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Part III Chapter 10

Multipole Modelling with MoPro and XD

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10.1 An introduction to Multipole Modelling

The surrounding chapters in this book highlight the pivotal role of the charge distribution in the qualitative and quantitative characterization of chemical bonds, and in the determination of molecular and crystal properties. Hence, the motivation to obtain accurate analytical models of the charge distribution, that arises from the electron density (ED).. Providing such models is the aim of the multipole modelling, summarized in this section. Next, the *XD2016* and *MoProSuite* programs, two among the most widely used packages in charge density analysis, will be described. These programs utilize the multipolar atom model and allow the determination, representation, and the property analysis of electron densities in crystal structures – be they molecular, polymeric, ionic or elemental, including metals.

It is well known that crystal structures can be determined by the means of single crystal X-ray diffraction experiments. As X-rays interact with electrons, diffraction experiments image

the ED distribution in the crystal, from which the positions of atomic nuclei in the unit cell can be deduced. The aim of routine X-ray diffraction experiments is indeed often limited to the determination of the three-dimensional structure of the studied compound. In other words, the experimentally measured ED is interpreted only in terms of local maxima, indicating where the nuclei are located in the unit cell. The most common methods to determine the crystal structures resort on a simple model, where the crystal is seen as an assembly of non-interacting atoms and the corresponding electronic distribution is described as a collection of spherically symmetric atomic electron densities, centred on the coordinates of the corresponding nuclei. The atoms may define a molecule or not, but this does not affect the model which is invariant with respect to a prejudicial chemical insight (i.e. the connectivity among atoms). A molecule, whose ED is approximated in this way, is called a “promolecule” within the field of charge-density studies, nowadays termed “quantum crystallography” (see **part III, chapter 9**).

10.1.1 The shortcomings of spherical atom model

In the process of determining a crystal structure, the stage of refinement is especially important and needs to be briefly recalled here. The crystallographic refinement corresponds to the process of adjusting parameters of the structural model against the data provided by the X-ray diffraction experiment. In routine structure determination, the refined parameters are the atomic fractional coordinates and the mean square displacements of nuclei, around their equilibrium positions, due to thermal vibrations. These can either be seen as isotropic, leading to one single parameter per atom, or anisotropic, described by up to six independent values within the framework of a harmonic model. In crystallographic refinements, the approximation of non-interacting atoms is called “Independent Atom Model” (IAM), valid for both molecular and non-molecular crystals. Indeed, atomic parameters are optimized by minimizing an error function S written as a sum, over all used experimental data, of squared differences between observed ($F_{obs}(\vec{H})$) and computed ($F_{calc}(\vec{H})$) structure factors amplitudes, or intensities. Such procedure is therefore termed as “least-squares refinement”:

$$S = \sum_{\vec{H}} w_{\vec{H}} (|F_{obs}(\vec{H})| - |F_{calc}(\vec{H})|)^2 \quad (10.1)$$

where \vec{H} is the scattering vector and $w_{\vec{H}}$ a weighting coefficient related to the experimental uncertainty associated to the corresponding $|F_{obs}(\vec{H})|$. The calculated structure factor $F_{calc}(\vec{H})$ depends on the model which is adopted for the atomic electron distribution and nuclear vibration. The least squares minimization is inherently non-linear, but it can be linearized by using as variables the shifts from an initial model of the parameters needed to minimize S . This implies an iterative process that eventually converges to the set of best parameters that minimize

the disagreement between $|F_{obs}(\vec{H})|$ and $|F_{calc}(\vec{H})|$. Noteworthy, for a more accurate model, such as the multipole model, the IAM could be a reasonable starting point.

For a unit cell containing N_{at} atoms, the calculated structure factor is written as:

$$F_{calc}(\vec{H}) = \sum_{j=1}^{N_{at}} f_j(\vec{H}) T_j(\vec{H}) \exp(2i\pi\vec{H}\cdot\vec{r}_j) \quad (10.2)$$

where, for the j^{th} atom, $T_j(\vec{H})$ is the Debye-Waller factor depending on the thermal displacement parameters, \vec{r}_j is the vector of its fractional coordinates and $f_j(\vec{H})$ represents its scattering factor. The atomic scattering factor (or form factor) is the Fourier transform of the atomic electron density. In the IAM model, given the spherical approximation of atomic electron densities in real space, the scattering factors are spherically symmetric in the reciprocal space as well. For a given chemical species, they depend only on the norm $|\vec{H}| = \sin(\theta)/\lambda$ of the scattering vector \vec{H} , with θ being the Bragg angle and λ the wavelength of the X-ray beam used in the experiment.

A major drawback of the promolecular ED approximation is that, although acceptable to build a sufficiently correct structural model, it is chemically inconsistent. In fact, the wavefunction that produces such a density does not represent a bound state and the typical features of chemical bonding would be missing. This should not surprise us, because the percent difference between a purely spherical distribution of electrons in atoms and the correct electron density is of the order of magnitude of 1%. In order to better describe the asphericities, a more sophisticated model is necessary, which relies on extra parameters. The augmented number of parameters of an accurate ED modelling requires significant extension of the diffraction resolution. A consensual resolution limit of $\sin(\theta)/\lambda = 0.7 \text{ \AA}^{-1}$ is often taken as a reference. Above this limit the resolution becomes “subatomic”. If coupled with high precision measurements of the diffracted intensities, deviations from the spherical ED approximation become clearly visible. The main deformations from sphericity affect of course the valence electron density, mainly because of chemical bonding. Importantly, these electrons scatter only at low resolution (*i.e.* below $\sin(\theta)/\lambda = 0.7 \text{ \AA}^{-1}$). Nevertheless, the high-resolution data are important because they allow fixing with precision nuclear positions and atomic displacement parameters as they strongly depend on core electrons that dominate the diffraction at high-resolution. In turn, this enables reducing the correlation between position parameters and the additional parameters necessary to accurately describe the electron density.

The quality of the refined model can be assessed by computing Fourier transformation maps of the difference between the observed structure factors amplitudes and their computed equivalents, see eq. (10.3).

$$\rho_{resid}(\vec{r}) = \frac{1}{V} \sum_{\vec{H}} (|F_{obs}(\vec{H})| - |F_{calc}(\vec{H})|) \exp(i\varphi_{calc}) \exp(-2i\pi\vec{H} \cdot \vec{r}) \quad (10.3)$$

where φ_{calc} represents the phase of the computed complex structure factor $F_{calc}(\vec{H})$.

If using an IAM model, these residual electron density maps reveal accumulations of non-modelled ED on covalent bonds (where they are found shared by the bonded atoms), or at expected positions of electron lone pairs [1] (Coppens 1967). An example of residual map can be found in **Fig. 10.1**. High and localized peaks in maps of $\rho_{resid}(\vec{r})$ clearly indicate that the spherical atom approximation is insufficient, because the information available from the diffracted intensities is not and cannot be properly exploited with the IAM model. Even worse: the refined positional and thermal atomic parameters are in this case necessarily biased by the non-modelled aspherical distribution of the valence ED. This is especially true for the atomic anisotropic displacement parameters, which represent the only degrees of freedom accessible in the IAM approach to partially account for the anisotropic features of the ED. In this case, the deformation ED and the atomic displacement parameters are said to be convoluted, and the IAM model is therefore wrong in trying to reproduce both the electron density and the atomic displacements.

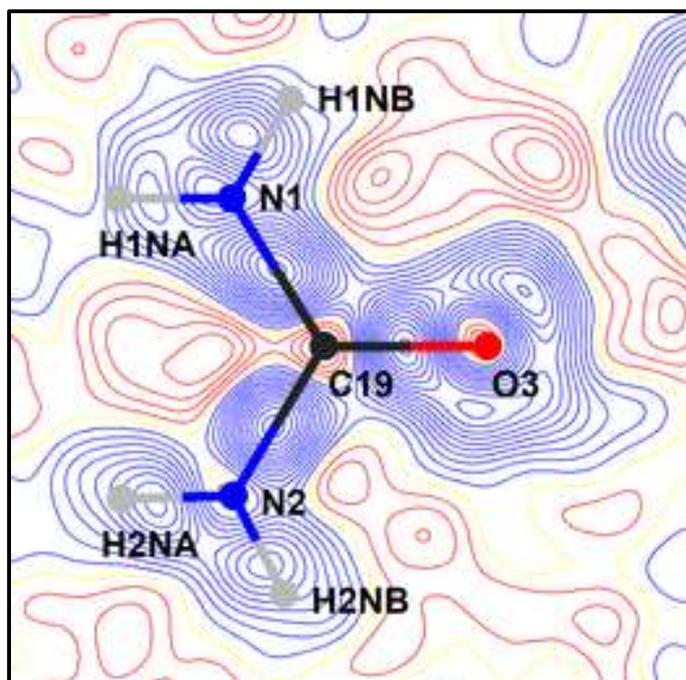


Fig. 10.1: Fourier residual map in the plane of urea, after IAM refinement with *MoPro* of the estradiol-urea diffraction data up to $\sin(\theta)/\lambda = 1.16 \text{ \AA}^{-1}$ (Parrish *et al.*, 2006). Contour $\pm 0.05 \text{ e/\AA}^3$. Positive: blue; negative: red; zero: yellow lines.

