underline{r}) = 1/V \sum_{\text{hkl}} F_{\text{obs}}(\underline{H}) \exp(-2\pi i \underline{H} \cdot \underline{r})$$

2. Multipole analysis of $\rho(\underline{r})$

(Stewart, R. F., *Acta Cryst.*, **1976**, A32, 565)

$$\rho(\underline{r}; \mathbf{Q}_e) = \sum_{p=1}^N \sum_{l=1}^L \left[\sum_{m=0}^l C_{plm}^e \cdot B_{plm}^e(\underline{r} - \mathbf{R}_p) + \sum_{m=1}^l C_{plm}^o \cdot B_{plm}^o(\underline{r} - \mathbf{R}_p) \right]$$



RDG surfaces vs. topological descriptors

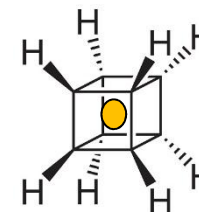
	RDG-NCI	AIM
Atom-atom picture	No	Yes
$\nabla\rho(\mathbf{r}_{cp})=0$	Not strictly required	Bond critical point required
NCI classification	Attractive -repulsive	Open-closed shell; A cp always implies a stabilizing interaction

Critical points

Critical points are classified according to their **rank** (number of nonzero Hessian eigenvalues) and their **sign** (number of positive Hessian eigenvalues minus the number of Hessian negative eigenvalues)

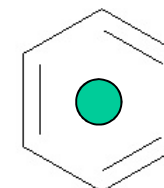
$$(3,+3) \quad 0 < \lambda_1 < \lambda_2 < \lambda_3$$

Cage critical point
(minimum)



$$(3,+1) \quad \lambda_1 < 0 < \lambda_2 < \lambda_3$$

Ring critical point
(saddle)





Critical points

$$\nabla^2 \rho(\mathbf{r}_{cp}) = \frac{\partial^2 \rho(\mathbf{r}_{cp})}{\partial x^2} + \frac{\partial^2 \rho(\mathbf{r}_{cp})}{\partial y^2} + \frac{\partial^2 \rho(\mathbf{r}_{cp})}{\partial z^2}$$

ED Laplacian: *the trace of the Hessian matrix.* Provided that the latter is diagonalized:

$$\nabla^2 \rho(\mathbf{r}_{cp}) = \lambda_1 + \lambda_2 + \lambda_3$$

To understand the physical meaning of the ED Laplacian, integrate it in a neighborhood, small to desire, of a critical point:

$$\int_V \nabla^2 \rho(\mathbf{r}_{cp}) d\mathbf{r} = \int_V \nabla \nabla \rho(\mathbf{r}_{cp}) d\mathbf{r}$$



