Charge density refinement at ultra high resolution with MoPro software

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1) Crystallography at ultra high resolution

2) The MoPro software for electron density analysis

3) Derived Properties / Exemple of applications

4) Practical training on the software MoPro

WHAT IS OBSERVABLE by X-Ray CRISTALLOGRAPHY

RESOLUTION

HIGH

$d \approx 2$ Å

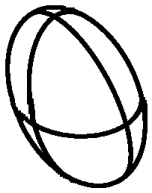
X Y Z

Thermal *B* factor isotropic

(Protein crystallography)

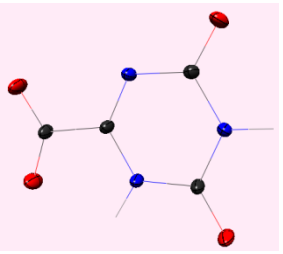
ATOMIC

$d \approx 1$ Å



Thermal *B* anisotropic

Hydrogen atoms

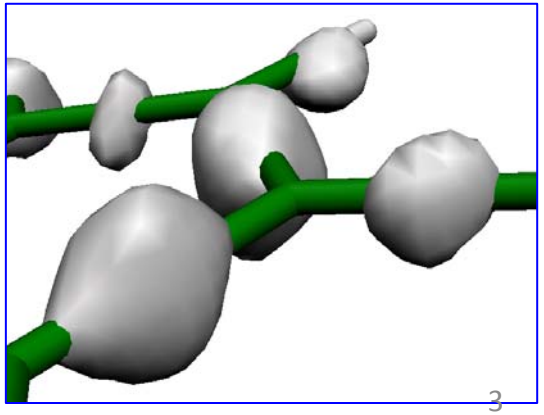


SUB-ATOMIC
or
ULTRA HIGH

$d \approx 0.5$ Å

Deformation of Electron Density

Atomic Charges

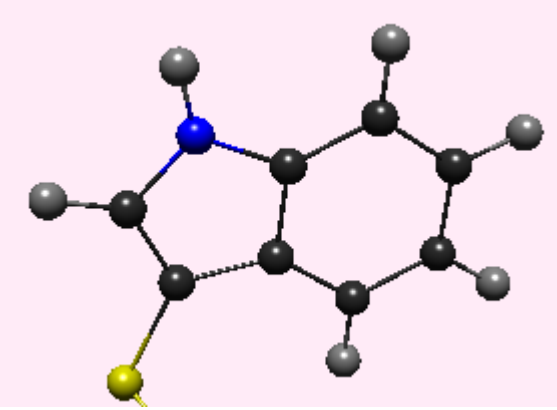


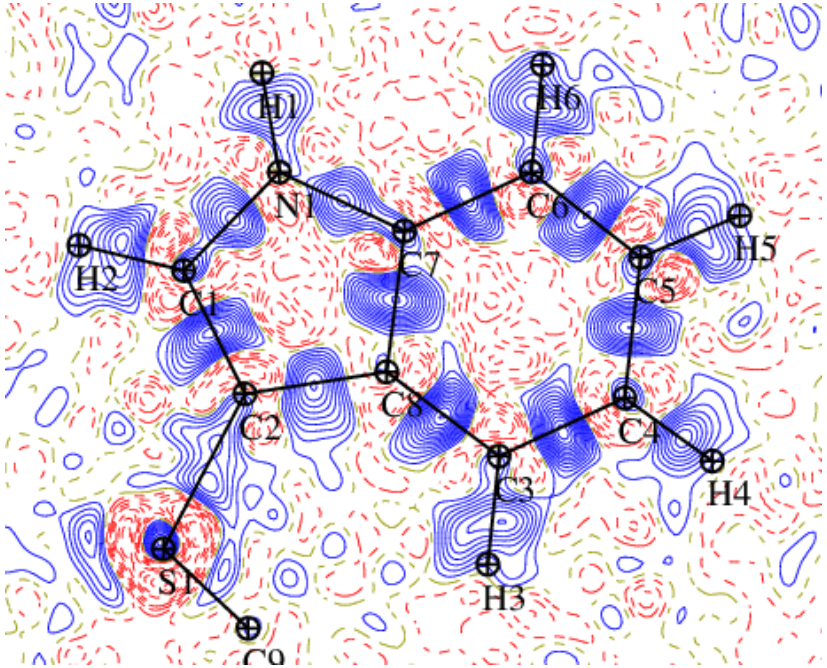
Spherical Atom Model

Fourier Residual Electron Density: $F_{obs} - F_{calc}$

Usual crystallography : spherical atoms

Resolution 0.5 Å or $\sin\theta/\lambda$ = 1 Å^{-1}



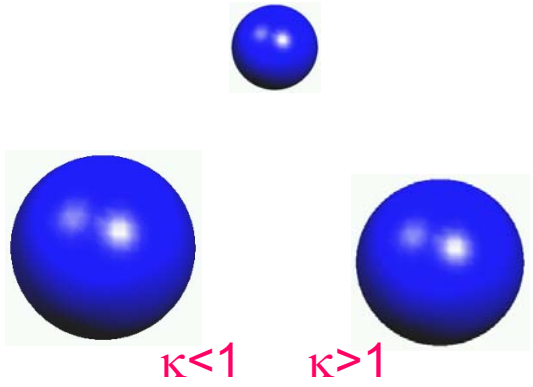


Residual peaks
on covalent bonds

2-(indol-3-yl)-1,1,3,3-tetramethylthiouronium nitrate Lutz *et al*. *Acta Cryst.* (2008). C**64**,

Multipolar Atom Model

$$\rho_{atom}(r) = \rho_{core}(r) + P_{val}\,\kappa^3\,\rho_{val}(\kappa r) + \Sigma_l\,\kappa'^3\,R_l(\kappa' r)\,\Sigma_m\,P_{lm}\,Y_{lm}$$