10.1.2 The multipolar atom model

Obviously, the objective of properly modelling the fine electron density details, and at the same time properly de-convoluting atomic displacements parameters and deformation ED features, can only be achieved using a more adequate atomic model than the crude spherical approximation of the IAM approach. This is exactly the purpose of the multipole model, elaborated by, among others, Hansen and Coppens [2], Stewart [3,4] and Coppens [5]. The multipole model preserves the partition of the electron density in terms of atomic contribution, which characterizes the IAM model. However, the atomic terms are no longer spherical. In fact, the atomic electron density $\rho_{atom}(\vec{r})$ result from the sum of three terms, accounting respectively for the core, the spherical and the aspherical deformation of valence electrons:

$$\rho_{atom}(\vec{r}) = \rho_{core}(|\vec{r}|) + \kappa^3 P_{val} \rho_{val}(\kappa|\vec{r}|) + \sum_{l=0}^{l_{max}} \kappa'^3 R_l(\kappa'|\vec{r}|) \sum_{m=-l}^{+l} P_{lm} Y_{lm}(\theta, \varphi) \quad (10.4)$$

The total molecular electron density $\rho_{mol}(\vec{r})$ is then obtained by summing up these atomic contributions describing so-called ‘‘multipolar pseudo-atoms’’:

$$\rho_{mol}(\vec{r}) = \sum_{atoms} \rho_{atom}(\vec{r}) \quad (10.5)$$

Let us now describe in more detail equation (10.4), as it is central in multipole modelling. The first term accounts for the core electron shell of the considered atom. As these electrons are usually not involved in interatomic bonds, in the Hansen & Coppens model, they are kept unperturbed so that $\rho_{core}(|\vec{r}|)$ follows the same spherical approximation as atoms in the IAM model with a fixed number of electrons. More precisely, $\rho_{core}(|\vec{r}|)$ is a spherically averaged core ED computed from theoretical wave-functions of the ground state electronic configuration of the unperturbed isolated atom. The parameters of the core orbital functions (coefficients and exponents of Slater type functions) come from Roothaan-Hartree-Fock calculations (see for example Clementi & Roetti [6]) or from Dirac-Fock numerical solution of the atomic Schrödinger equation and wave-function fitting (Su & Coppens [7]; Macchi & Coppens [8]).

The second term in eq. (10.4) describes the spherical part of the valence electron shell. This ED is calculated like the core density from the corresponding valence orbitals of the atomic wave-function, however the associated population P_{val} is allowed to vary in the course of the refinement as well as the associated volume. Indeed, the $\rho_{val}(\kappa|\vec{r}|)$ term represents here a spherical valence ED, normalized to one electron. The P_{val} parameter allows to represent the charge flow among atoms of the compound and consequently gives access to an estimation of the experimental atomic charge. Indeed, knowing N_{val} , the number of valence electrons in the

neutral state, the atomic charge q can be defined by simply computing the difference $q = N_{val} - P_{val}$.

The spherical valence term depends also on the κ coefficient, which is again an atomic parameter that can be fitted in the course of the refinement. This κ parameter describes the contraction or expansion of the valence electron shell around the atomic nucleus. If P_{val} increases (for example for the most electronegative atoms), the increased electron-electron repulsion produces an expansion of the atomic volume. Because in the $\rho_{val}(\kappa|\vec{r}|)$ term, κ appears as a parameter scaling the radial coordinate $|\vec{r}|$, the expansion of the shell implies $\kappa < 1$. In fact, when $\kappa < 1$, then $\kappa|\vec{r}| < |\vec{r}|$ which means that the same valence ED value is found at a larger value of $|\vec{r}|$, corresponding to an expanded spherical valence shell. The inverse situation occurs when $\kappa > 1$: in this case, the valence shell is contracted. In eq. (10.4), the κ^3 factor is due to a normalization factor of the atomic orbital functions, as $\rho_{val}(\kappa|\vec{r}|)$ should remain normalized to one electron.

The third term in the Hansen & Coppens model accounts for non-spherical features of the valence electron density deformation. At variance from the other two terms, which are spherical, the third term is written by splitting the radial (function of $|\vec{r}|$) and the angular (function of (θ, φ)) dependencies of the aspherical valence ED using, respectively, single- ζ Slater-type functions R_l and density-normalized real spherical harmonics Y_{lm} . The outer sum in eq. (10.4) runs over a positive integer l , which corresponds to the order of spherical harmonic functions used to model the considered atom. The second summation runs over a second integer m with $-l \leq m \leq +l$. Clearly, this resembles the mathematical representation of the angular part of hydrogenic orbitals in quantum mechanics; however, it is important to understand what the difference is. Orbitals are atomic wave-functions, whereas the multipole formalism models atomic electron densities. The density of an atomic orbital is the square of the orbital function, which implies squaring also the angular part. In analogy with the atomic orbitals, it is convenient to adopt the spherical coordinates $(|\vec{r}|, \theta, \varphi)$. While a global coordinate system (equal for all atoms) would be computationally easier, Hansen and Coppens (1978) suggested instead the possibility to adopt a local coordinate system for each atom [2]. This is defined using orthonormal Cartesian basis vectors chosen to follow the local symmetry around the considered atom or anyway a pseudo-symmetry generated by the chemical environment. The atomic axes are generally defined by using interatomic vectors towards bonded neighbour atoms.

The single- ζ Slater functions, representing the radial dependency of the aspherical valence ED, are node less atomic orbitals expressed by the general formulas:

$$R_l(\kappa'|\vec{r}|) = \frac{\zeta^{n_l+3}}{(n_l+2)!} (\kappa'|\vec{r}|)^{n_l} \exp(-\zeta\kappa'|\vec{r}|) \quad (10.6)$$

The parameters n_l and ζ are related to coefficients of analogous hydrogenic orbital functions (Clementi and Raimondi, 1963 [9]). At variance from core and spherical valence, constructed from Roothaan type atomic wave-functions (meaning that each orbital is a combination of many Slater type functions), the aspherical radial part is a single Slater type orbital transformed into a Slater type density function (meaning $\zeta = 2\zeta_{orbital}$). In addition, the ζ values are taken as averages of energy optimized single- ζ valence orbitals, computed by theoretical methods for the electron shells of isolated atoms. This means that for the valence shell of a second row atom (e.g. C), only one radial density function is used, with a ζ exponent that is the twice the average between exponents for single- ζ orbitals $2s$ and $2p$.

The exponents n_l should be in principle determined by the valence orbitals ($n_l = 2(n-1)$), where n is the principal quantum number of the atomic orbital). However, in order to satisfy Poisson equation, $n_l \geq l$. This implies that for higher poles (for which $l > 2(n-1)$) a direct connection between the radial density function and the valence atomic orbital function is lost. Suitable sets of values are given, for various atomic species, in the library files of specialized multipole modeling programs such as *XD2016* or *MoProSuite*. Being an integer, n_l remains fixed during the refinement of a multipole model, whereas the ζ exponents can be optimized using a κ' scaling similar to the κ scaling of the spherical valence. A change in κ' implies a larger or smaller exponent of the Slater type radial density function and therefore a contracted or expanded density shell, respectively. Indeed, computing the root of the derivative of $R_l(\kappa'|\vec{r}|)$ with respect to $|\vec{r}|$ leads to a maximum value located at $|\vec{r}| = n_l/(\zeta\kappa')$. Again, the κ'^3 factor found in the last term of eq. (10.4) is required for normalization purposes. The aspherical deformation integrates over all space to zero (assuming $P_{00} = 0$) as it describes a re-organization of valence electrons whose total amount is imposed by the P_{val} value.

10.1.3 The spherical harmonic functions

The real spherical harmonics $Y_{lm}(\theta, \varphi)$ are used as density functions in eq. (10.4) to represent the angular dependencies of the valence non-spherical deformation ED. Real spherical harmonics are very important functions found in many fields of mathematics, physics and quantum chemistry. They are related to the real parts of the angular portion of the solutions to Laplace equation $\Delta f(r, \theta, \varphi) = 0$ in three dimensions. As $Y_{lm}(\theta, \varphi)$ are solely angular functions, they can be defined on the surface of a sphere of unitary radius, where they are orthogonal. In other words, they form a basis set with closure property, so that they can be linearly combined and complemented by a radial dependency to model any anisotropic three-dimensional shape. This is exactly what is achieved in the Hansen & Coppens multipole formalism. The closure property is very important because it assure that any product of two such functions is a linear combination of spherical harmonics.

Because density functions arise from orbital products, and the angular part is equally important as the radial part described above, spherical harmonics are ideal for the atomic multipolar expansion. Core and spherical valence only use one spherical harmonic (the monopole, which is the total symmetric irreducible representation of the spherical symmetry group). On the other hand, combinations of angular real spherical harmonics, modulated by Slater radial functions, are able to model the shape of atomic valence electron densities which are deformed from sphericity upon formation of interatomic bonds. Even if they depend only on angular directions, Y_{lm} functions can be plotted in various ways in three dimensions. For instance, their standard representation consists in distorting a unit sphere, by scaling each point radially by the absolute value of the Y_{lm} function, then coloring it based on its sign. Apart for $l = 0$ which corresponds to Y_{00} of purely spherical (monopolar) shape, this method of representation highlights the presence of positive and negative lobes, or “poles”, separated by angular directions for which the function is equal to zero (Fig. 10.2).

They are orthonormal multipolar functions on which is based the “multipole” modelling. For instance, when $l = 1$, the three Y_{1m} spherical harmonics are dipolar functions, characterized by one single negative and one single positive pole. The value of l_{max} found in the external sum of eq. (10.4) depends on the nature of the considered atom, as l_{max} dictates the shapes and the symmetries of the highest order of real spherical harmonics used in the modelling. For instance, hydrogen atoms, involved in a single covalent bond, are often described by a single dipolar function (hence $l_{max} = 1$) oriented along the bond. This way, the positive lobe of the single spherical harmonic (for instance Y_{11}) accounts for the accumulation of electrons shared along the covalent bond between the hydrogen atom and its neighbour.

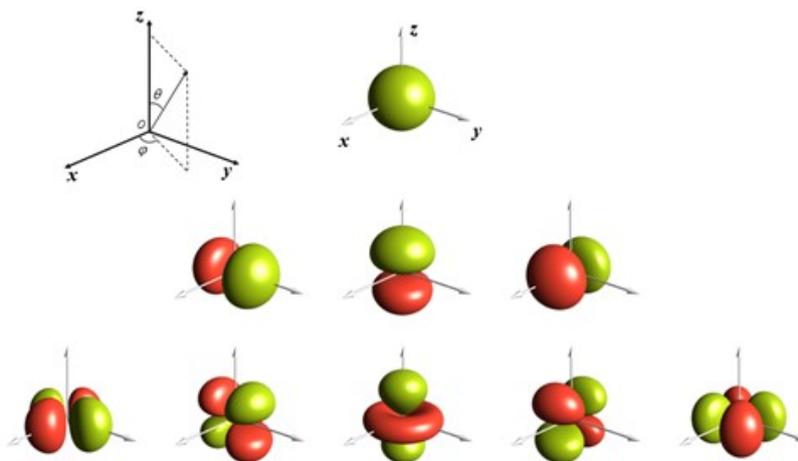


Fig. 10.2: Representations of real spherical harmonics up to the order $l_{max} = 3$ using the method given in the text. Positive poles are drawn in green, negative ones in orange. The reference Cartesian basis is represented for each multipole. The associated spherical coordinates system is represented next to the monopolar function ($l_{max} = 0$).