The multipole formalism

Basis
Functions

$$B_{plm}(\mathbf{r} - \mathbf{R}_p)$$

VALRAY code

XD code

The multipole formalism

**Basis
Functions**

$$B_{plm}(\mathbf{r} - \mathbf{R}_p)$$

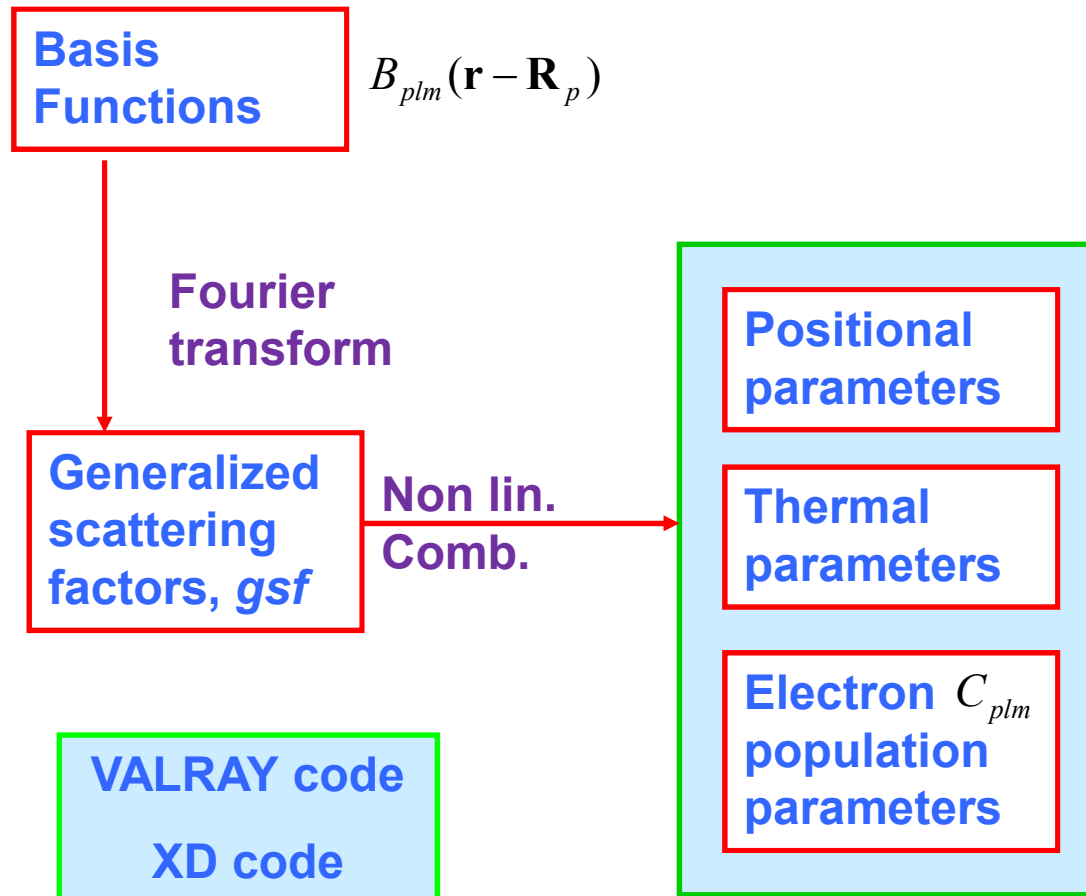
Fourier
transform

**Generalized
scattering
factors, *gsf***