P_{val} valence population

κ κ' expansion/contraction

P_{lm} multipoles

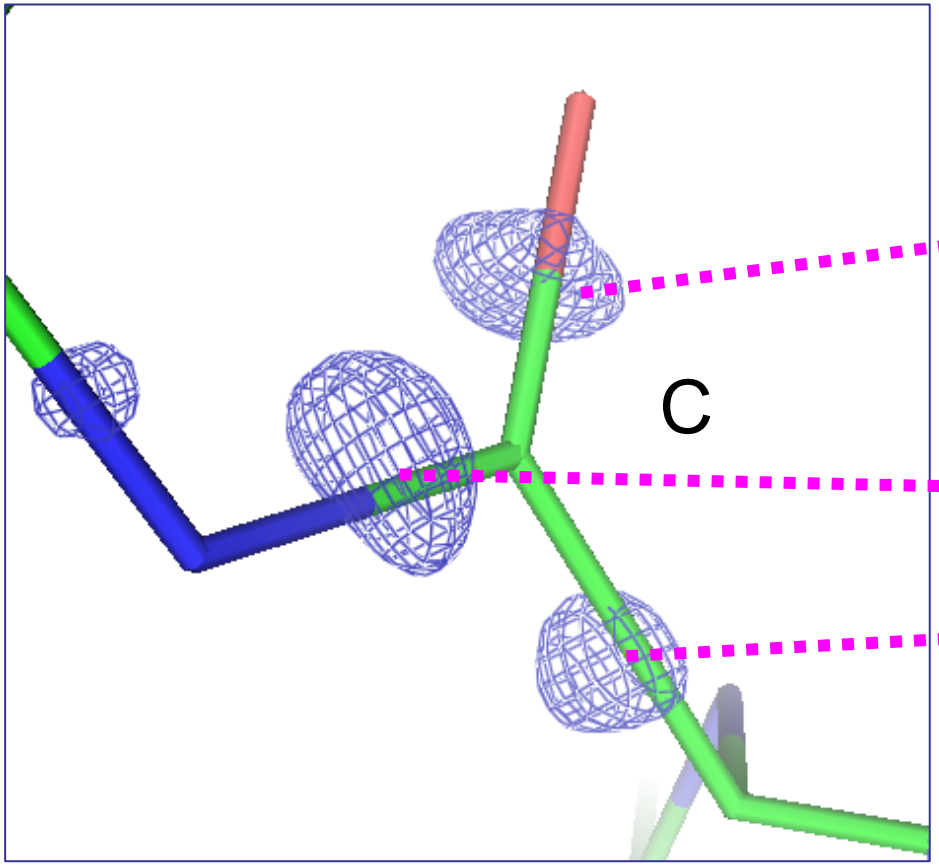
Hansen & Coppens (1978)

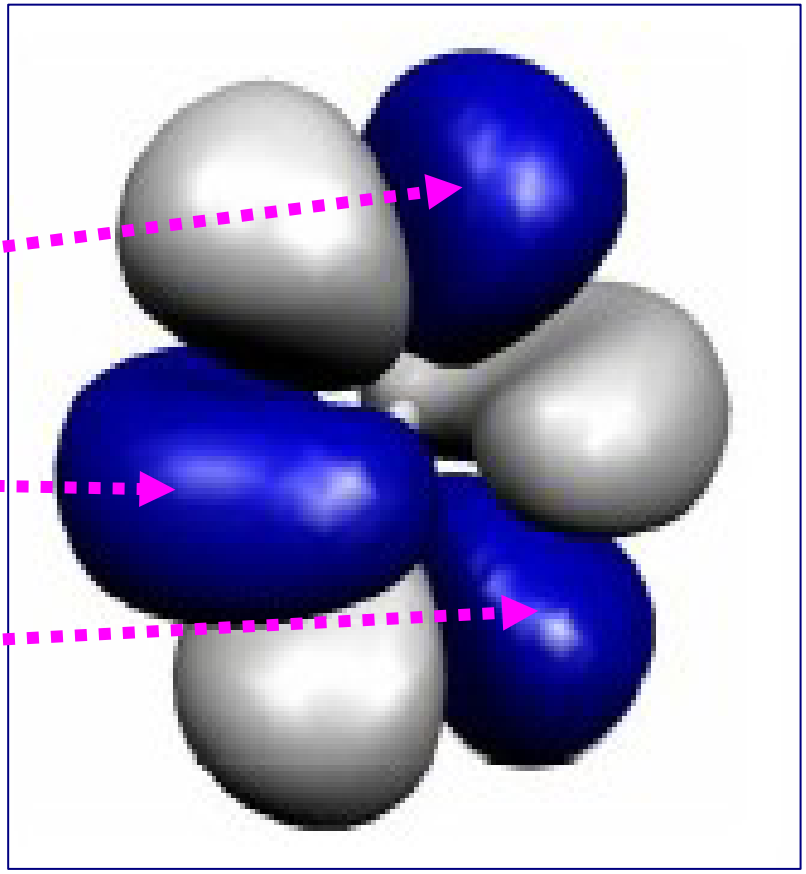
Acta Cryst. A34, 909

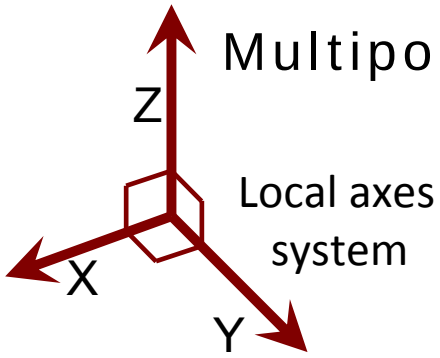
Multipoles & Deformation Electron Density