10.1.4 Guidelines on the multipolar atoms

As rule of thumb, one can consider that $l_{max} = 1$ (dipoles) is sufficient for hydrogen atoms, $l_{max} = 3$ (octupoles) is adequate for first-row atoms while $l_{max} = 4$ (hexadecapoles) should be used for heavier atoms. However, we have to consider which atomic orbitals form the valence shell and what is the atomic stereochemistry. H atoms only have a 1s orbital, but they form one bond and therefore feature a preferential direction of polarization of the electron density. For this reason, a dipolar function along this special direction is necessary. The flexibility of the electron density model strongly depends on the treatment of the atomic thermal motion.

For instance, using an anisotropic model for hydrogen atoms nuclei enables extending to $l_{max} = 2$ (quadrupoles). Alkyllic, tetrahedral (sp^3 hybridized) C atoms are obviously different from olefinic or aromatic (sp^2 hybridized) ones. The former requires more flexible description than the latter, and expansion to hexadecapoles is necessary. Similarly, fluorine is often modelled in the literature using a multipolar expansion up to hexadecapoles in order to better represent its three lone pairs [10]. Transition metal elements have d -type electrons in their valence and their orbital products produce hexadecapolar density functions, which are therefore essential for a proper modelling. For the same reason, f -block elements require $l_{max} = 6$.

Of course, the aspherical deformation term of the Hansen & Coppens model includes parameters that must be adjusted against experimental data in a crystallographic refinement. These parameters are the multipole populations P_{lm} and, as for the spherical valence deformation described above, the expansion/contraction parameter κ' . The multipole populations, P_{lm} , represent fractions of electrons being “moved” from the region of negative values (a pole) of the corresponding Y_{lm} function toward the region of positive values. This way, the number of valence electrons of the considered atom depends only on P_{val} , whereas the deformation from sphericity is represented by the set of P_{lm} coefficients. Hence the ED of atoms is deformed when they become involved in chemical bonds, as it is the case in molecules. The P_{00} population, associated to the Y_{00} monopolar spherical harmonic is a special case as it allows to describe, just as $\rho_{val}(\kappa|\vec{r}|)$, a spherical component of the valence ED. Often, the P_{00} valence population is fixed to zero in a multipole refinement, but is deemed necessary mostly to model the diffuse outer s -electron shell of transition metal atoms when P_{val} is used for the d -electrons.

In the crystallographic refinement based on the multipole formalism, as implemented in the *XD2016* and the *MoProSuite* programs, the minimized function S takes exactly the same form than eq. (10.1), using structure factors amplitudes (or intensities) depending now on the ED parameters described previously. More precisely, as the atomic scattering factor is the Fourier transform of the atomic ED, the multipolar parameters appear in aspherical scattering factors, Fourier transform of the aspherical electron density defined in eq. (10.4). For a given multipolar

pseudo-atom j included in the structure factor expression (eq. (10.2)), the corresponding aspherical scattering factor $f_{j,mult}$ takes the form:

$$f_{j,mult}(\vec{H}) = f_{j,core}(|\vec{H}|) + P_{val}f_{j,val}\left(\frac{|\vec{H}|}{\kappa}\right) + \sum_{l=0}^{l_{max}} \sum_{m=-l}^{+l} P_{lm}f_{lm}\left(\frac{\vec{H}}{\kappa'}\right) \quad (10.7)$$

in which $f_{j,core}(|\vec{H}|)$ and $f_{j,val}\left(\frac{|\vec{H}|}{\kappa}\right)$ are the core and valence isotropic form-factors obtained by Fourier transform of the spherical $\rho_{core}(|\vec{r}|)$ and $\rho_{val}(\kappa|\vec{r}|)$ electron densities, respectively. Similarly, $f_{lm}\left(\frac{\vec{H}}{\kappa'}\right)$ is the Fourier transform of the aspherical ED function (third term in eq. (10.4)) and depends on the direction of the scattering vector. Hence, $f_{lm}\left(\frac{\vec{H}}{\kappa'}\right)$ is the contribution of the (l,m) multipole function (radial and angular part) to the scattering factor, whose detailed expression and calculation can be found in Coppens (1997) [5]. The dependence in $|\vec{H}|/\kappa$ or $|\vec{H}|/\kappa'$ of the valence form factors reflects the fact that a scaled $\rho_{val}(\kappa|\vec{r}|)$ in direct space results in an inversely scaled scattering function in reciprocal space. This “inverse scaling” relationship between direct and reciprocal space has an important practical consequence in multipole modelling. Indeed, atomic core electron shells are necessarily more contracted, around the nucleus, than the spherical valence shells. Their scattering factors obey to an inverse relationship: core electrons scatter further in the reciprocal space than valence electrons. Consequently, data related to the valence electron distribution are located in the low or the medium resolution ranges of diffracted intensities, while information related to core electrons (and, indirectly, to atomic nuclei) are located also at high-resolution. This actually offers a practical way to partially solve the convolution problem mentioned before. Refining the structural parameters using the IAM model and against data located only in the very high-resolution range allows avoiding the bias due to the non-modelled valence deformation ED affecting the lower resolution. Such procedure is termed “high order refinement”, in reference to the larger values of Bragg angles characterizing the high-resolution ranges of diffraction data.

To summarize, beyond atomic fractional coordinates and the atomic displacement parameters, the multipole formalism implies extra parameters to model the ED of an atom. There are two κ and κ' expansion/contraction coefficients, the spherical valence populations P_{val} and $(l_{max} + 1)^2$ multipoles populations P_{lm} (including the additional spherical P_{00}). Assuming $l_{max} = 4$ (hexadecapole level) a total of 37 parameters per atom are necessary, although often P_{00} is not refined and the contraction/expansion parameters κ and κ' are cumulatively refined for atoms of the same element in similar chemical environments. This reduces the parameters to 34 per atom, 2 per atom type and one (or more) scale parameter necessary because the measured intensities are on an arbitrary scale.

10.1.5 Extensions of the multipole model.

For the sake of completeness, it must be noted that several modifications of the original multipole model [2] (Hansen and Coppens, 1978) have been tested and can be found in the literature. All these modifications of the multipole model have in common to further increase the number of atomic parameters needed to represent a given pseudo-atom, but underline its powerful inherent flexibility.

For instance, core polarization effects in, mostly inorganic, crystals of very high diffracting power have been modelled by allowing the refinement of an extra core population parameter P_{core} associated to a dedicated contraction/expansion coefficient κ_c [11]. This is achieved simply by replacing the $\rho_{core}(|\vec{r}|)$ term in eq. (10.4) by $\kappa_c^3 P_{core} \rho_{core}(\kappa_c |\vec{r}|)$, in which ρ_{core} is normalized to one electron. The refinement of κ core may also be useful when refining against theoretical structure factors which may yield high residual density around the nuclei. The κ core may correct for the mathematical discrepancy between theoretical density issued from Gaussian functions and the modelled density using Slater functions [12].

Another extension of the multipole model is the use of several κ' parameters each associated to a given level of the multipolar expansion. In other words, in this approach, κ' become a function of l and is included in the outer sum of eq. (10.4) [13]. Similarly, another noteworthy modification of the multipolar expansion radial functions consists in the duplication of the aspherical valence deformation term of eq. (10.4), in order to introduce a second ζ Slater exponent [14]. This allows performing double- ζ multipole refinements providing more flexibility to the radial dependency of the aspherical valence term than in the conventional, single- ζ , Hansen & Coppens model.

An overwhelming majority of published charge-density studies based on the multipolar formalism reported expansions limited to $l_{max} = 4$. However, studying elements with many electronic shells (like heavier elements of the main groups, transition metal atoms, lanthanides or actinides) imposes the use of modified forms of the Hansen & Coppens equation to account for deformation effects occurring in their inner electron shells. An approach which has been successfully tested in such cases consists in attributing one term akin to the full eq. (10.4) to each electron shell of the heavy element, and extending its multipole expansion up to $l_{max} = 6$ or $l_{max} = 7$ to model the ED of their highly aspherical orbitals of large principal quantum numbers [15-17]. This further increases the number of parameters of the model, which can be problematic in a least-square refinement. At first, there is a serious risk of overfitting: increasing the number of degrees of freedom may lead to model experimental noise, or chemically irrelevant features. Secondly, the least-squares method is sensitive to the “observation over parameter” ratio, which should be maintained over about 10. The inverse of the least-squares normal matrix is the variance-covariance matrix of the least-squares variables. The very last stage of a refinement should include all atomic parameters and an inversion of the full least-squares normal

matrix, to ensure a correct final convergence of the refinement and to gain access to uncertainties on the model parameters.

10.1.6 Constraints and restraints.

This step might be problematic if the number of refined parameters is too large. Fortunately, applying constraints on the structural and ED parameters of the multipolar pseudo-atoms is a way to reduce the size of the least-squares matrix. Alternatively, restraints applied can render the normal matrix definite positive. Constraints give a fixed target to a parameter or to a derived function while restraints allow for a tolerance around the target value. There are two main types of constraints/restraints on the charge density.

The first one corresponds to local symmetry. The choice of the local Cartesian axis system associated to a pseudo-atom (Fig. 10.2) can be done in such a way that it follows the local pseudo-symmetry of the considered atom's neighbourhood. In this case, only the multipole populations P_{lm} of real spherical harmonics Y_{lm} satisfying these symmetries will be freely refined. Other P_{lm} values will be constrained to a zero value or restrained to be close to zero within a standard deviation σ_r . Symmetry constraints, of course, hold also for atoms lying on special positions in the unit cell. The Y_{lm} that are not invariant under the point symmetry operations of their Wyckoff position, must be discarded and their associated P_{lm} fixed to zero.

The second category of constraints/restraints are called chemical equivalences: multipolar pseudo-atoms of the studied compound that are chemically equivalent (same nature, same covalent neighborhood, same hybridization ...) are forced to share the very same (constraint) or similar (restraint) ED parameters. Constraints results in a diminished number of refined variables while restraints increase the number of observations. Applying, until the very last stages of the multipolar refinement, such chemical and symmetry constraints/restraints on the ED have been shown to be especially relevant to reduce the risk of overfitting [18, 19].