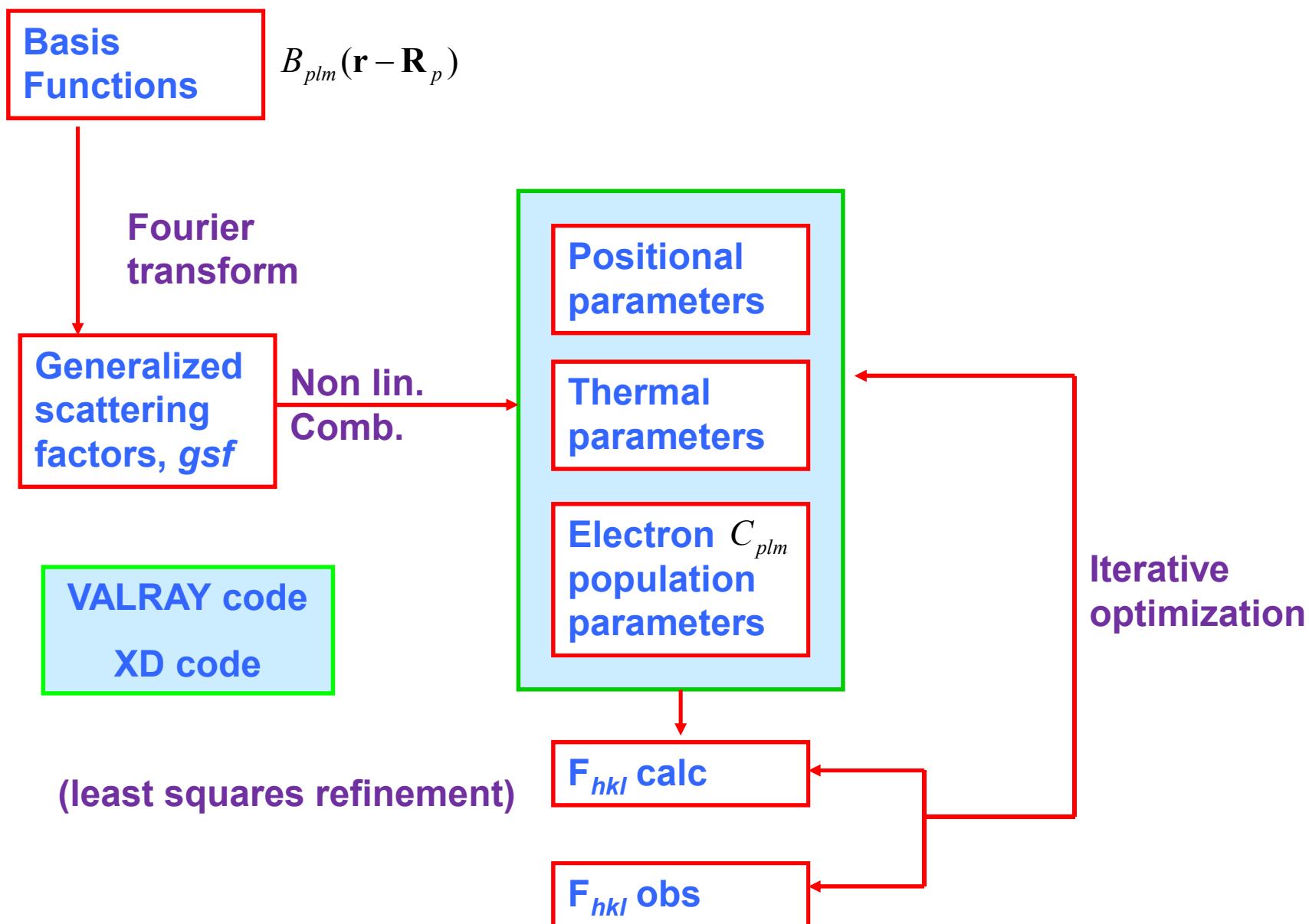
VALRAY code

XD code

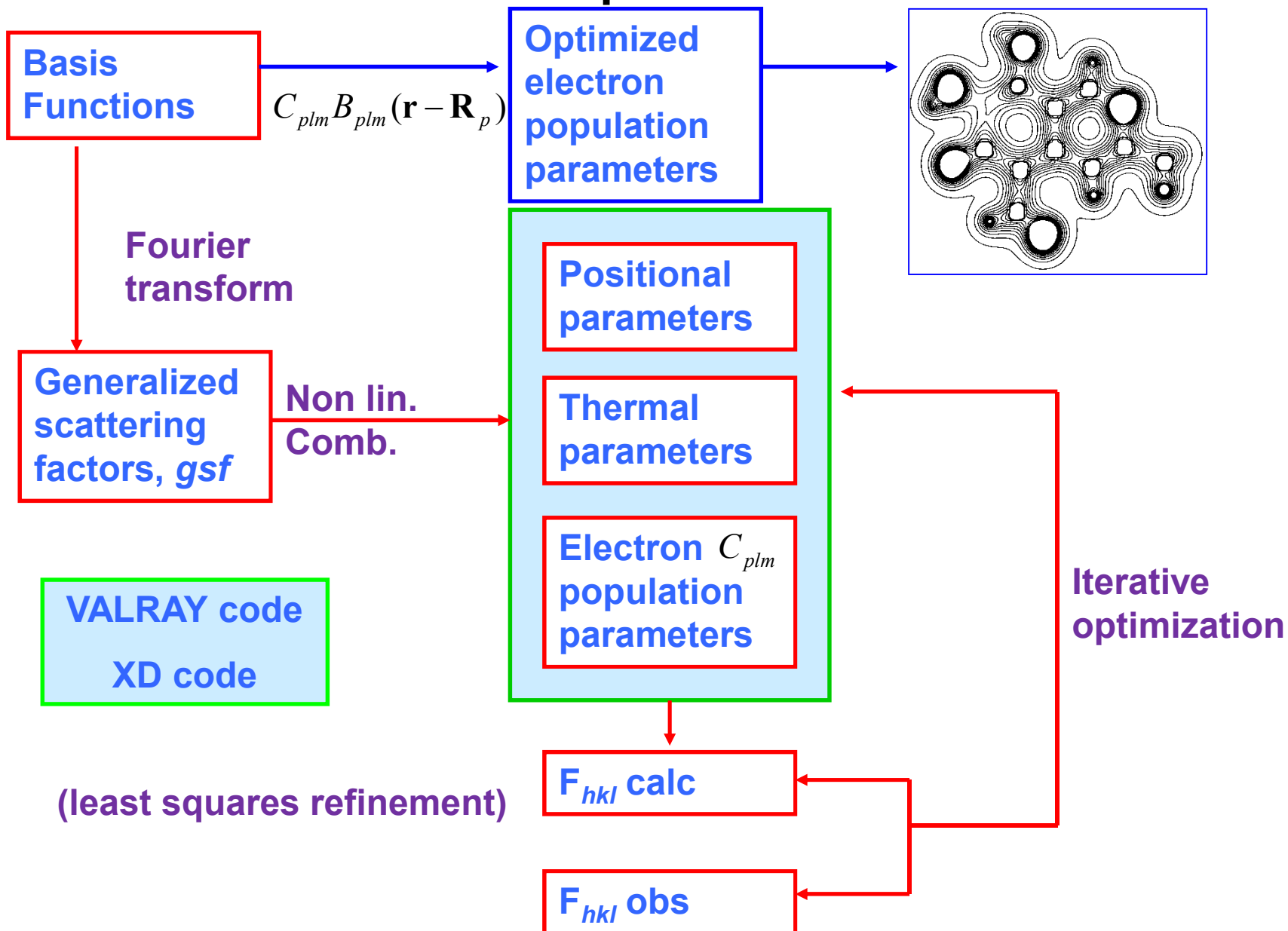
The multipole formalism

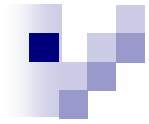


The multipole formalism



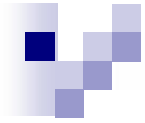
The multipole formalism





Outline

1. The Quantum Theory of Atoms in Molecules
