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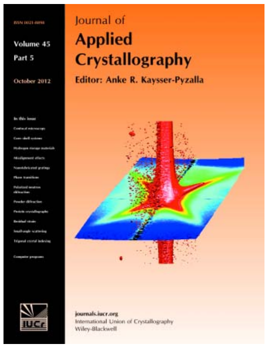

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CRYSTALS enhancements: asymmetric restraints

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The traditional Waser distance restraint, the rigid-bond restraint and atomic displacement parameter (ADP) similarity restraints have an equal influence on both atoms involved in the restraint. This may be inappropriate in cases where it can reasonably be expected that the precision of the determination of the positional parameters and ADPs is not equal, *e.g.* towards the extremities of a librating structure or where one atom is a significantly stronger scatterer than the other. In these cases, the traditional restraint feeds information from the poorly defined atom to the better defined atom, with the possibility that its characteristics become degraded. The modified restraint described here feeds information from the better defined atom to the more poorly defined atom with minimal feedback.

1. Introduction

Under favourable conditions, X-ray diffraction data span the observational space sufficiently completely, and are of sufficient accuracy (and precision), that simply adjusting the model parameters to reduce the squared discrepancy between the observed and calculated structure factors (F_o and F_c) or their squares will lead to parameter values that reliably represent the 'true' structure. This parameter optimization is usually achieved by the method of iterative nonlinear least squares. The least-squares method is iterative because the relationship between the atomic parameters [positional parameters and atomic displacement parameters (ADPs)] and the structure factors is nonlinear, so that in each cycle successive improvements to the parameters are computed. If a 'reasonably' well parameterized initial model can be proposed, the least-squares process will refine this model.

It was recognized half a century ago that, as well as yielding structure amplitudes in agreement with the observations, the final model should also conform to established geometric norms (Waser, 1963), that is, amongst other things, it must have reasonable bond lengths and angles. Waser argued that, since these established values can be assigned as soon as the atomic connectivity has been determined, they can be used as targets to be achieved simultaneously with minimizing the X-ray data residual. The minimization function thus becomes

$$M = \sum_0^i w_i(F_{oi}^2 - F_{ci}^2)^2 + \sum_0^j w_j(D_{tj} - D_{cj})^2, \qquad (1)$$

where D_{tj} and D_{cj} are the expected and calculated values of a geometric function.

The proposal was to use these additional equations of restraint to increase both the speed and the radius of convergence in least-squares refinement, as well as providing a mechanism for introducing information that is complementary to the X-ray data. The equations are easy to implement, economical to compute and effective, and they were therefore rapidly included in most program systems. Direct methods for phasing small-molecule data sets became more powerful during the 1970s and 1980s, largely as a consequence of interleaving within a single program the tangent formula, the Fourier synthesis and, sometimes, the least-squares methods of refinement of trial models, each stage of which has a different susceptibility to errors in the data or in the model. The use of restraints to accelerate convergence became unpopular for small-molecule work, because as computing power increased they became less necessary, and because the restraints had to be hand-crafted for each new structure. In macromolecular crystallography, where large structures can be built from a library of small well established building blocks, regularization using restraints could be automated and remains useful (Tronrud, 2004).

In small-molecule crystallography, restraints were sometimes essential for modelling and stabilizing the refinement of disordered structures, and they also became a tool for hypothesis testing. When a molecular parameter (such as bond length) looked suspicious, the accepted value could be added as an equation of restraint. If the restraint became satisfied without a serious deterioration of the X-ray data-minimization function, the implication was that the conventional value was just as compatible with the X-ray data as the unconventional value. The strength of the hypothesis could be varied by altering the restraint weights, w_j, with respect to the weights of the X-ray data. The weights are usually computed from an estimate of the standard uncertainty (s.u.) of the restraint target, and they are put onto the same scale as the X-ray data using the relationship

$$w_j = \frac{\sum_0^i w_i(F_{oi}^2 - F_{ci}^2)^2}{(n-s)\sigma^2(D_j)}, \qquad (2)$$

for n X-ray observations and s adjustable parameters (Rollett, 1970).