10.1.7 Assessing the data and model quality

A multipole modelling, eventually providing a chemically meaningful and accurate experimental electron density model of a studied compound, is usually not an easy task. At first, it requires experimental data of adequate quality. As already stated, collecting X-ray diffraction data of subatomic resolution is a compulsory requirement, but might not be sufficient. The diffraction experiment must indeed be conducted at cryogenic temperature. Low temperature reduces the thermal smearing of the electron density and for this reason increases the scattered intensities. This makes ED easier to observe and model. At the same time, a stronger scattering implies better precision of the measurement. To yield a well observable deformation density the thermal displacement parameters of atoms should be lower than typically 0.015 \AA^2 . For the same reason, the presence of static disorder in the unit cell will hamper the observation of the deformation density. Anyhow, the overall diffraction data quality should be optimized by targeting close to 100% completeness, very high redundancy and strong signal over noise ratio of

the collected intensities. For crystal containing heavy elements (sulphur, chlorine, bromine, metals...), it is necessary to make proper absorption correction.

All resolution shells are equally important for a multipole modelling. As stated earlier, the low and medium resolution ranges carry information related to the scattering of valence electrons while the highest resolution ranges concern core electrons. Moreover, crystals described in highly symmetric space groups, enabling merging of many equivalent reflections are usually more favourable. Centrosymmetric space groups are preferable, if possible, to eliminate the uncertainties of the phase of structure factors.

Although the focus is here on the determination of multipolar density models against experimental diffraction data, nothing disallows to perform a multipolar refinement against theoretically computed structure factors. This approach is actually very commonly followed, as it allows comparing experimental and theoretical ED models or their derived properties based on a common formalism [20].

To conclude, let us enumerate some criteria that can be used to evaluate the quality of a multipolar refinement. Because a multipole model is somewhat an extension of the IAM typically adopted for conventional structure solution, the traditional agreement factors, such as $R(F)$ or $wR2(F)$, and the goodness-of-fit ($Gof(F)$), hold:

$$R(F) = \frac{\sum_{\vec{H}} (|F_{obs}(\vec{H})| - |F_{calc}(\vec{H})|)}{\sum_{\vec{H}} (|F_{obs}(\vec{H})|)} \quad (10.8)$$

$$wR2(F) = \sqrt{\frac{\sum_{\vec{H}} w_{\vec{H}} (|F_{obs}(\vec{H})| - |F_{calc}(\vec{H})|)^2}{\sum_{\vec{H}} w_{\vec{H}} (|F_{obs}(\vec{H})|)^2}} \quad (10.9)$$

$$Gof(F) = \sqrt{\frac{\sum_{\vec{H}} w_{\vec{H}} (|F_{obs}(\vec{H})| - |F_{calc}(\vec{H})|)^2}{n_{obs} - n_{var}}} \quad (10.10)$$

where n_{obs} is the number of experimental data and n_{var} the number of refined parameters. Alternatively, these discrepancy indices can be written using net integrated intensities (or squared structure factors amplitudes), instead of $|F_{obs}(\vec{H})|$ and $|F_{calc}(\vec{H})|$, leading to $R(I)$, $wR2(I)$ and $Gof(I)$.

Of course, a multipole model should produce a significant improvement compared with IAM and indices should be lower. However, improved R -factors is not a sufficient criterion to ensure the chemical validity of the refined ED model. This is why the model itself and the resulting deformation density must be carefully analysed during the multipolar refinement process. Notably, ED parameters must stay within realistic ranges of values. As a rule of thumb, P_{lm} populations larger, in absolute value, than about 0.5 can be considered suspect. Similarly, κ or κ' parameters are expected to stay relatively close to unity. κ values are expected to be

smaller/larger than unity for electronegative/electropositive atoms, respectively. Notably, κ' values significantly deviating from unity undoubtedly indicate a problem in the refinement, which might be due to an incorrect definition of the n_l or ζ parameters of the radial functions of the corresponding atom. The κ' parameters are actually well known to be difficult to refine in a multipole modelling. They are sometimes restrained or even fixed to values taken from the literature or from theoretical computations, especially for hydrogen atoms for which recommended κ' values are in the [1.2-1.4] range [21].

The multipolar ED model should be visually checked using for instance static deformation electron density maps $\Delta\rho_{mol}(\vec{r})$. They are simply obtained by subtracting to eq. (10.5) spherical and neutral atomic references (eq. (10.11)). This way, such maps highlight the deformation (both spherical and aspherical) of the valence ED and are said “static” as they are obtained directly from the Hansen & Coppens model without including any effects of atomic displacement parameters:

$$\Delta\rho_{mol}(\vec{r}) = \sum_{atoms} (\rho_{atom}(\vec{r}) - \rho_{ref}(\vec{r})) \quad (10.11)$$

where $\rho_{atom}(\vec{r})$ corresponds to eq. (10.4) and $\rho_{ref}(\vec{r}) = \rho_{core}(|\vec{r}|) + N_{val}\rho_{val}(|\vec{r}|)$. Examples of static deformation density maps can be seen in Fig. 10.3 and 10.4.

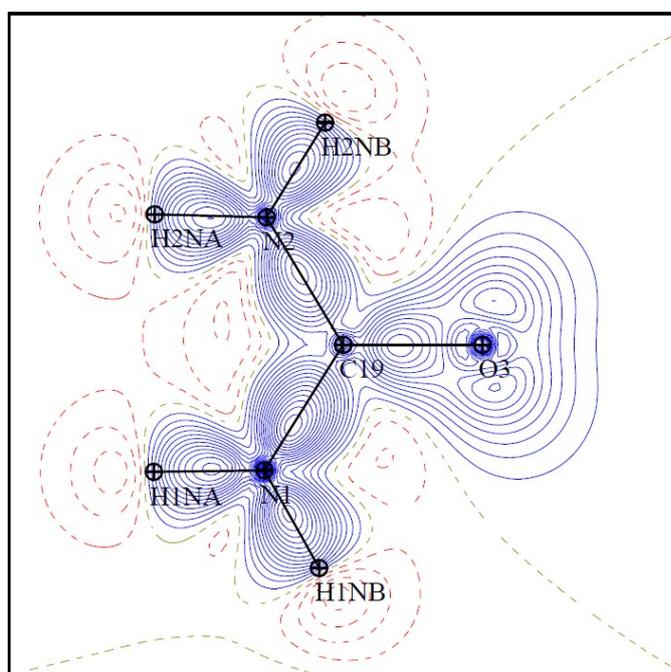


Fig. 10.3: Example of deformation electron density map in the plane of urea molecule, after charge density refinement of the estradiol/urea crystal [22]. Contours are the same as in Fig. 10.1. While the bonding density is well defined, the electron lone pairs on the oxygen atom are weaker than expected presumably due to the non-centrosymmetric space group and the relatively high thermal motion $U_{eq} > 0.02 \text{ \AA}^2$.

Finally, the non-modelled deformation electron density peaks visible after the IAM refinement should eventually vanish as they are accounted for by the multipole atom model. Hence, the final residual electron density map should be flat, apart from randomly distributed weak peaks related to experimental noise. At the end of the multipolar refinement, it is strongly recommended to use residual density analysis (RDA) tools, such as *jnk2RDA* [23]. Significant deviations from the ideal distribution of a Gaussian noise might be indicative of an error in the electron density model or of systematic errors in the diffraction data.

10.2 The MoProSuite software package

10.2.1 Overview of the programs

MoProSuite is a versatile least-squares refinement package which implements both the IAM and the Hansen & Coppens multipole models. It is compatible with the structural and the electron density refinement of crystal structures ranging from small compounds to reasonably sized macromolecules. Besides the features related to the least-squares refinement, *MoProSuite* also allows the computation and the representation of a wide range of ED-derived properties, such as the electrostatic potential and the topology of the electron density. *MoProSuite* is made of several modules we shall now describe. The core components of *MoProSuite* are the *MoPro*, *VMoPro* and *Import2MoPro* programs [24, 25].

Import2MoPro is a utility program for the conversion of common crystal structure file formats (such as CIF, INS, RES, PDB, XD, xyz ...) into the one needed by the *MoProSuite* programs. *Import2MoPro* can determine suitable atomic local axis systems (needed to orient ED deformation functions of eq. (10.4)) following the local pseudo-symmetry of the considered atoms. These optimal atomic axes are written in the *MoPro* parameter file by *Import2MoPro* and allow the definition of chemical and symmetry constraints on ED parameters.

MoPro is dedicated to the least-squares refinement. It implements the usual chemical equivalences and symmetry constraints used in multipole modelling, but also numerous restraints applying both on structural and on electron density parameters. Available restraints and constraints can be automatically generated by *MoPro* and written in dedicated text files. Therefore, they can be afterward checked or edited by the user. Restraints in *MoPro* are of two kinds: target or similarity restraints. Target restraints force parameters or functions of parameters (e.g. interatomic distances) to remain close to target values within a given tolerance. Similarity restraints impose that values of two parameters, or function of parameters, must stay similar within a user-defined tolerance. Restraints are implemented in the least-square refinement by adding terms to the minimized residual function S (eq. (10.1)), which becomes:

$$S = \sum_{\vec{H}} w_{\vec{H}} (|F_{obs}(\vec{H})| - |F_{calc}(\vec{H})|)^2 + \sum_{Nt} w_t (f - f_{target})^2 + \sum_{Ns} w_s (g - h)^2 \quad (10.12)$$

where Nt and Ns are the number of target and similarity restraints of a given type. h and g are parameters or functions of parameters whose values must remain similar. f_{target} is the target value of the restrained function f . w_t and w_s are the weights associated to the target and similarity restraints, respectively. A strong weight will reduce the tolerance of deviations between restrained parameters. The restraints implemented in *MoPro* increase significantly its versatility, making it compatible with the refinement of protein or nuclei acids structures at atomic or subatomic resolution. In this optic, *MoPro* also implements the conjugate-gradient minimization approach which allows when the number of parameters is large to avoid the costly matrix inversion needed in standard least-squares routines.

MoPro is interfaced with the ELMAM2 electron density database [26-28]. This library contains transferable multipolar pseudoatoms describing many common organic chemical groups. These pseudoatoms have been obtained by averaging multipolar parameters issued from numerous accurate subatomic resolution charge density analyses of small compounds (amino acids, various organic molecules...). Parameters were averaged per “atom types”, i.e. per atoms presenting similar covalent neighborhood, and can be transferred to any molecular structure containing compatible atom types. This approach, rooted in the so-called “transferability principle”, allows fast reconstructions of multipolar ED models of large biological molecules. The resulting transferred model can be exploited directly to compute ED derived properties [29] or be used as a starting model for a constrained multipolar refinement, assuming diffraction data of sufficiently high resolution is available [30, 31].