2. **Charge density** from single-crystal X-ray diffraction
3. Applications



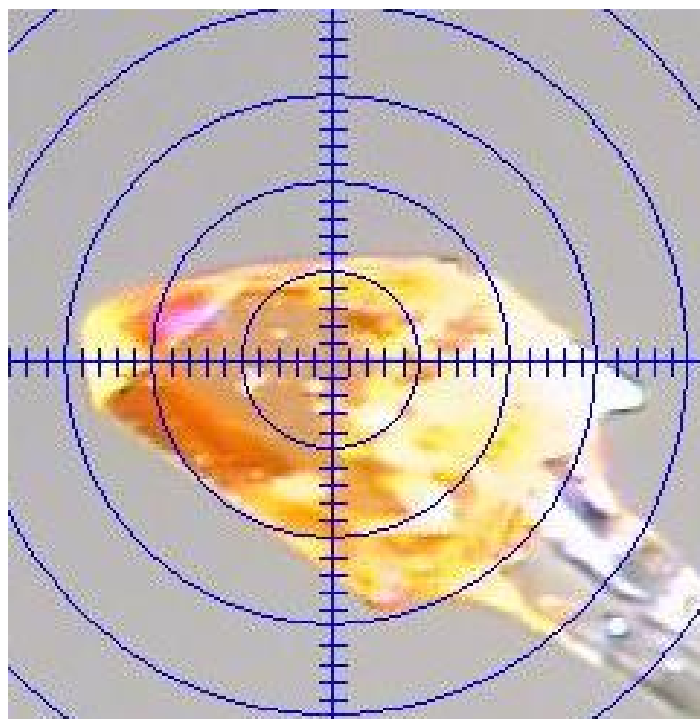
CHARGE DENSITY FROM THE EXPERIMENT

Requirements for an accurate determination of $\rho(\mathbf{r})$

- High-quality crystals
- Excellent instrumentation
 - Low Temperature

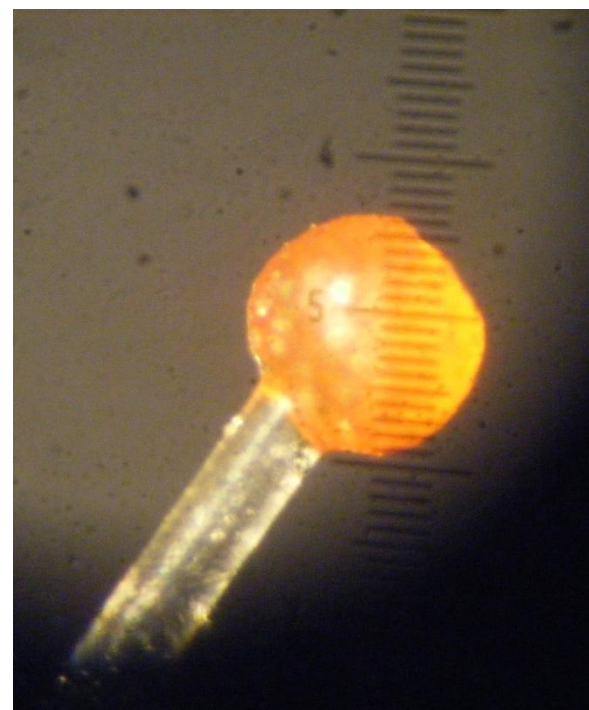