Example : sp^2 Carbon atom

Octupole



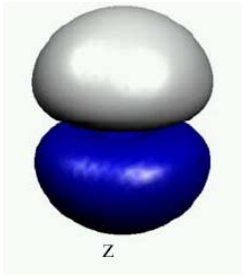




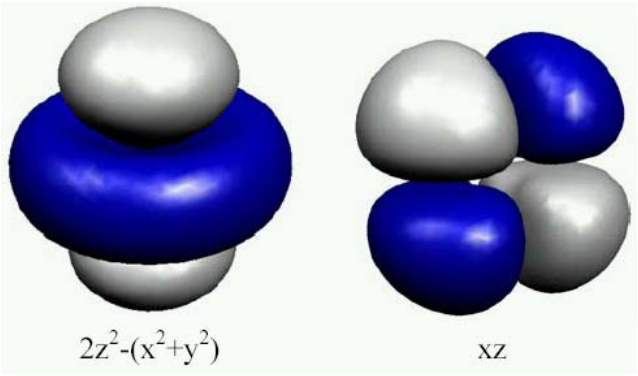
Multipoles

Local axes system

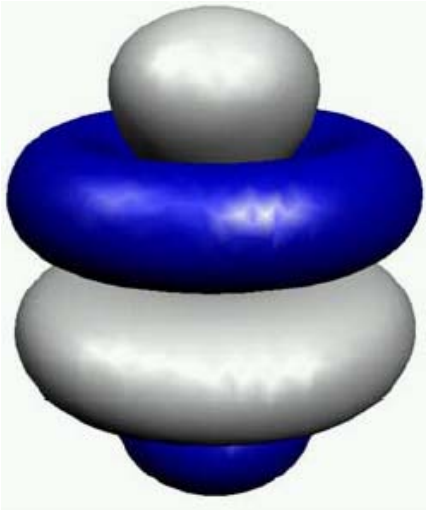
3 dipoles



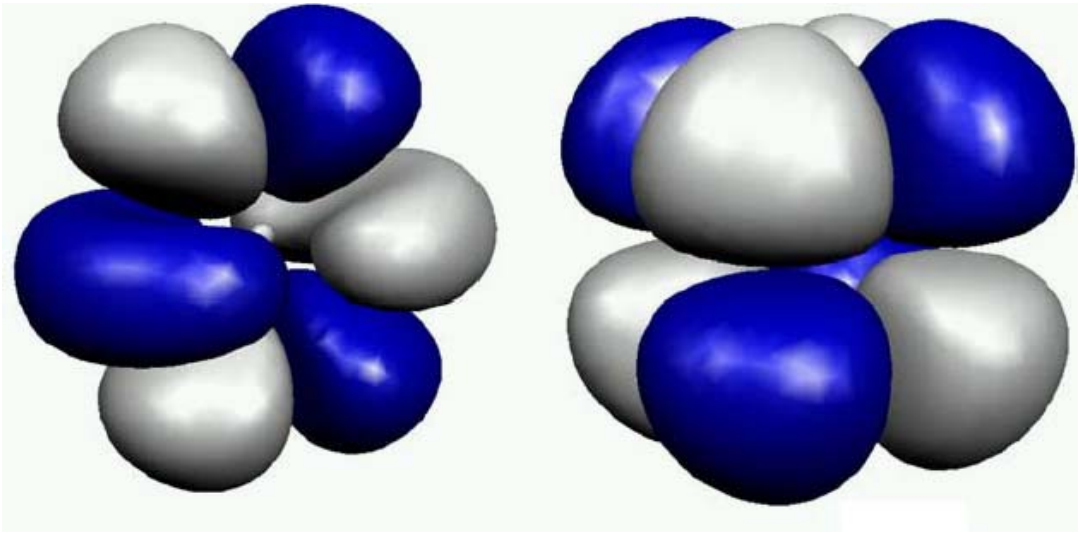
5 quadripoles



7 octupoles



$2z^3 - 3z(x^2+y^2)$



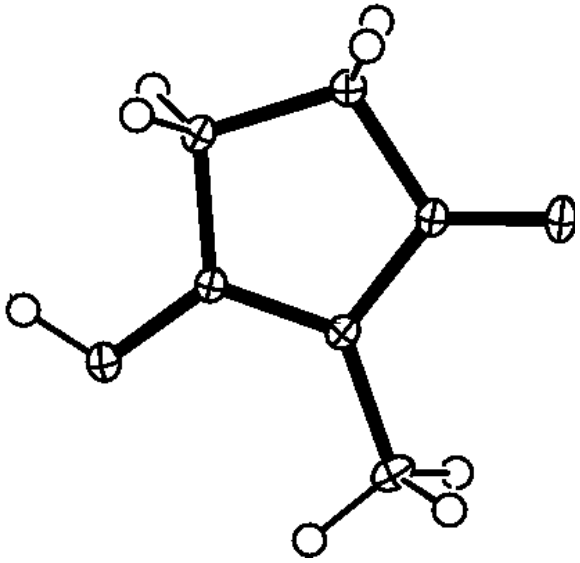
$x[4z^2-(x^2+y^2)]$ $y[4z^2-(x^2+y^2)]$ xyz

$x(x^2-3y^2)$ $y(y^2-3x^2)$ $(x^2-y^2)z$

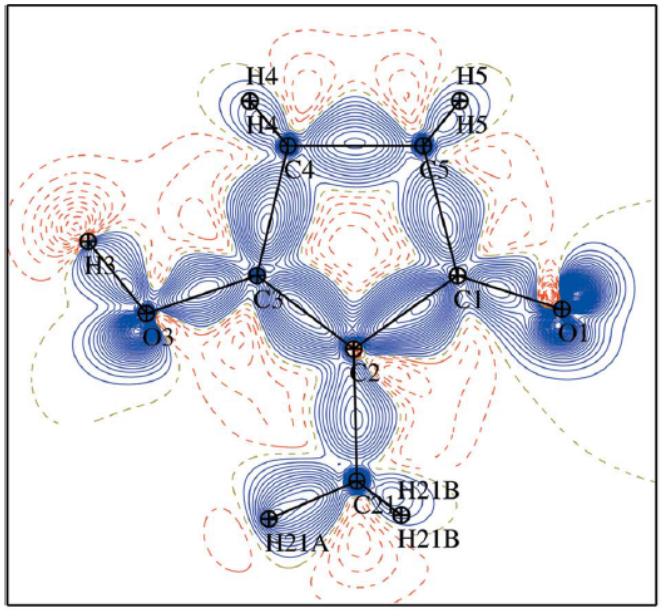
Deformation of Electron Density

$$\Delta\rho = \rho_{\text{molecule}} - \rho_{\text{isolated atoms}}$$

multipolar neutral & spherical



Static : computed for atoms at rest



+/-

0.05 e-/Å^3

2)

The MoPro software for

electron density analysis

MOPRO Crystallographic Refinement Software

Subatomic Resolution *Structure & Electron Density*

~0.5Å

Atomic Resolution Structure with Hydrogen Atoms

0.7 – 1.4 Å Transfer Electron Density Databank

Small Compounds & Biological Macromolecules

Developped at CRM2 laboratory, Nancy, Lorraine University

Jelsch *et al*. *J. Appl. Cryst.* (2005) 38, 38-54

Guillot Acta Cryst A. (2012). A**68**, s204.

LEAST SQUARES MINIMIZATION

Program MoPro Minimizes

$$E = \sum_H w_H (I_H^{calc} - I_H^{obs})^2$$

$$+ \sum_r [(R_{calc} - R_{target}) / \sigma_r]^2$$

H=(*h*,*k*,*l*) reflection

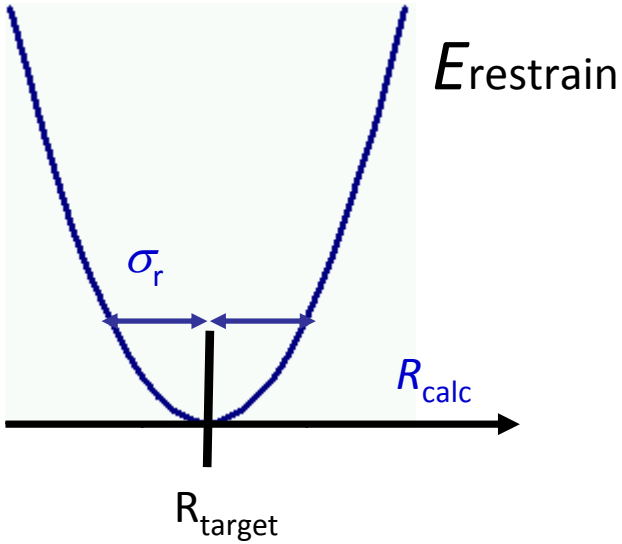
I intensity R restraints

RESTRAINTS :