In addition, *MoPro* proposes a model combining real and additional virtual spherical atoms as an alternative to the multipole modelling [12, 32]. In this approach, the charge density can be refined using a model based on real spherical atoms and additional dummy charges on the covalent bonds and on electron lone-pair sites. Compared to multipoles, this spherical charge modelling needs fewer parameters to describe the deformation electron density (Fig. 10.4). For each atom, only the valence population P_{val} and the contraction/expansion κ coefficients are refined. Most of the deformation density is modelled and molecular electrostatic properties are very close to those modelled with the multipole model. A database of transferable spherical “*real+virtual*” atoms issued from theoretical calculations is also available to model structures at lower resolution and bio-macromolecules.

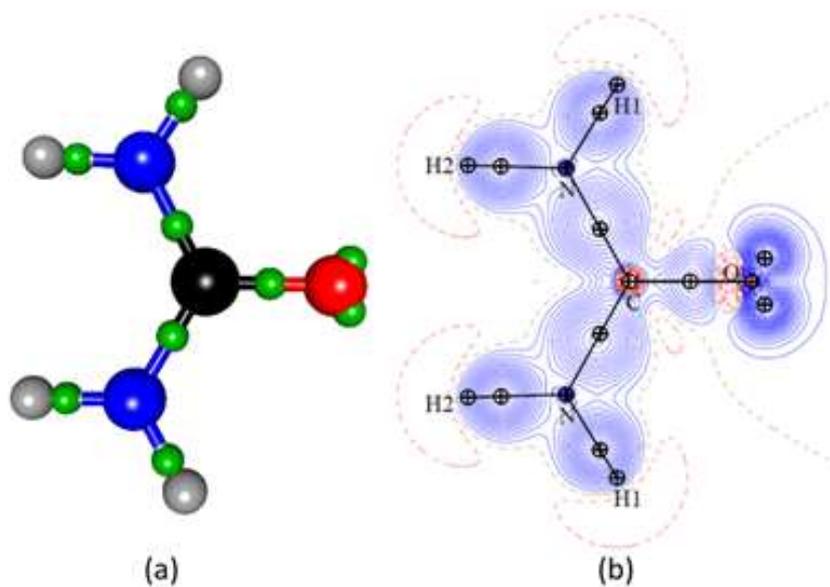


Fig. 10.4: (a) urea molecule with virtual atoms (in green) located on the covalent bonds and on the electron lone pairs sites of the oxygen atom. (b) deformation valence electron density map in the plane of urea modelled using transferred “*real+virtual*” atoms.

VMoPro is the *MoProSuite* component dedicated to the computation of ED derived properties. It gives access to static electron densities or electrostatic potentials using any contribution of the multipolar charge density (nuclei, core, spherical or deformation valence etc...). It allows also the computation of Fourier maps, including dynamical electron densities. Any of these properties can be represented with *VMoPro* in the form of 2D contour plots (in postscript format) or exported as 3D regular grids (e.g. in the Gaussian CUBE format). Topological analyses of 3D scalar fields, within the QTAIM framework (see part II, chapter 1) can be performed with *VMoPro*, using the electrostatic potential, the total ED or its Laplacian (which can also be obtained independently in the form of 2D or 3D maps). Atomic charges can be computed by integrating the charge density over the Bader atomic basins [33]. *VMoPro* also implements the computation of electrostatic interaction energies using the EP/MM approach [34].

10.2.2 The Graphical User Interfaces *MoProGUI* and *MoProViewer*

MoPro runs using a user-created input commands file containing keyword base instructions (e.g. “*mopro.inp*”) containing keywords-based instructions. A complete description of all available keywords and options can be found in the *MoPro* documentation. By contrast, *VMoPro* and *IMoPro* are interactive programs. They can be used either by prompting instructions directly in the console or giving scripted input files using standard input redirection. Even if convenient in a console-based environment, for instance to execute the programs in batches, that

kind of usage can be advantageously replaced by the use of the graphical user interfaces *MoProGUI* and *MoProViewer*.

MoProGUI is the graphical user interface of *MoPro*. It allows the user to easily configure and execute a multipolar refinement, and to follow its outcomes, without using the keyword-based approach needed to execute *MoPro* in command-line mode. Unlike with the IAM model, the multipolar refinement implies the notion of “refinement strategy”. Indeed, the multipole model is based on parameters of different types, either global (e.g. the scale factor), related to the structure (e.g. fractional atomic coordinates) or to the spherical and aspherical deformation electron density (P_{val} , P_{lm} , κ and κ'). Moreover, these parameters present various degrees of correlations between them (e.g. between P_{val} and κ , or between P_{lm} and thermal displacement parameters), can be subject of various kind of constraints or restraints and may depend on different resolution ranges of the available diffraction data. Altogether, it means that a multipolar refinement is usually not straightforward, and often implies trial and errors before obtaining an adequate strategy leading to a chemically meaningful electron density model.

MoProGUI has been specifically designed to ease the elaboration of multipolar refinement strategies. It appears obvious that the various functionalities of a multipolar refinement program can be sorted in categories: options related to experimental data (e.g. resolution limits, $I/\sigma(I)$ cut-off...), to the restraints or the constraints, to the refinement (refined parameters, number of refinement cycles ...), to data exportation, and so on. This is exploited in *MoProGUI*, in which the user can graphically build a refinement strategy by combining groups of instructions, named “blocks” in the *MoProSuite* jargon. The refinement strategy in *MoProGUI* appears then as a list of successive blocks, which will be executed sequentially by *MoPro*. As said earlier, each block gathers categories of instructions. The first block of any *MoProGUI* strategy list is always a “Files” block. The “Files” block allows indeed to specify the (initial) atomic parameter file, the experimental diffraction data file and the constraints / restraints files. In this first “Files” block is also given the location of the library tables, provided with the *MoProSuite* package, containing default n_l and ζ coefficients of the atomic radial functions and the parameters of the orbital functions needed for ρ_{val} and ρ_{core} spherical ED (eq. 10.4).

One of the most important instruction block in *MoProGUI* is obviously the “Refinement” block. It is where the user can graphically select (i) a type of parameters to refine, (ii) atoms which will be included in the refinement using inclusion / exclusion logic and (iii) a refinement method and its corresponding options. For instance, a user can, with few mouse clicks, configure a refinement block corresponding to “*the refinement of thermal displacement parameters and fractional coordinates of every non-hydrogen atoms using 10 cycles of least-squares matrix inversion method and a damping of parameter shifts of 0.5*”. The choice of the data resolution

limits used in a given refinement stage is made using a “Resolution” block, whose inclusion in the refinement strategy will affect resolution limits until the next “Resolution” block.

Another example of block, as group of instructions, that can be included in a *MoProGUI* strategy list is the “Preparation” block. This block is intended to automatically prepare various kind of restraints or constraints (either structural or related to the electron density). Once executed, this block in *MoProGUI* will prompt *MoPro* to create restraints and constraints files, which can be used in subsequent refinement steps. Hence it has to be executed only once, at early stages of the refinement. Finally, “Output” blocks can be used at any position in the strategy list. Using “Output” blocks, the user can ask, for instance, for the creation of intermediary molecular parameter files, CIF files or files containing $|F_{obs}(\vec{H})|$, $|F_{calc}(\vec{H})|$ and associated phases (computed using the current model parameters) needed for Fourier maps. Instruction blocks can be configured in a very flexible way in the *MoProGUI* interface. Any block can be drag and dropped within the refinement strategy, commented / activated or even included in loops in which groups of blocks will be executed several times, for instance up to convergence of the refinement of a given set of parameters. They can also be renamed and saved for future use, which is especially convenient for “Refinement” blocks. A user can this way create a refinement strategy using his own set of custom preconfigured “Refinement” blocks.

A last peculiarity of the *MoPro* / *MoProGUI* philosophy is the versioning of molecular parameter files. In *MoPro*, a parameter file contains basically the crystallographic data (e.g. cell parameters and symmetry operations), the global parameters (scale factor, extinction coefficient ...), the list of atoms in the asymmetric unit with their parameters and their local atomic axis systems. The name of a *MoPro* parameter file contains a version number (e.g. “*my-compound.par01*”), which will be incremented at each execution of *MoPro*. At the cost of a larger number of files ending up in the user working directory, this versioning system allows to keep track of what has been done along the refinement and, of course, to restart the refinement from any stage using the adequate parameter file version.

Once *MoPro* is executed through *MoProGUI*, an “Output panel” appears in the *MoProGUI* interface. It displays data allowing the user to follow the progression and the outcome of the refinement strategy configured in the Input panel. Notably, the full “*mopro.out*” file is displayed and updated in real time during the progress of the refinement along with plots showing the evolution of user selected crystallographic agreement factors.

MoProViewer is the graphical user interface for *VMoPro*, and a molecule / crystal structure viewer especially designed for the charge density field [35]. It features specific functionalities related to the multipole modeling such as the representation of atomic local axes systems or chemical equivalences constraints using color-coded symbols. One of important features of *MoProViewer*, among many others, is its capability to allow the user to configure directly, from

the representation of the molecule, the computation with *VMoPro* of ED-derived properties. For instance, any 2D plot (or 3D relief maps) can be obtained with a few mouse clicks on atoms to define a plane, then *MoProViewer* runs silently *VMoPro*, retrieves its results and represent them in a dedicated contour maps viewer. 3D properties can be computed in a similar way, and can be represented in *MoProViewer* using 3D iso-surfaces, possibly colour-mapped by any other 3D property. Similarly, the search for ED critical points with *VMoPro* can be configured from *MoProViewer*, and the resulting bond critical points can be displayed with their associated bond paths. Fig. 10.6 illustrate some of the representations of ED-derived properties available in *MoProViewer*.