If, after refinement, the restraint error $|D_{tj} - D_{cj}|$ is less than about three times the requested s.u. $\sigma(D_j)$, the restraint is usually regarded as being compatible with the X-ray data. The process of applying restraints in this way is visualized in the schematic diagram in Fig. 1. The vertical axis is the electron density in a line passing through the two bonded atoms. The dotted line represents a case where the electron density is 'peaky', so that, from the equivalence between Fourier refinement and least squares (Cochran, 1948), the un-

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restrained atoms will refine to the positions of the electron-density maxima. Attempts to impose a restraint that tries to move the atom away from the maximum will fail. The dashed line represents a case where the electron density for one atom is flatter. Although there will be some local maximum in the density to which the coordinate will refine, there is no real difference in the density at points adjacent to the maximum. This kind of situation can arise because of (i) large differences in scattering density between the two atoms, so that one of them contributes very little to the structure factors (*e.g.* $M{-}$H); (ii) libration of one atom about the other, leading to a significant difference in their ADPs; and (iii) disorder of one of the atoms. Under these conditions, the restraint chooses points on the plateau compatible with the requested bond length.

Care needs to be exercised when evaluating interatomic distances for atoms in librating groups. If the atomic displacements are represented by the usual second-order tensor, the centre of mass will be displaced towards the centre of libration. This is an artefact of the model. The displacement can be estimated so that the refined bond length can be adjusted *a posteriori*, and it is quite unacceptable to use restraints (or constraints) to hold the interatomic distance to a value obtained from nonlibrating systems. The shortened target bond length can be estimated using **TLS** analysis of ADPs (Johnson, 1970). However, the calculation is ill-determined for small groups of atoms and, in cases where an asymmetric restraint may be required, the displacement parameters are likely to be poorly defined in the first place. An approximation for bonded librating atoms (Busing & Levy, 1964) gives the corrected bond length

$$d = d_0 + \frac{\left(\overline{w_B^2} - \overline{w_A^2}\right)}{2d_0}, \qquad (3)$$

where $\overline{w_A^2}$ is the mean-square radial displacement of atom A in the plane perpendicular to the direction of the AB bond (similarly for $\overline{w_B^2}$) and d_0 is the uncorrected bond length. The value of d_0 for use in a restraint can be computed from knowledge of the ideal bond length, d, and the ADPs of two atoms by rearranging this equation and solving for d_0.

Under normal circumstances, bond-stretching vibrations occur at a frequency that makes them unobservable by X-ray diffraction. This means that the components of the ADPs of bonded atoms must be more or less equal and opposite in the direction of the bond – the Hirshfeld condition (Hirshfeld, 1976). Rigid-bond models (Rollett, 1970) also suggest that, in many circumstances (for example, in an extended aliphatic chain undergoing concerted thermal motion), the ADPs of one atom will be similar to those of adjacent atoms. These ideas can be incorporated into ADP restraints. As a restraint, the Hirshfeld condition (now commonly called DELU) tries to ensure that the components of displacement along the vector between bonded atoms are similar, and the more general supposition that adjacent atoms have similar ADPs is achieved by restraining the individual components of the two ADPs to be similar (commonly called SIMU). Again, caution needs to be exercised in applying ADP restraints. While it is likely that the DELU restraint can generally be applied safely, the SIMU restraint needs more consideration: in a $-$CF$_3$ group with a small magnitude of libration, the C atom might be expected to have an ADP more or less cylindrically symmetric about the bond to the root atom. The F atoms are likely to have their longest axes tangential to the C$-$F bond, although the components along the C$-$F direction will satisfy the Hirshfeld condition. More recently, an enhancement of the rigid-bond criteria has been described (Thorn *et al.*, 2012) which, in addition to the existing rigid-bond condition, restrains the relative motion of the two atoms to be perpendicular to the direction of the rigid bond.