CHARGE DENSITY FROM THE EXPERIMENT

High-quality crystals



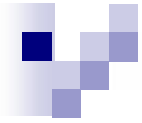
~ 0.5 mm, $C_6H_{12}O_5$

Austdiol

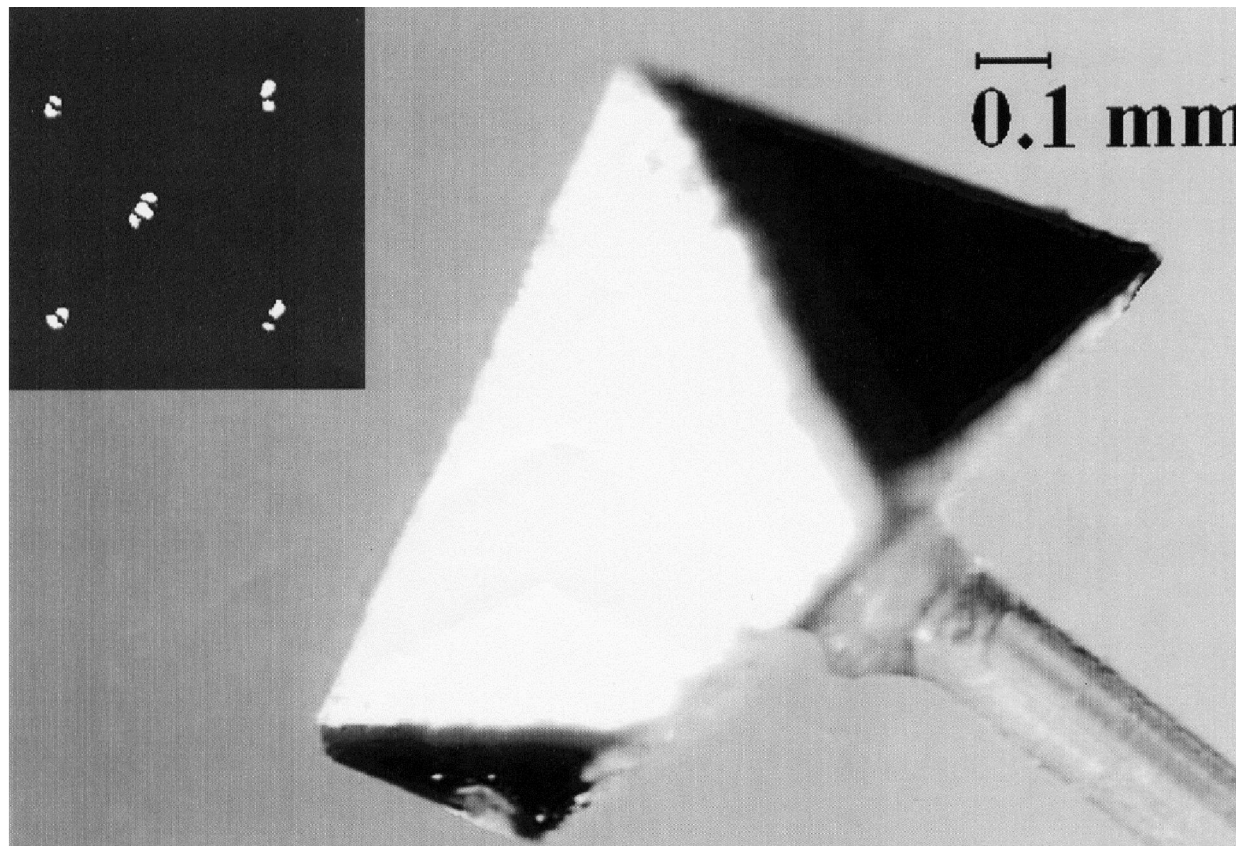


$\varnothing \sim 0.35$ mm, $C_{16}H_{10}O_2$

Bis-carbonyl[14]annulene



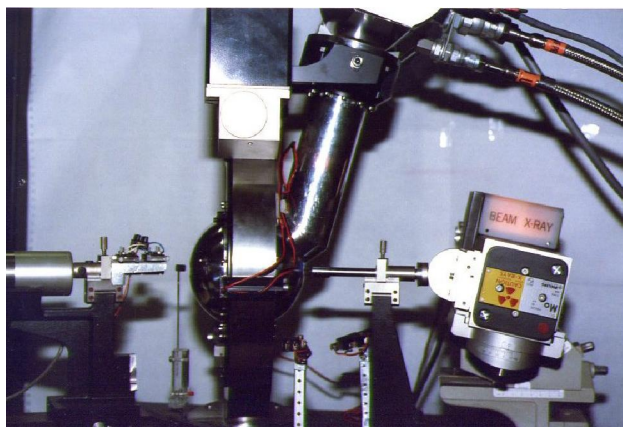