The software has some links to other programs developed by other authors:

- The fractal analysis of Meindl and Henn (2008) [23] can be performed on residual ($F_{\text{obs}} - F_{\text{calc}}$) maps of XPLOR or Gaussian CUBE format computed by fast Fourier transform.
- The analysis of diffraction data quality with program DRK [36] can be performed on the output reflections file using FCFW option, which replaces $\sigma(I_{\text{hkl}})$ in order to have a unitary goodness of fit ($\text{gof}=1$).
- The SHADE or SHADE3 servers [37, 38] prepare the values of modelled anisotropic thermal parameters of hydrogen atoms to be inserted in the *MoPro* constraints file (FIXUIJ).

10.2.3 A practical example : charge density refinement of estradiol/urea with *MoProSuite*.

The practical use of the *MoProSuite* is here briefly described, based on the Estradiol-Urea complex (Fig. 10.5) published by Parrish *et al.* in 2006 [22].

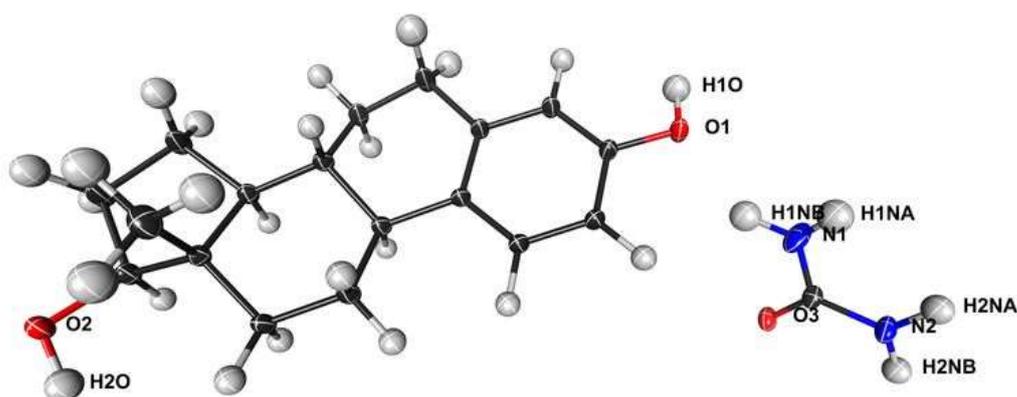


Fig. 10.5: *MoProViewer* view of the thermal ellipsoids (50% probability presence) of the estradiol/urea crystal structure.

A tutorial based on this molecule is actually included in the *MoProSuite* package. Diffraction data “*estradiol.lhkl*” and “*estradiol.cif*” files can be found in the “*Tutorial_estradiol*” examples folder of the *MoProSuite* installation directory. Upon importation of the CIF file, the program will set automatically the atomic axes systems to orient the multipoles, based on the neighbors.

The first refinement step is the adjustment of scale factor. In the next step, the constraints and restraints need to be prepared by the program. Indeed, the stereochemical restraints (or constraints) are necessary for proper treatment of hydrogen atoms. In this case, the following ones can be selected:

- X-H bond distances adjusted to standard values from neutron diffraction.
- X-H bond distances similarities ($d(\text{A-H1}) \sim d(\text{A-H2}) \pm \sigma_d$).
- U^{iso} thermal parameters of hydrogen riding on that of bonded atom (multiplied by 1.2 or 1.5).
- Equivalent atoms have same/similar charge density parameters κ , κ^2 , P_{val} , P_{lm}
 Multipoles of some atom obey a local symmetry (mirror, inversion centre ...).

The second refinement step applies on the structural parameters (XYZ & U^{ij}). After structural refinement, the “experimental deformation density”, or residual ED, can be observed by computing a Fourier residual map (Fig. 10.1). The signal can be enhanced by applying a “high order refinement”, i.e. refining XYZ and U^{ij} of non-H atoms against high resolution reflections only (typically $\sin(\theta)/\lambda > 0.7 \text{ \AA}^{-1}$).

When the Fourier map shows distinct bonding density and electron lone pairs with limited noise, the charge density can then be refined favorably. Several procedures are possible. Charge density parameters may be introduced progressively in the refinement, starting with multipoles P_{lm} 's. *MoPro* "refinement" menu allows to do customized refinement where parameters refined are chosen by the user. "automatic refinement" menu proposes automated procedures where all the parameters can be refined iteratively or together. A fully automatic procedure is also available and will most likely work for a structure with good diffraction data and no complications (disorder, anharmonic thermal motion, special positions...). A significant *R*-factor drop is expected upon multipolar refinement.

The refinement can be carried out till convergence. Ideally all parameters should be refined together in the last stages.

10.2.4 Properties derived from the charge density

This paragraph highlights some of the most important properties and results which can be computed from a successful charge density refinement.

Electrostatic potential.

The electrostatic potential $V(\vec{r})$ (ESP) can be obtained by integration over space of the total charge density $\rho_{tot}(\vec{r}')$ (i.e. including atom nuclei) divided by the distance:

$$V(\vec{r}) = \int \frac{\rho_{tot}(\vec{r}')}{|\vec{r}' - \vec{r}|} d^3r' \quad (10.13)$$

The Hansen & Coppens modeling of the electron density enables to compute the ESP generated by a molecule which is far more accurate than that derived from point atom charges placed at the nuclei. Electrostatic potential provides more information than the electron density on the chemical reactivity and the intermolecular interactions. Several types of representations can be selected (Fig. 10.6). For instance, the C=O electronegative group of urea forms bifurcated hydrogen bonds with the NH₂ group of a neighbor urea molecule (Fig. 10.6c); in the molecular dimer, electropositive and electronegative regions are in interaction.

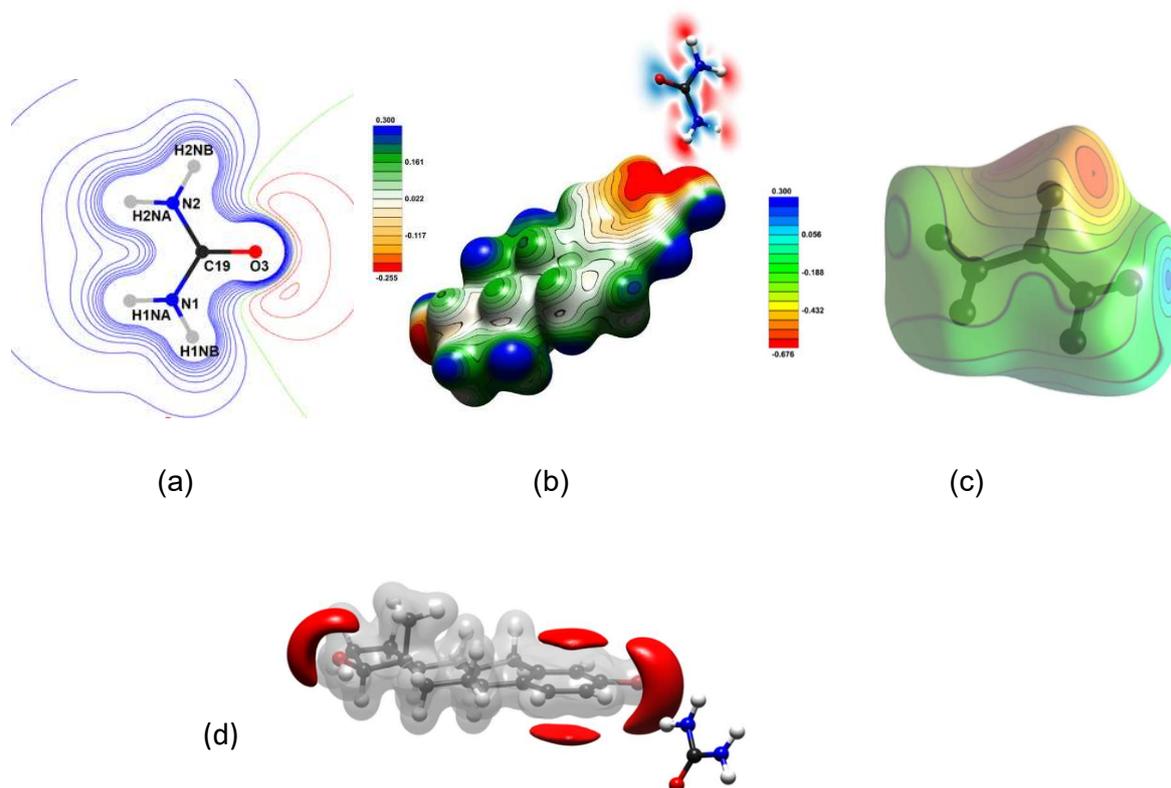


Fig. 10.6: Representations of the molecular ESP using *MoProViewer*.

- (a) Generated and shown in the urea plane. Contours: $\pm 0.05 \text{ e}/\text{\AA}$, positive in blue, negative in red, zero line in green
- (b) A qualitative semi-transparent contour map of static deformation ED is shown in the urea plane. The estradiol molecule is surrounded by a $0.1 \text{ e}/\text{\AA}^3$ total ED isosurface coloured by its ESP, with the colour legend ranging from -0.25 to $0.3 \text{ e}/\text{\AA}$.
- (c) Hirshfeld surface around the urea molecule. The surface is colored according to ESP values (range -0.6 to $0.3 \text{ e}/\text{\AA}$).
- (d) ESP Isosurfaces of the estradiol molecule. Positive contour in grey: $+0.2 \text{ e}/\text{\AA}$. Negative contour in red: $-0.092 \text{ e}/\text{\AA}$.

The estradiol molecule shows two electronegative lobes at $-0.15 \text{ e}/\text{\AA}$ around the two C-O-H groups. Less electronegative regions at $V = -0.09 \text{ e}/\text{\AA}$ appear on both sides of the aromatic C6 cycle due to π electrons (Fig. 10.6d). The urea molecule generates an electronegative potential around the C=O oxygen atom (Fig. 10.6a,c).

Laplacian.

The Laplacian of the total electron density shown in Fig. 10.7 is an alternative way to highlight electron charge local concentrations and depletions. Regions with negative Laplacian correspond to local negative charge concentration. The lone pairs of the C=O oxygen atom of urea appear as two peaks in the Laplacian map.