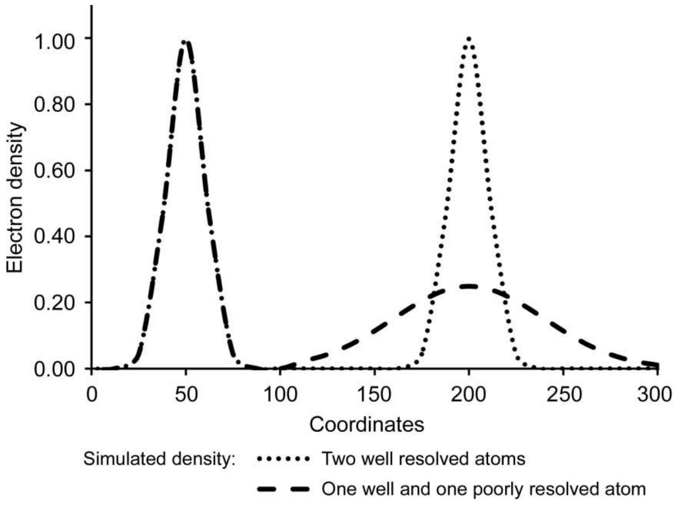

Figure 1
Schematic diagram simulating electron-density maxima for atoms with well resolved positions (dotted line) and one well resolved and one poorly resolved atom (dashed line). In the latter case a restraint can have more influence on the position of the less well resolved atom, since there is no real difference in the electron density at points adjacent to the maximum.

2. Asymmetric geometric restraints

In large-molecule structures, or otherwise poorly crystalline materials, it is often observed that the ADPs become progressively more ill-defined towards the exterior of the molecule, becoming less consistent in both DELU and SIMU senses. This observation led G. M. Sheldrick and A. Thorn (personal communication) to suggest that the conventional ADP restraints, which cause each atom in a bond to have an equal influence on the other atom, might be inappropriate. Arguing *reductio ad absurdum*, given a sufficient number of cycles of refinement incorporating SIMU restraints with sufficiently large weights, all the atoms in a molecule would end up with more or less the same values of ADPs. One solution to this problem has been programmed into *CRYSTALS* (Betteridge *et al.*, 2003) as a set of asymmetric restraint functions. One of the two atoms in a bond is treated as a template, in that its characteristics are assumed to be reliable and can be propagated to the other atom *via* the restraint, while the second atom is treated as unreliable and does not contaminate the template atom *via* the restraint. There is of course feedback between the two atoms through the off-diagonal terms in the normal equations, so that the template atom is not totally unaffected. New restraints using this concept are asymmetric DELU, SIMU and DISTANCE restraints. In each of these, pairs of atoms forming a bond are specified, and the target restraint is sought by computing contributions to the shift of the second named atom only. The implementation closely follows that of the equivalent conventional Waser restraints (Waser, 1963) in *CRYSTALS* except that, for each cycle of refinement, the parameters of the template are included as constants in the equation of restraint. They remain variables in the structure factor and other restraint equations.

A related type of asymmetric restraint is found in the macromolecular refinement program *CNX*, which provides restraints based on van der Waals forces which account for asymmetric interactions between atomic chains containing discretely disordered groups (Accelrys, 2005)

The principle of treating some atomic parameters as constants in the equations of restraint is applicable to situations involving more than just two atoms. This idea has not been explored here, but examples might be to restrain poorly determined atoms to a plane defined by better determined atoms, or to implement SAME restraints which restrain multiple distances and angles in poorly determined fragments using a well defined fragment as the template.

3. Results

The following example, based on the unpublished *CRYSTALS* demonstration molecule *cyclo*-$C_7H_{11}NO_3$, serves to demonstrate the operation of the above-mentioned restraints. In the fully refined molecule shown in Fig. 2, the unrestrained terminal C2—C11 bond refines to 1.501 (2) Å. In order to demonstrate the effect of the new restraints clearly, we can now impose the unrealistic restraint that the distance should be 1.5500 Å with an improbably small s.u. of 0.0001 Å. Refinements using these targets with both conventional and asymmetric restraints were carried out starting from the same conventional model. Table 1 shows the shifts for each coordinate of both atoms with normal and asymmetric restraints. In both cases the target distance is achieved. However, in the case of the conventional distance restraint the shift is shared approximately equally between the two atoms, whereas in the asymmetric case the bulk of the shift is made to the position of the second atom.