introduce

additionnal information

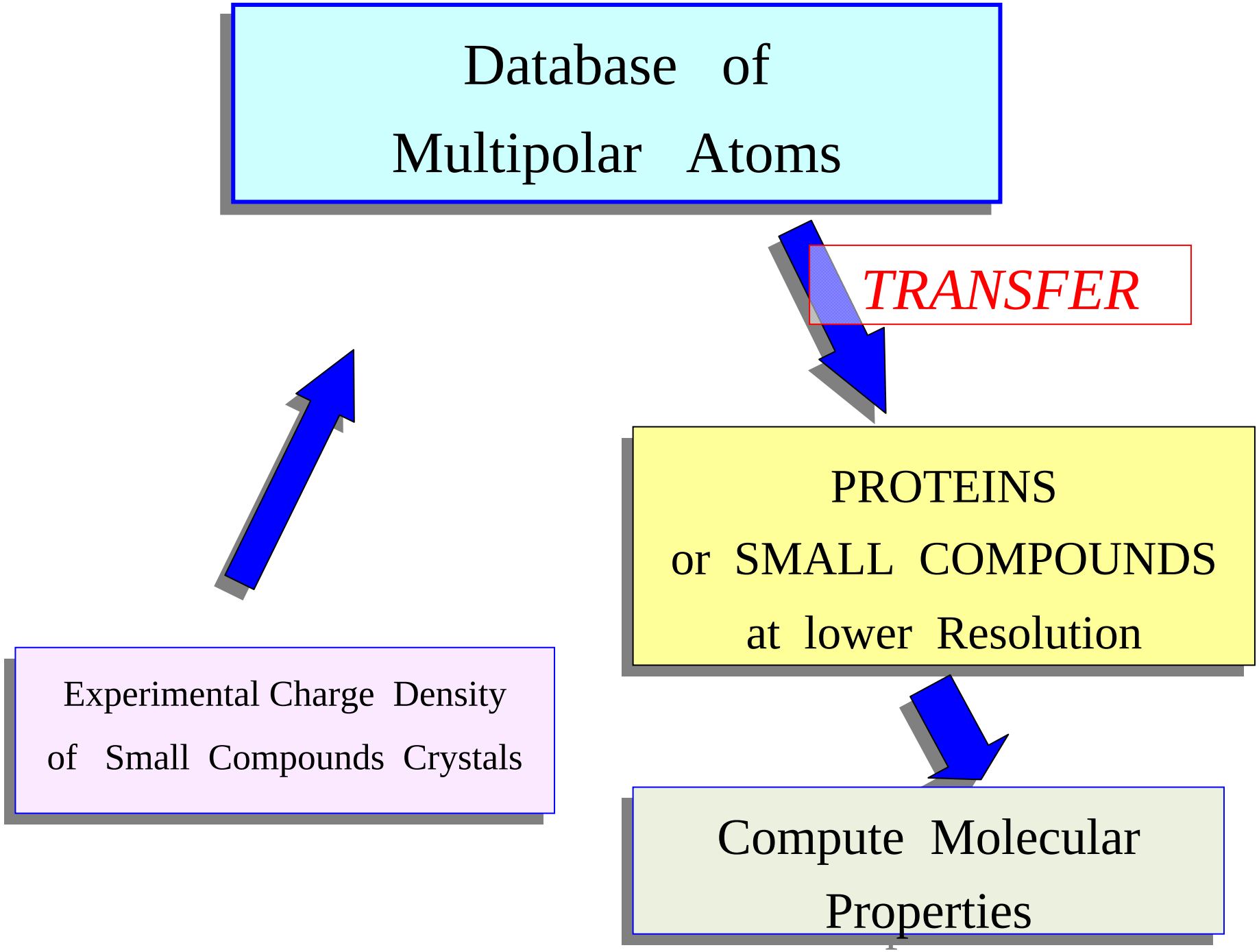
into the system



Some RESTRAINTS/ CONSTRAINTS in MoPro

$P \approx P_{target}$ $P = P_{target}$

R/C	Distance		Stereo-chemistry
R/C	Angle		
R/C	Planarity		
R	Similar Distances	D1 ≈ D2	
R	Similar Angles	A1 ≈ A2	
R/C	Similar Valence Populations		Charge density
R/C	Similar Multipoles		
R/C	Similar Expansion/ Contraction coef		


Database of
Multipolar Atoms
TRANSFER
PROTEINS
or SMALL COMPOUNDS
at lower Resolution
Compute Molecular
Properties
Experimental Charge Density
of Small Compounds Crystals

3)

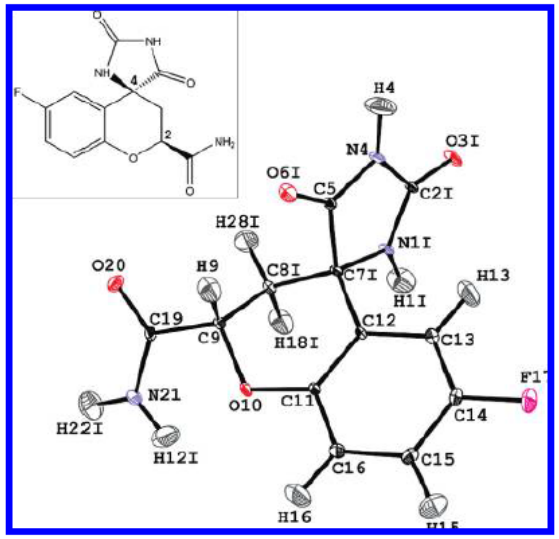
Derived Properties

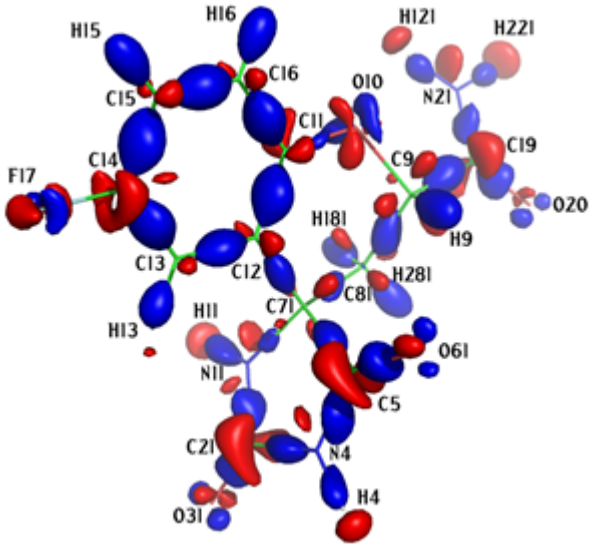
Exemple of applications

Electrostatic Potential derived from the Multipolar Atom Model

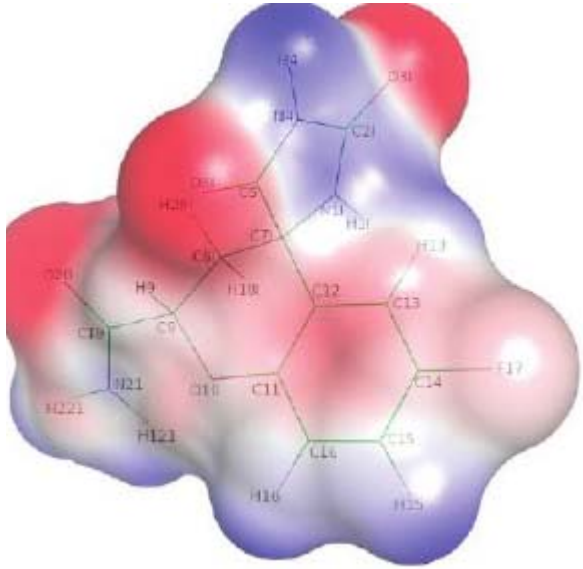
$$V(\mathbf{r}) = \sum q_i / r_i + \int\int\int \rho(\mathbf{r}) / r_i \, d^3\mathbf{r}$$