WARNING!



Daubreelite, FeCr_2S_4

CHARGE DENSITY FROM THE EXPERIMENT

Excellent instrumentation



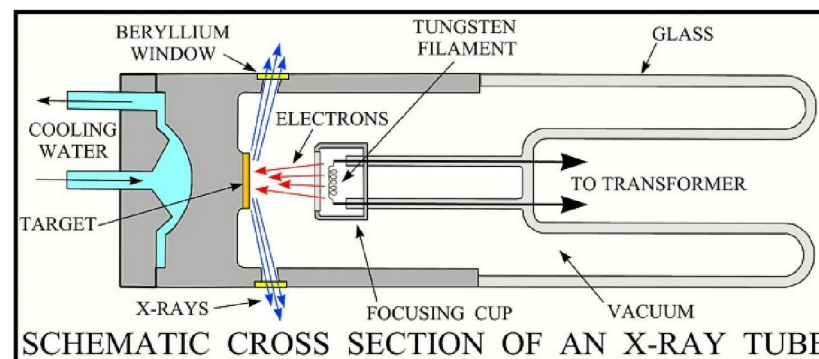
Precise and accurate goniometers

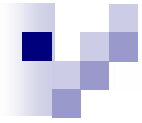


Sensitive detectors
(state-of-art CCD, Silicon-pixel
photoelectric detectors...)