A comparison of symmetric and asymmetric similarity restraints on ADPs is shown in Table 2. The refinements start from the original model using ADP similarity restraints with standard uncertainties of 0.001 Å^2 and without the distance restraints used above. This restraint attempts to make each pair of components of the anisotropic displacement parameters of both atoms similar. In the conventional symmetric restraint, more or less similar shifts are applied to the components of both atoms (rows labelled ‘C2 shifts’ and ‘C11 shifts’ in Table 2), reducing the overall mean Δ from 0.0040 to 0.0016. In the asymmetric restraint case, the components of the ADP of the second atom are made to be similar to those of the first atom, so that the shifts for C11 are much greater than those for C2. Because shifts are mainly made to the ADPs of C11, and these have to be reconciled with both the ADPs of C2 (the restraints) and the X-ray data, the final mean residual is 0.0021, not quite as low as with the symmetric restraint. It must be remembered that, in this example, the X-ray data are of fair quality, so the unrestrained ADPs probably represent reality, and the restraints, though satisfied, are marginally inappropriate.

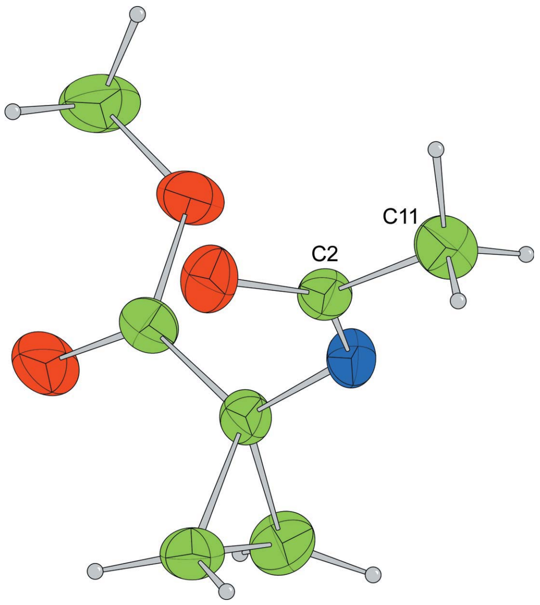

Figure 2
The terminal C2—C11 bond in the *CRYSTALS* demonstration molecule, *cyclo*-$C_7H_{11}NO_3$, is used here to demonstrate the effect of asymmetric restraints.

Table 1
Results of a refinement using normal and asymmetric restraints.

The distance restraint target of 1.5500 (1) Å is set to conflict with the X-ray data. C11 is a terminal atom, which may be deemed unreliable. Atom C2 is nonterminal and its position is assumed to be reliable so that it can be used as the template atom. The shifts for these atoms away from the X-ray minimized structure after applying normal and asymmetric restraints are listed. The atom-shift column shows the total shift for each atom, and the bond-length shift column shows the change in the bond length.

		x shift (Å)	*y* shift (Å)	*z* shift (Å)	Atom shift (Å)	Bond-length shift (Å)
Normal restraints	C2	0.01428	0.00618	0.01961	0.02504	
	C11	−0.00719	−0.00629	−0.02268	0.02461	0.04904
Asymmetric restraints	C2	0.00497	−0.00232	−0.00398	0.00678	
	C11	−0.02049	−0.01291	−0.04551	0.05155	0.04985

The effect of the rigid-bond restraint (DELU) is less easy to demonstrate, since all the terms in the ADPs vary together to produce the required shift along the bond vector, so that only the components of the ADPs in the direction of the bond from C2 to C11 are restrained. Again, refinement was started from the original X-ray structure, with either symmetric or asymmetric Hirshfeld restraints. Table 3 lists the mean-square displacement of the components of the ADPs in the direction of the bond from C2 to C11, before restraints are applied, and after either symmetric or asymmetric restraints. The symmetric restraint makes significant adjustments to both C2 (a shift of −0.00030 Å^2) and C11 (a shift of 0.0028 Å^2). In the asymmetric restraint case, C2 changes less (a shift of −0.0005 Å^2) than the symmetric case and less than C11 (a shift of 0.00044 Å^2). The mean-square displacement along the bond is a function of all six ADP components and as a result there is no simple way to visualize the shifts in the individual components of the ADPs.