Fidarestat
Inhitor of protein aldose reductase



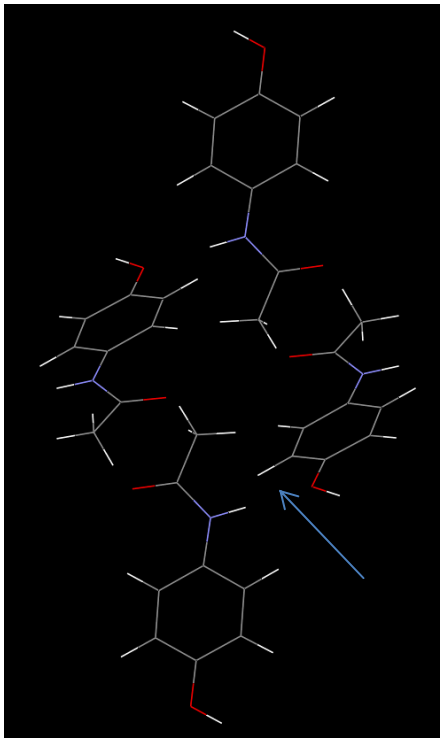


$\Delta\rho(\mathbf{r})$ deformation density
accumulation/depletion



Color surface according to $V(\mathbf{r})$
+ / -

Electrostatic Interaction Energy between dimers in the crystal packing

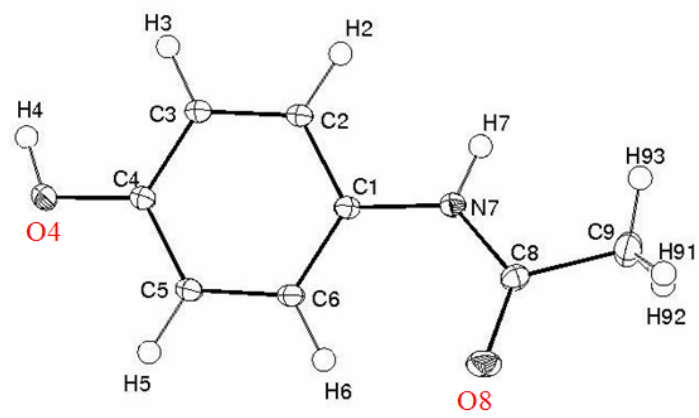


Bouhmaida *et al.*

Acta Cryst B

2009

Paracetamol

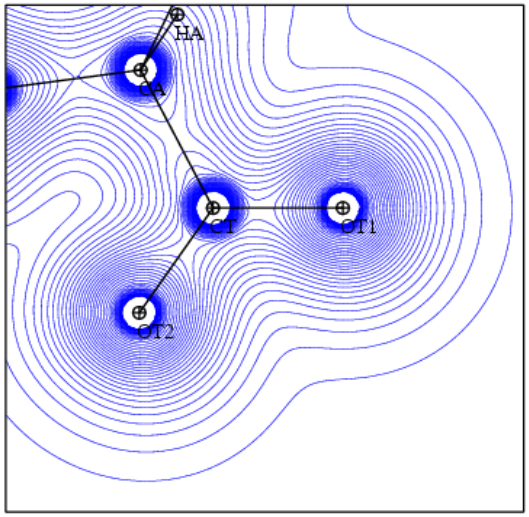


Dimer #	Atom 1	Atom 2	Distance (Å)	Symmetry	E_{def} kcal/mol
1	O4	H7	1.9275	X-½ ; -Y+½ ; Z-½	-15.23
	H7	O4	"	X+½ ; -Y+½ ; Z+½	"
2	O8	H4	1.6966	X-½ ; -Y+½ ; Z+½	-11.15
	H4	O8	"	X+½ ; -Y+½ ; Z-½	"
3	H92	O8	2.7062	-X+3/2 ; Y-½ ; -Z+3/2	-9.86
	O8	H92	"	-X+3/2 ; Y+½ ; -Z+3/2	"
4	H92	H4	2.6565	-X+2 ; -Y ; -Z+1 (inv)	-5.69
5	H93	H2	2.5015	-X+5/2 ; Y-½ ; -Z+3/2	-0.32
	H2	H93	"	-X+5/2 ; Y+½ ; -Z+3/2	"
6	H6	H6	2.2263	-X+1 ; -Y ; -Z+1 (inv)	-0.01
7	H5	H4	2.7269	-X+3/2 ; Y-½ ; -Z+½	1.71
	H4	H5	"	-X+3/2 ; Y+½ ; -Z+½	"

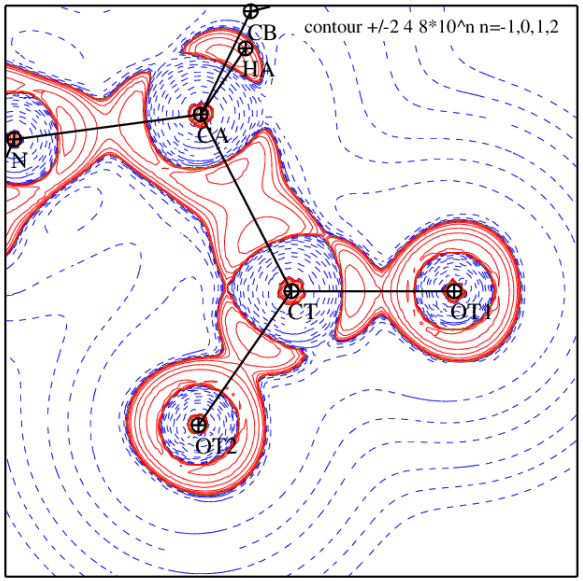
Closest interacting atoms

Topological Analysis

Total electron density ρ

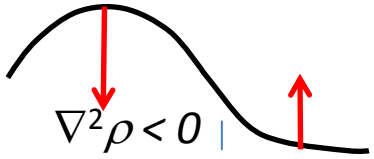


Laplacian

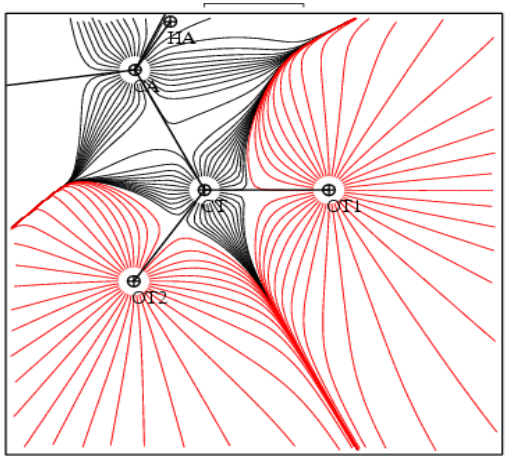


$$\nabla^2\rho = \partial^2\rho/\partial x^2 + \partial^2\rho/\partial y^2 + \partial^2\rho/\partial z^2$$

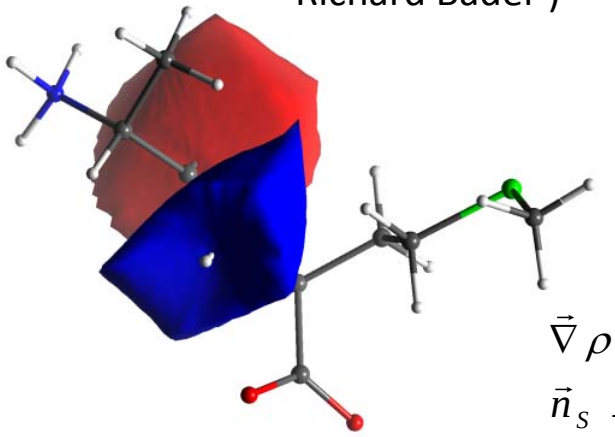
Negative Laplacian in red : Electron accumulation