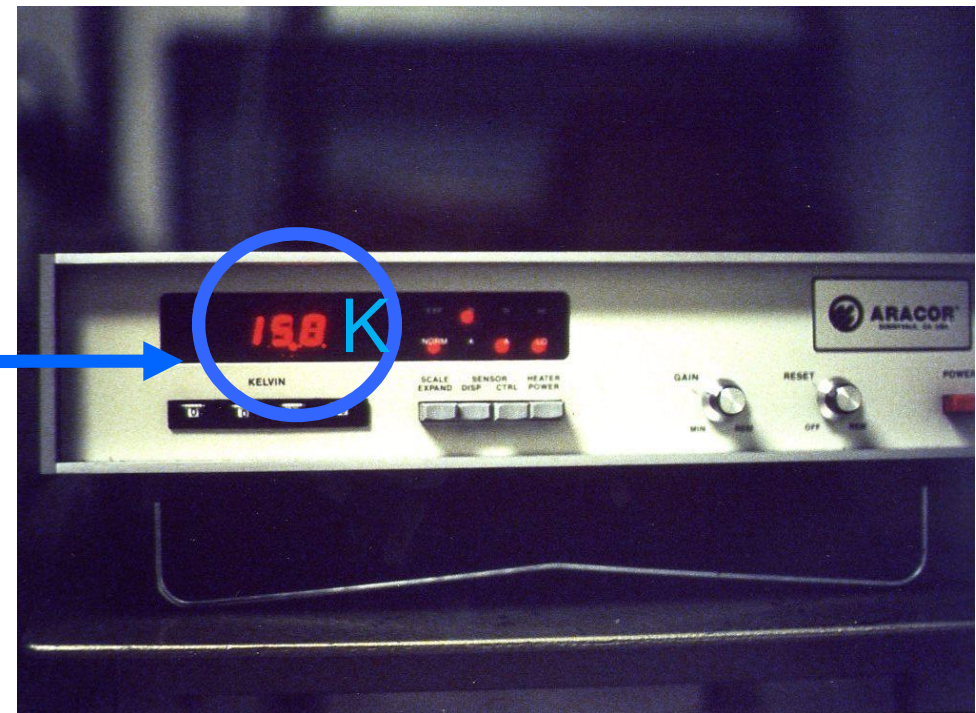
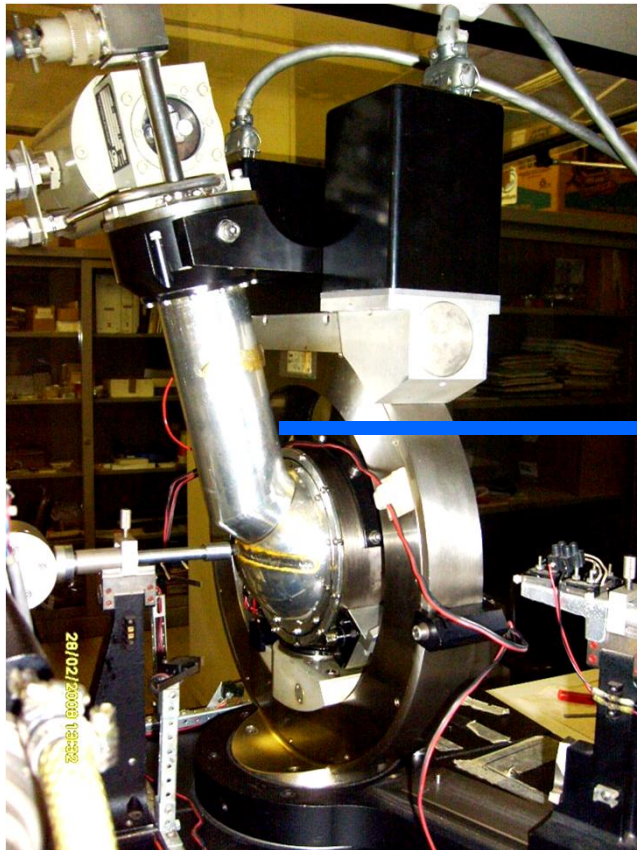
Intense X-ray beams
(rotating anodes, liquid metal
anodes, focusing optics...)





CHARGE DENSITY FROM THE EXPERIMENT

Low Temperature





CHARGE DENSITY FROM THE EXPERIMENT

Why low temperature?

Reduction of the Thermal Diffuse Scattering (TDS)

Increase of the number of measured intensities

Easier deconvolution of the thermal motion from the
static electron density

$$\bar{\rho}(\mathbf{r}) = \sum_m \left\{ \left[\frac{\exp(-E_m/kT)}{\sum_i \exp(-E_i/kT)} \right] \int \underbrace{\chi_m^*(\mathbf{R})}_{\text{Vibrational wavefunction}} \underbrace{\rho(\mathbf{r}; \mathbf{R})}_{\text{Vibrational wavefunction}} \underbrace{\chi_m(\mathbf{R})}_{\text{Vibrational wavefunction}} d\mathbf{R} \right\}$$