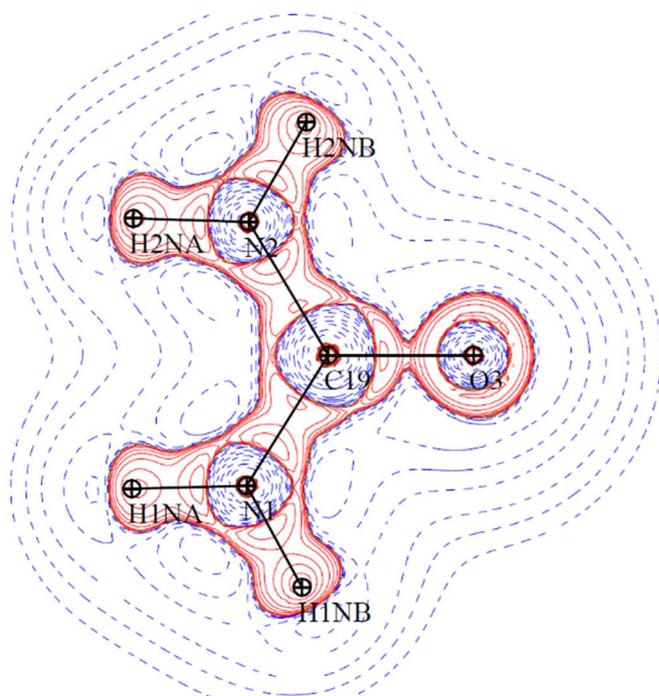


Fig. 10.7: Laplacian of the total electron density ($e/\text{\AA}^5$). $L(\rho) = \partial^2\rho/\partial x^2 + \partial^2\rho/\partial y^2 + \partial^2\rho/\partial z^2$. Contours are quasi-logarithmic $\pm 2, 4, 8 \times 10^n$ with $n = -1, 0, 1, 2$. Positive: blue discontinuous line, Negative: red lines.

Critical points.

The critical points (CPs) are the region of space where the gradient of a property, here the total electron density ρ , is zero. Minima and maxima correspond to (3,+3) and (3,-3) CPs, respectively, where the Hessian matrix $\partial^2\rho/\partial x_i x_j$ has 3 positive/negative eigenvalues. Figure 10.8a shows the saddle CPs: the cycle (3,+1) CPs and the bond (3,-1) CPs within the asymmetric unit. After searching with *MoPro* all symmetry neighbors involved in hydrogen bonds around the estradiol molecule, the (3,-1) CPs were searched with *VMoPro* and are displayed in Fig. 10.8b.

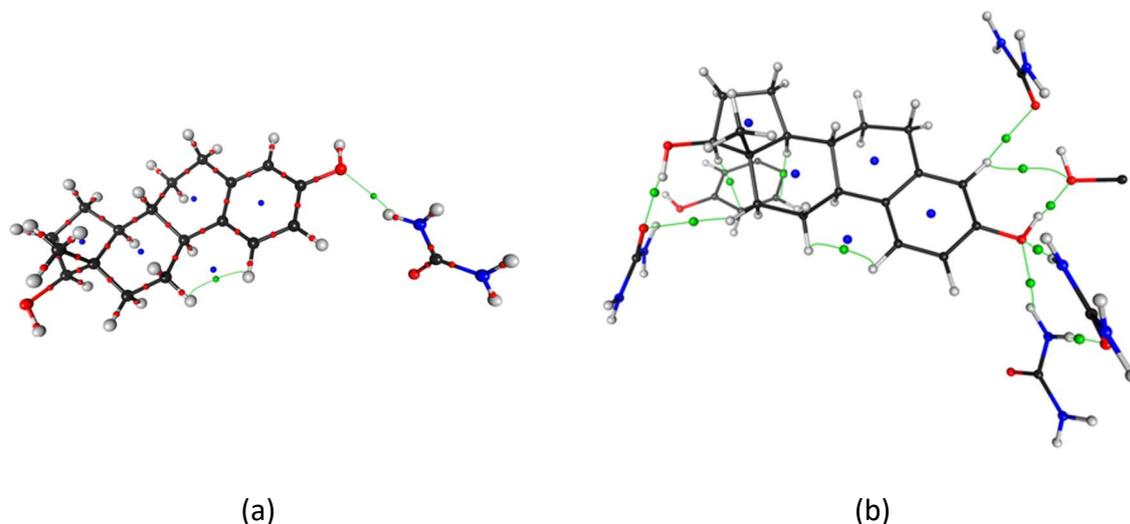


Fig. 10.8: Critical Points. (a) CPs within the asymmetric unit: bond CPs (in red), cycle CPs (in blue). For the H-bond and H...H interaction CPs (in green) the bond path is shown. (b) View of the intermolecular hydrogen bonds around estradiol molecule. The (3,-1) CPs and bond paths are shown in green.

Tab. 10.1: Topological properties at the critical points of the hydrogen bonds. G_{cp} and V_{cp} are the kinetic and potential energy densities at the CP ($\text{kJ}\cdot\text{mol}^{-1}\cdot\text{Bohr}^{-3}$). The electron density and Laplacian values are also given.

Atom 1	Atom 2	Symmetry ^a	G_{cp}	V_{cp}	Distance (Å)	Density ($e/\text{Å}^3$)	Laplacian ($e/\text{Å}^5$)
H2O	O3	43504	120.0	-104.2	1.682	0.2424	4.98
H1O	O2	34402	116.8	-99.3	1.704	0.2315	4.93
O3	H1NA	54403	81.5	-71.5	1.824	0.1950	3.36
O1	H2NB	55403	48.1	-38.1	2.022	0.1217	2.13
H2NA	O2	44402	35.6	-26.1	2.120	0.0890	1.66
H4	O3	45403	15.9	-10.9	2.494	0.0472	0.77
H12B	O3	43504	12.7	-8.6	2.666	0.0409	0.61
H4	O2	34402	14.3	-10.2	2.673	0.0490	0.67
H17	C2	43504	10.1	-7.5	2.789	0.0432	0.46
H14	C1	43504	10.1	-7.3	2.820	0.0407	0.48

^a : Symmetry codes

34402 : $-X^{-3/2}$; $-Y^{-1}$; $Z^{-1/2}$; 43504 : $X^{-1/2}$; $-Y^{-3/2}$; $-Z$

44402 : $-X^{-1/2}$; $-Y^{-1}$; $Z^{-1/2}$; 45403 : $-X^{-1}$; $Y^{+1/2}$; $-Z^{-1/2}$

54403 : $-X$; $Y^{-1/2}$; $-Z^{-1/2}$; 55403 : $-X$; $Y^{+1/2}$; $-Z^{-1/2}$

After search of the critical points, the properties of the CPs are summarized in GcpVcp.dat file, which can be found in the *MoPro* working directory. In addition to the electron density ρ_{cp} , the Laplacian $\nabla^2\rho_{cp}$ and the ellipticity, the kinetic and potential energy density values are also retrieved (Tab. 10.1).

Electrostatic energy.

To understand the electrostatic forces within crystals, the energy can be computed between neighboring molecules using *VMoPro*, with or without the help of its graphical interface *MoProViewer*. In the case of the estradiol-urea complex given here as example, the electrostatic energy is the strongest for a urea...urea dimer interacting via a N-H...O=C hydrogen bond (Fig. 10.8b, at the right bottom). In *MoProSuite*, the contribution of the electrostatic part to the lattice energy may be approximated by computing the E_{elec} value between a reference molecule and a surrounding shell of sufficiently large size.

10.3 The XD2016 software package

10.3.1 Overview of the package

Like *MoPro*, *XD2016* [39] is also based on the Hansen and Coppens multipolar formalism [2], while being compatible also with the Stewart formalism [3] as well as with some of the model extensions mentioned in 10.1.5, like the double- ζ valence radial function [14] or the core refinement [11]. As mentioned in section 10.1.4, a reasonable starting point for a multipolar refinement is the structural model obtained with an IAM refinement. For molecular crystals, the gold standard software are SHELX [40] or Olex2 [41], both well tested, reliable and world-wide adopted for many years (in particular SHELX). They both export the output of a refined structure as a crystallographic information file (CIF) or a res file. XD2016 can use both kinds of files to import the basic structural and experimental data, namely:

- Unit cell parameters;
- Atom types, setting the corresponding atomic form factors;
- Atomic fractional coordinates within the asymmetric unit;
- Atomic displacement parameters (isotropic or anisotropic, within the harmonic approximation);
- Wavelength of the radiation used for the X-ray diffraction experiment;
- Scale factor;
- Weighting schemes adopted in the refinement (see equations 10.9 and 10.10)

An additional file (extension hkl) contains all the measured structure factors, with their associated uncertainties and potentially the subset number, in case the data have not been previously merged and each reflection is present in several measurement taken in different runs of a data collection. The hkl file may contain also information on the path length of each reflection in the

crystal, which could be important for an accurate (anisotropic) correction for secondary extinction.

With these data, the appropriate xd files are generated:

- A master file (xd.mas) with all fixed parameters (e.g. unit cell, wavelength, atom type) and all instructions to run the different routines of the program package.
- An input file (xd.inp) containing all the parameters that are potentially variables of the multipole model (atomic coordinates, atomic displacement, multipole population parameters, scale factors, extinction coefficients).
- The reflection file (xd.hkl), containing the same information as the one used by SHELX or Olex, but potentially including also all direction cosines of each reflection in case an extinction correction is applied, for example with the model by Becker and Coppens [42].

A graphical user interface, WinXD, can read all these files and enable their manipulation, in particular:

- Setting the model for the refinement (IAM model, Multipole Model, IAM or Multipole Model with anharmonic atomic displacement parameters). The anharmonic treatment of the atomic displacement parameters follows the classical treatment summarised by Johnson and Levy [43]. This is an expansion of the harmonic approximation, that requires up to 25 additional parameters per atom and therefore cannot be applied to all atoms in a structure, but only those for which it is really necessary.
- Setting the database for the atomic density functions for the core, spherical valence and deformation valence, as explained in section 10.1. This means selecting among:
 - o the classical Roothaan Hartee-Fock atomic wavefunctions of Clementi and Roetti [6] for core and spherical valence and the single- ζ Slater functions from Clementi and Raimondi [9] for the aspherical density;
 - o the relativistic wavefunctions from Su and Coppens [7] and Macchi and Coppens [8] for the core and spherical valence and the single- ζ Slater functions from Clementi and Raimondi [9] for the aspherical density;
 - o the zero-order regular approximation atomic wavefunctions [39] for the core and spherical valence (available for all atoms) and the best single- ζ Slater functions approximating them for the aspherical valence;
 - o a free database of atomic wavefunctions, compiled by the user with the standard XD2016 format.
- Defining which parameter is a variable of the model and which constraint is applied. By default, an electro-neutrality constraint is activated to guarantee that the total number of electrons in the unit cell remains constant. Additional constraints may involve the κ or κ' parameters. In principle, any atom may hold its own set of contraction/expansion parameters, but more conveniently atoms of the same type in a similar chemical environment are grouped to reduce the model instability and the number of parameters. Moreover, different

κ' may be defined for each multipole level (meaning one for the dipoles, one for the quadrupoles, etc.) but a simple instruction enables defining a single κ' for all the multipole levels of an atom type, which is the standard.