Gradient lines of ρ



Atomic Basins: (Atoms In Molecules ; Richard Bader)



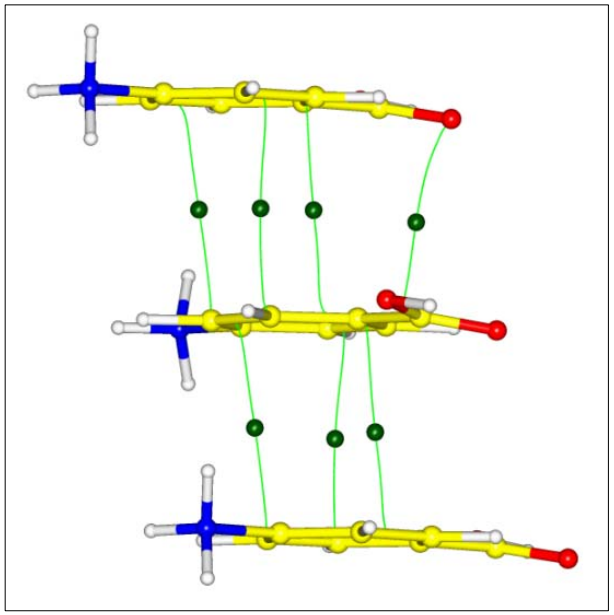
→ Integrated Property : **atomic charges**

$$\vec{\nabla}\rho(\mathbf{r}).\vec{n}_S(\mathbf{r}) = 0$$

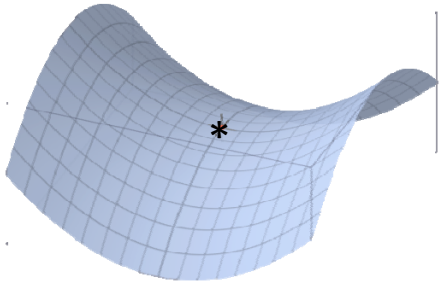
$\vec{n}_S \perp Surface$

Topological Analysis : Critical Points

Places where the gradient of total electron density is zero



Bond paths



Saddle CP

→ Permits to caracterize nature & force of interactions (hydrogen bonds)

$$H_{ij} = \frac{\partial^2 \rho(\vec{r})}{\partial x_i \partial x_j}$$

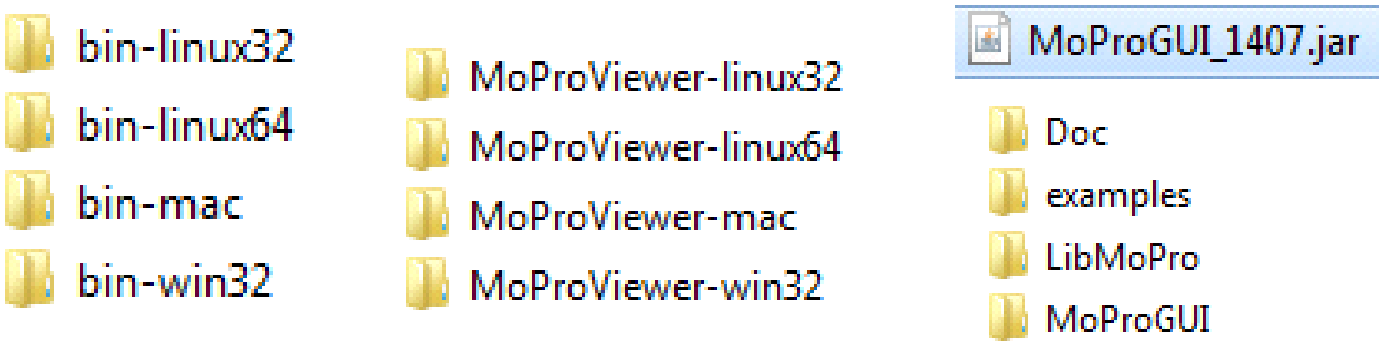
Diagonalization of Hessian matrix:

Ellipticity of a covalent bond : π bonding

5) Practical presentation of the software MoPro

MoProSuite

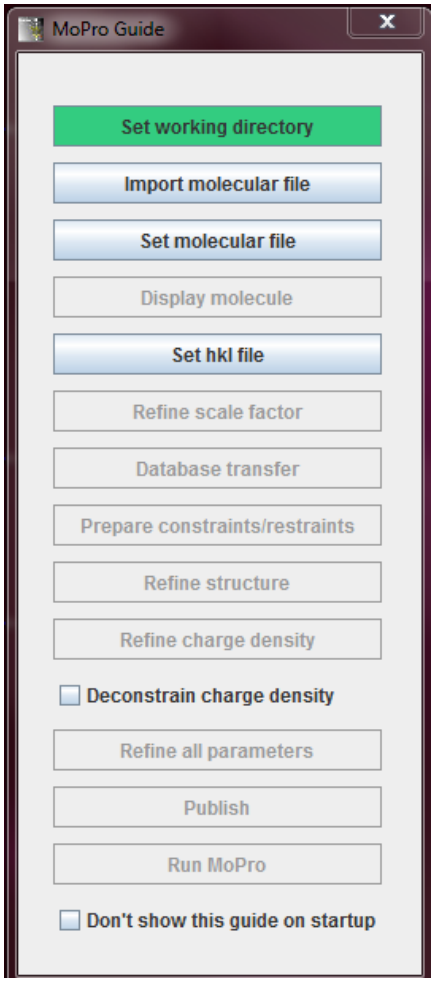
Molecular Viewer & GUI

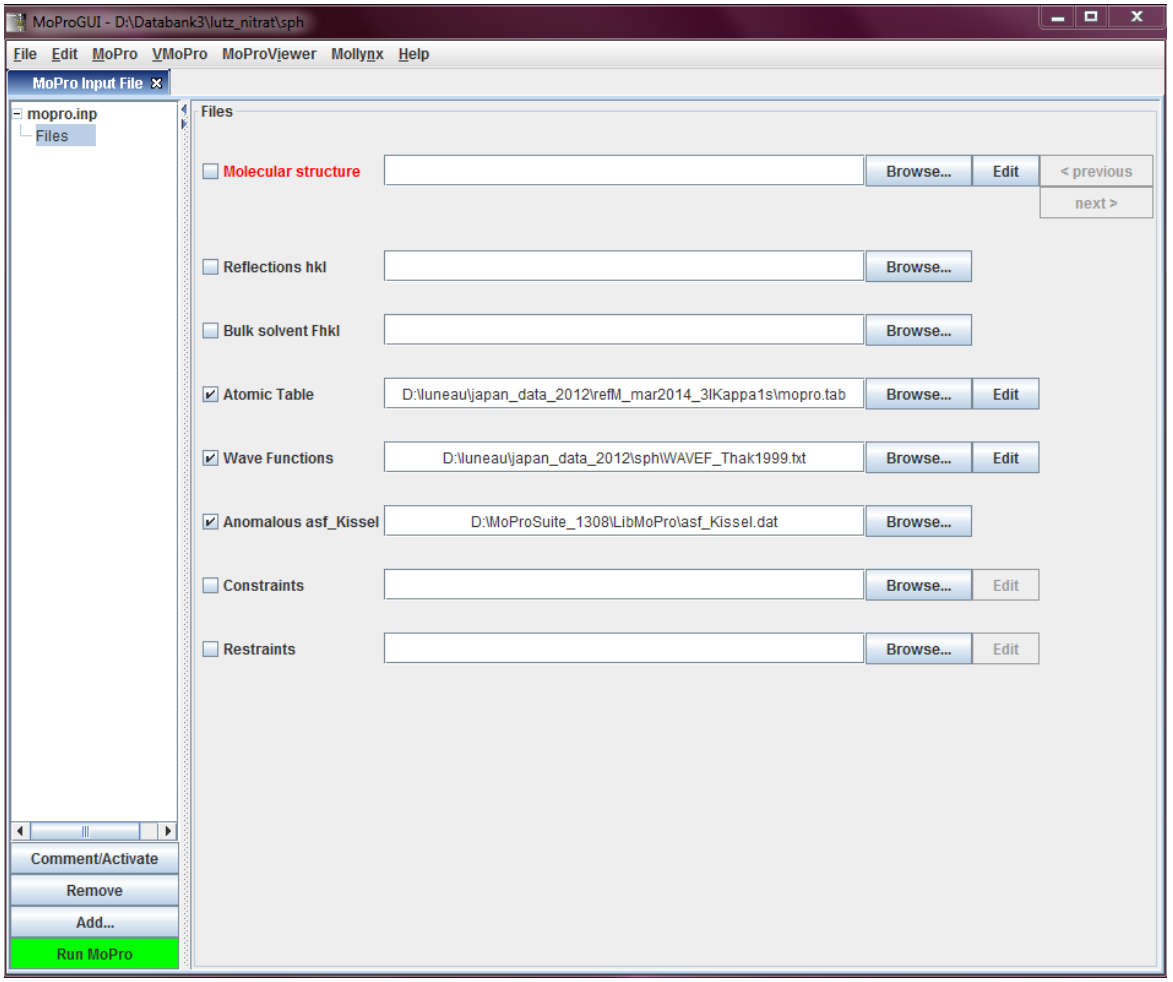


MoProSuite Software components

MoProGUI	general Graphical User Interface
Import2MoPro	read .cif .pdb .xyz .res files
MoPro	Crystallographic refinements
VMoPro	Calculation of Molecular Properties (density, potential, Laplacian..)
MoProViewer	Molecular Viewer & GUI