Because equations of restraint only add an extra row to the matrix of observational equations, it is perfectly straightforward and valid to include more than one equation relating to a specific atomic parameter. A hybrid type of restraint can be generated by including both a traditional symmetric restraint and an asymmetric restraint for a given pair of atoms, with relative weights suitably chosen by means of the requested s.u. values. These combinations provide a mechanism for fine-tuning the supplementary information being added to a refinement, allowing it to lie anywhere between equal confidence in the parameters of each atom (the traditional symmetric restraint) and no confidence in the parameters of one atom (the asymmetric restraint).

4. Conclusions

Restraints provide a method for introducing nondiffraction information into the least-squares refinement. If the X-ray data are of good quality and self-consistent, the structural model can be expected to refine to a reasonably sharp minimum, that is, the parameters will be well defined with small s.u. values. If, for some reason, the minimum is not well defined, the parameters will still refine to minimize the weighted residual. However, in this case a physically more sensible model may exist which is still compatible with the

Table 2
ADP similarity restraints.

Calculations started from the original model minimized against the X-ray data. No distance restraints applied. Results obtained from symmetric and asymmetric ADP similarity restraints with a standard uncertainty of 0.001 Å^2.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}	Mean	R.m.s.
Initial parameters								
C2 (Å^2)	0.02976	0.02526	0.03421	0.00279	−0.00012	0.00380		
C11 (Å^2)	0.04668	0.03883	0.03083	0.00155	0.00067	0.00129		
Δ (Å^2)	0.01692	0.01357	−0.00338	−0.00124	0.00079	−0.00251	0.0040	0.0090
Traditional similarity restraint on ADPs								
C2 shift (Å^2)	0.00525	0.00360	−0.00169	−0.00040	−0.00007	−0.00086		
C2 values (Å^2)	0.03501	0.02886	0.03251	0.00239	0.00039	0.00219		
C11 shift (Å^2)	−0.00719	−0.00522	0.00211	0.00043	−0.00051	0.00161		
C11 values (Å^2)	0.03949	0.03360	0.03293	0.00199	0.00074	0.00214		
Δ (Å^2)	0.00448	0.00474	0.00042	−0.00040	0.00035	−0.00004	0.0016	0.0027
Asymmetric similarity restraint								
C2 shift (Å^2)	0.00010	−0.00066	0.00051	−0.00010	−0.00052	−0.00067		
C2 values (Å^2)	0.02987	0.02460	0.03473	0.00269	0.00046	0.00240		
C11 shift (Å^2)	−0.01045	−0.00749	0.00410	0.00029	−0.00058	0.00140		
C11 values (Å^2)	0.03623	0.03134	0.03493	0.00184	0.00118	0.00195		
Δ (Å^2)	0.00636	0.00674	0.00020	−0.00085	0.00073	−0.00044	0.0021	0.0038

Table 3
ADP Hirshfeld rigid-bond restraints.

Calculations started from the original model minimized against the X-ray data. No distance restraints applied. Results obtained from symmetric and asymmetric rigid-bond ADP restraints with a standard uncertainty of 0.001 Å^2.

	Mean-square displacement of C2 along C2—C11 bond	Mean-square displacement of C11 along C2—C11 bond	Δ
Original (Å^2)	0.03389	0.03314	−0.00075
C11 (Å^2)	0.03359	0.03342	−0.00017
Δ (Å^2)	0.03384	0.03358	−0.00026

X-ray data. Application of restraints enables the structure analyst to propose physical models and test them against the X-ray data. These new asymmetric distance, asymmetric Hirshfeld and asymmetric ADP similarity restraints give the analyst finer control over the types of models that can be investigated. They provide an alternative in cases where conventional restrained refinement is problematic or exhibits slow convergence. While general criteria for their application are difficult to recommend at the current stage of research, the following classes of situations are likely to be suitable: (i) restraining H-atom distances using the connected atom as a template (*e.g.* C—H or N—H asymmetric distance restraints); (ii) commonly disordered or librating groups, where a central atom may be better resolved than the surrounding atoms (*e.g.* for PF_6^- and ClO_4^-, P—F and Cl—O asymmetric rigid-bond restraints, respectively); and (iii) an extended librating or disordered aliphatic chain (*e.g.* multiple C—C asymmetric similarity restraints along the chain, with the template atom closer to the fixed end of the chain in each case).

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