Moreover, the graphical interface enables running all modules of the program, namely:

- The file initialization module XDINI: it reads the structural files from SHELX, Olex2 or a crystallographic information file, and creates the XD2016 files.
- The structure factor handling routine XDHKL: it merges the data and calculates intensity statistics.
- The least square refinement module XDLSM: it launches the refinement of a model following the specifications.
- The Fast Fourier Transformation module XDFFT: it calculates a 3D residual density map and automatically locates the largest residuals (positive or negative).
- The Fourier Transformation module XDFOUR: it calculates a 2D or a 3D residual density map, as well as a deformation density using the difference between the measured structure factors and the IAM calculated structure factors, or a model deformation density, using the difference between the multipole model calculated structure factors and the IAM calculated structure factors.
- The module for the calculation of the properties based on the refined model XDPROP: it enables running topological analysis of the total electron density or electrostatic potential; computing all electrostatic moments; computing maps of all electron density derived functions (density, gradient, Laplacian, electrostatic potential, electrostatic field, electrostatic field gradient, one electron potential, reduced density gradient, density overlap indicator, single exponential detector, kinetic and potential energy densities, electron localization function, and localized orbital locator).
- The module for a comprehensive topological analysis in a crystal TOPXD: it calculates all density properties in a periodic 3D framework, whereas XDPROP calculates properties of an isolated fragment of the crystal (e.g. a molecule, a dimer, a small cluster, etc.).
- The module for graphical representation of the calculated functions, XDGRAPH.
- The module XDPDF: it calculates the nuclear probability density based on the refined harmonic or anharmonic atomic displacement parameters.
- The module XDVIB: it calculates atomic displacement parameters from theoretically calculated molecular vibrational frequencies, to set in the model calculated values which do not need further refinement (e.g. for H atoms).
- The module XDWTAN: it analyses the correctness of the adopted weighting scheme.

The graphical interface is also linked to other routines developed externally by other authors but tightly connected to the multipole refinement:

- The routine to calculate residual plots (PIXels stats), following the analysis by Meindl and Henn [23]. This routine is directly inserted in WinXD.
- The routine to analyse the residual of intensities (DRK), following the work by Zhurov *et al.* [36]. This routine is directly inserted in WinXD.
- The routine to calculate anisotropic displacement parameters for H atoms, using a rigid body approximation and the parameters of heavier elements in the molecule, following the procedure SHADE introduced by Madsen (2006) and Madsen and Hoser [37, 38]. This routine is linked externally, using the website of the program which provides the calculation. The graphical interface exports the proper files for SHADE or SHADE3 and import the results in XD2016 to continue a refinement.
- The software MoleCoolQt [44] is linked externally. This software enables additional graphical representations of calculated functions, as well as setting proper input files for special multipolar refinements with theoretically calculated multipolar coefficients.

Other small routines enable manipulation of XD2016 files, such as operations with functions computed on a grid, update of model from previous refinement strategies, writing tables and crystallographic information files, and creating graphical files in special formats, such as the Persistence of Vision Raytracer. Moreover, all functions can be written in a standard cube file that can be visualized using many software packages available for theoretical chemistry.

In Figure 10.9, a scheme of the working procedure of XD2016 is graphically summarized.

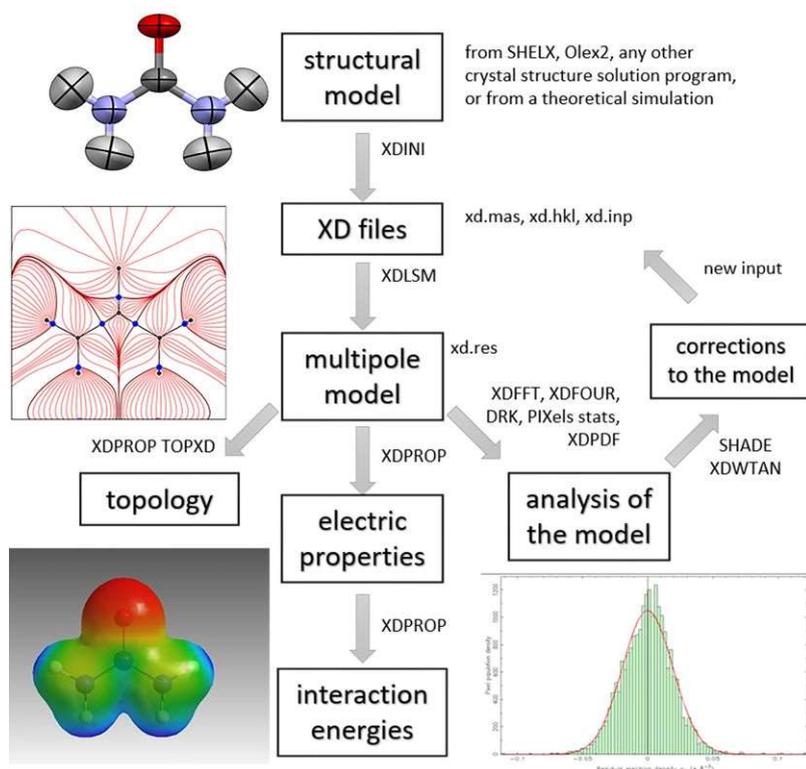


Fig. 10.9: The flowchart of XD2016 modelling and bonding analysis.

As introduced above, some special multipole refinement may be carried out against synthetic structure factors, calculated by *ab initio* crystal wavefunctions, or even molecular wavefunctions (embedding the molecule in a virtual unit cell). For these kinds of refinement, the number of variable parameters is much smaller, because the structure factors are typically static (i.e. they are not convoluted with the nuclear motion), the atomic coordinates are known and the anomalous scattering of atoms is also neglected in the simulation. This is easily set in the master file of XD2016, which has been in fact often used to produce these models refined against theoretical dataset (see for example ref. [14]). A special feature in this case is the so-called *phase constrained refinement*, where the phase of each reflection (that are of course known when coming from a simulated dataset) are kept rigidly fixed during the refinement, avoiding potential artefacts for non-centrosymmetric lattices. This may be important when refining a multipole model of a simulated molecular density, calculated with molecular orbital wavefunction and embedded in a unit cell without symmetry (typically with cubic metrics, but simply P1 space group). To run this refinement, it is necessary that the hkl reflection file also contains the calculated phase of the reflection.

For the scope of this textbook, the module XDPROP is very important. As mentioned, it calculates the electron density and electric properties of a molecule from the refined multipole

model, the interaction energies between two (or more) molecules in the crystal, and the lattice energies.

In **chapter 3**, the Quantum Theory of Atoms in Molecules (QTAIM; [33]) has been introduced. QTAIM is based mainly on the partition of the one-electron density distribution, which is the quantity that a multipole model is reconstructing. Therefore, a QTAIM chemical bonding analysis can be carried out using a multipole model of the electron density as well as a calculated wavefunction. In fact, the definition of an atomic basin only requires the gradient of the electron density, and many properties at the stationary points of the electron density (the so-called critical points) depend on derivatives of the electron density (for example the Laplacian).

This perfect correspondence between the wavefunction (theoretical) model and the multipolar (experimental or theoretical) model does not hold true for energy densities, however, because their calculation would require the wavefunction, which is not available from a multipole model (see also discussion in 10.1 concerning the orbital vs multipolar functions). Only approximated quantities of energy densities can be calculated, using some known approximations for the kinetic energy density like the one proposed by Kirzhnits [45]. For this reason, the analysis in terms of electron localization (see Chapter 4) is much less feasible and certainly less accurate because, apart from the experimental error and the approximation of the multipole model, there is an additional approximation to apply for the calculation of the kinetic energy density and all correlated quantities. Therefore, the error propagation may be huge.

Even more complicated would be to retrieve from experiment a two-electron (or pair) density, which again requires the knowledge of the wavefunction or of the second-order reduced density matrix” (which is the density matrix corresponding to the pair density).

10.4 Concluding remarks and outlook

The multipolar expansion of atomic electron density has a long historical tradition, nevertheless it remains a very useful and reliable method to model the electron density distribution from X-ray diffraction experiments. The major pitfalls concern the data quality and therefore the reliability of the experiments. Nonetheless, being an approximation, there are inherent limitations that may produce severe artefacts. The strength of the multipolar formalism stands in the ease of the interpretation of the resulting model, which maintains an atomistic perspective like the standard structural models for crystallography while being significantly more informative. When the diffraction data quality is not good enough for fitting the ED, the calculation of the model by ED database transfer is nowadays quite feasible and rarely a problem. Such a model is adequate to obtain an accurate structural model of very large molecular systems (up to proteins) for which in fact the measured data may be of poor quality.

As discussed in this chapter, the model has also undergone sophistications that enable extracting even more detailed information (for example, on the polarization of core electrons) that were not forecastable a few years ago. At the same time, approximated theories enable linking

the multipole model also with functions that in principle cannot be directly obtained without a wavefunction, as for example energy densities.

It is worth emphasizing that the multipole model is not just better than IAM in modelling the ED. In fact, the additional degrees of freedom in the fit remain chemically sensible because they can be associated with an atomic polarization due to a partial re-hybridization or a change of electronic state. In this respect, the multipolar model mimics the linear combination of atomic orbitals, the most popular approximation to solve the Schrodinger equation for a molecule.

This constant improvement and modification enable us to expect even more astonishing results in the future, when perhaps very high-resolution diffraction data may become more easily available and of sufficient quality also for organic (small or large) molecules, not only for inorganic systems. Moreover, integration of multipole-based formalism in standard packages for structure refinement, may encourage even more studies to support and extend the routine structural studies, given that the average quality of standard X-ray diffraction equipment available in university laboratories has increased tremendously in the last decade. Based on that we may conclude that the multipole model will live long and, as all living beings, will continue to transform and evolve.

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