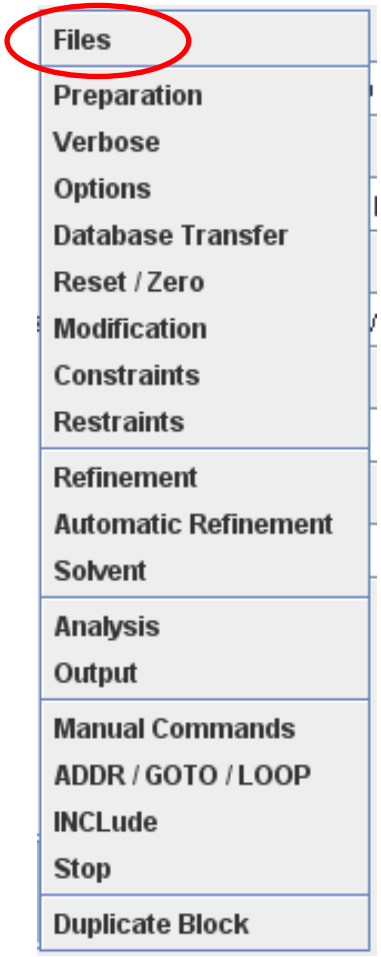
MoProGUI menu

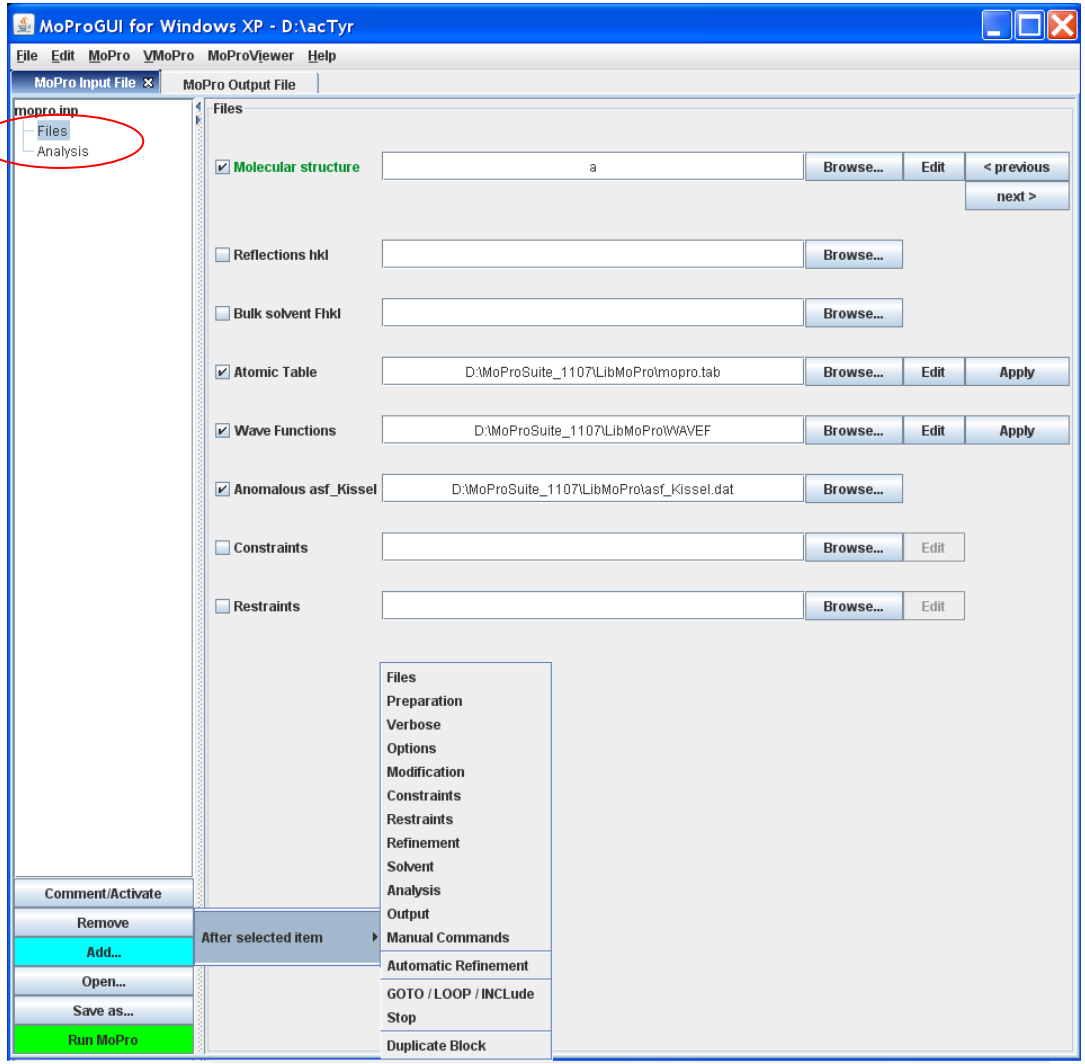




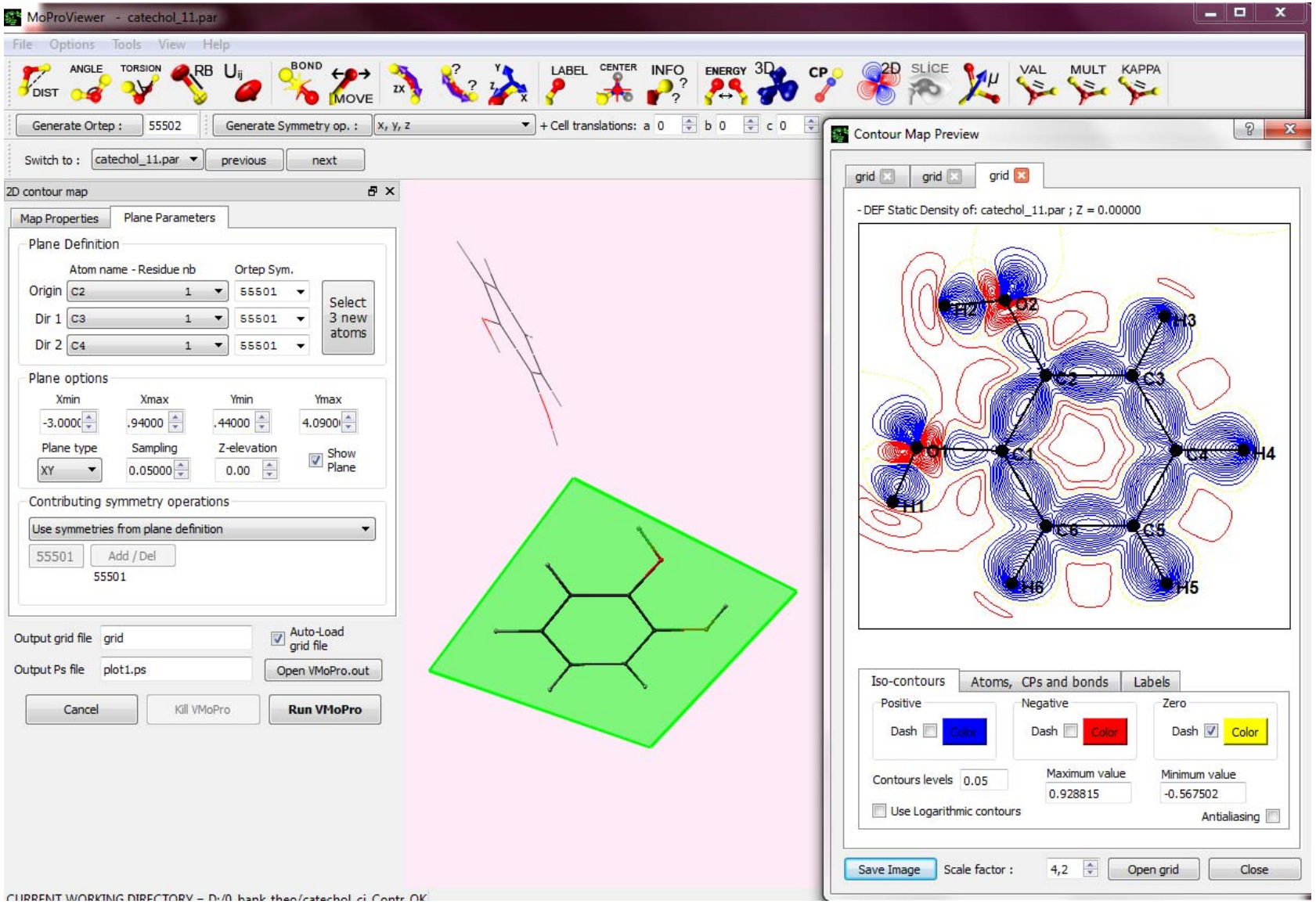
MoProGUI / MoPro Main Menus.

File declarations



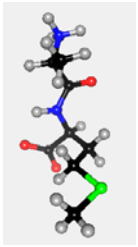


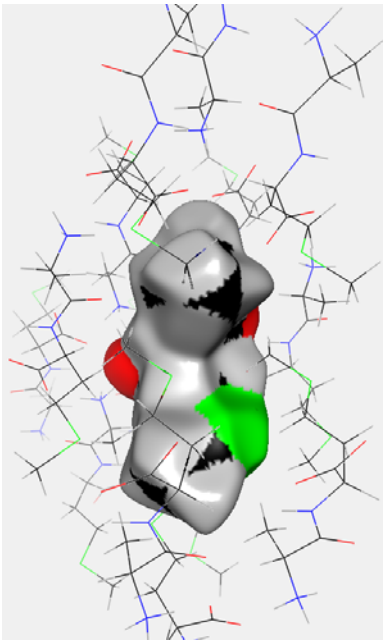
MoProViewer developed by Benoît Guillot, University Lorraine

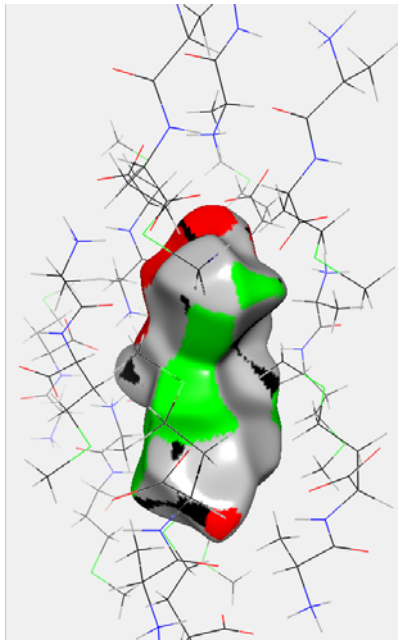


MoProViewer : a recent functionnality

Automatic calculation of **Hirshfeld surface** of a molecule In its crystal packing







Coloring according to interior or exterior atom types

Statistical analysis of crystal contacts

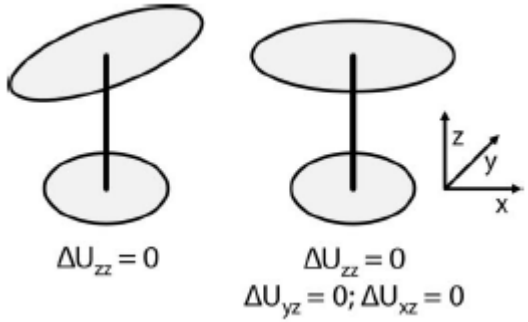
cf Jelsch *et al*. IUCrJ (2014). 1, 119–128

RECENT extensions/improvements in MoPro

* Multipoles beyond hexadecapoles *L*=5 & *L*=6

* Several Kappa2 parameters for an atom
  (each multipole level)

* Enhanced rigid-bond restraints
  (Thorn, Dittrich & Sheldrick,
  2012, Acta Cryst A)



* Eigenvalue filtering [Radek Kaminski, Warsaw]

* Block diagonal refinement