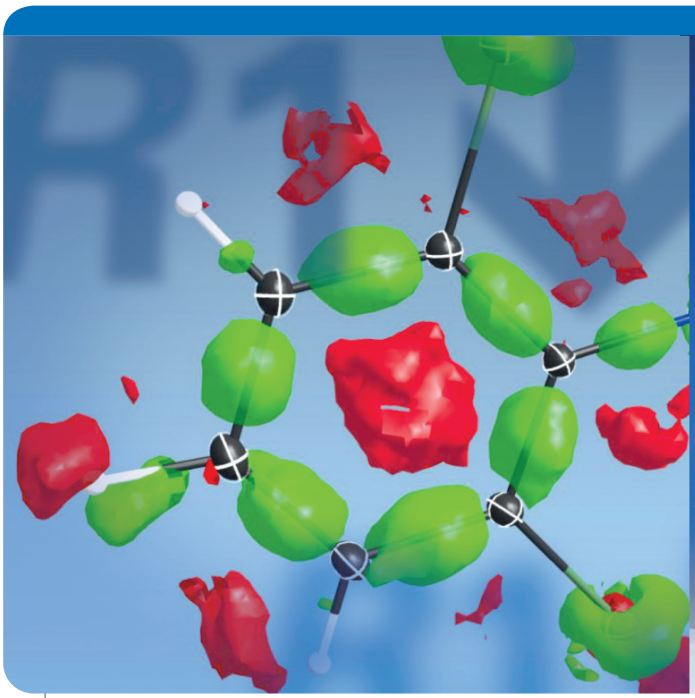


Application Note SC-XRD 526

Improved Models with IDEAL (Invariom Derived Electron AnaLysis)

A Journey Beyond the Traditional Independent Atom Model

Introduction

For more than 50 years crystallographers successfully applied the Independent Atom Model (IAM) using spherical scattering factors to model atoms in structures derived from X-ray diffraction data. However, the IAM, developed at a time when X-ray diffraction instrumentation had very limited capabilities, oversimplifies the description of electron densities because the charge cloud of an atom is rarely spherical. It is rather an electron cloud deformed by neighboring atoms, bonds and lone pairs. The scientific field of charge density analysis better describes these phenomena by introducing elaborate multipole models, which employ spherical harmonic models to simulate the charge distribution. Careful data acquisition is required to attain the necessary data quality at highest resolution. Experiments take extensive time, and establishing and refining meaningful multipole models is a very time-consuming effort that only few crystallographers are willing to undertake. In the past, instruments were less capable and measurement times were long, even for high-quality crystals. For these reasons, experiments were typically limited to lower resolutions, justifing the use of the IAM.

This paradigm changes with Bruker's advanced SC-XRD instrumentation: large photon-counting PHOTON III detectors and high-brilliance X-ray sources enable crystallographers to routinely collect high-precision, high-resolution data with short experiment times. Now, newly developed IDEAL, the **I**nvariom **D**erived **E**lectron **A**na**L**ysis, provides intuitive and comprehensive tools to fully use modern instruments' superior data.

- IDEAL goes beyond the traditional IAM by expanding it to aspheric atom models using scattering contributions from bonds and lone pairs[1].
- IDEAL improves structure models significantly, making full use of the exceptional data collected on your Bruker instrument.
- IDEAL is easy to use within the APEX3 software suite and is fully integrated into the IUCr's checkCIF routines.
- IDEAL is available as the latest add-on to the APEX3 suite (www.bruker.com/apex3).

Due to its ease of use and significantly improved refinement results, IDEAL sees an ever growing popularity. Improvements include significantly smaller residual densities, more precise bond lengths, and easier identification of missing or incorrectly assigned atoms. As a consequence of the better model, subsequent modeling of disordered segments is getting much easier. In this application note, we describe a number of structures of various compounds, refined with IAM and IDEAL, to demonstrate the impact of IDEAL on the final structure model.

Better Model with Lower Residuals – Easy as child's play

IDEAL is seamlessly implemented in the APEX3 suite's *Refine Structure* plugin (Figure 1a, Figure 1b). When a structure refinement has converged to your satisfaction, open the IDEAL interface (Figure 1a), select *Match automatically* for an automated assignment of the model fragments and the subsequent generation of all required refinement parameters. After a quick visual check, confirm the assignments and perform just one extra refinement cycle. Compared to standard IAM refinements, using IDEAL increases the computing time by only about 15%. In addition to the automatic fragment assignment IDEAL provides manual model fragment selection and adaptions (Figure 1b). Whatever your preferred route, you'll notice a significant improvement in the residual values. Figure 2 compares the $R1_{obs}$ and *wR*2 of IAM and IDEAL refinements for a variety of compounds[2]. In every case, the clear improvement of the agreement factors is worth the small effort of setting up the refinement and the little extra computing time.

The overall approach makes IDEAL unique with respect to computing time, but also in the sense of program flexibility and robustness.

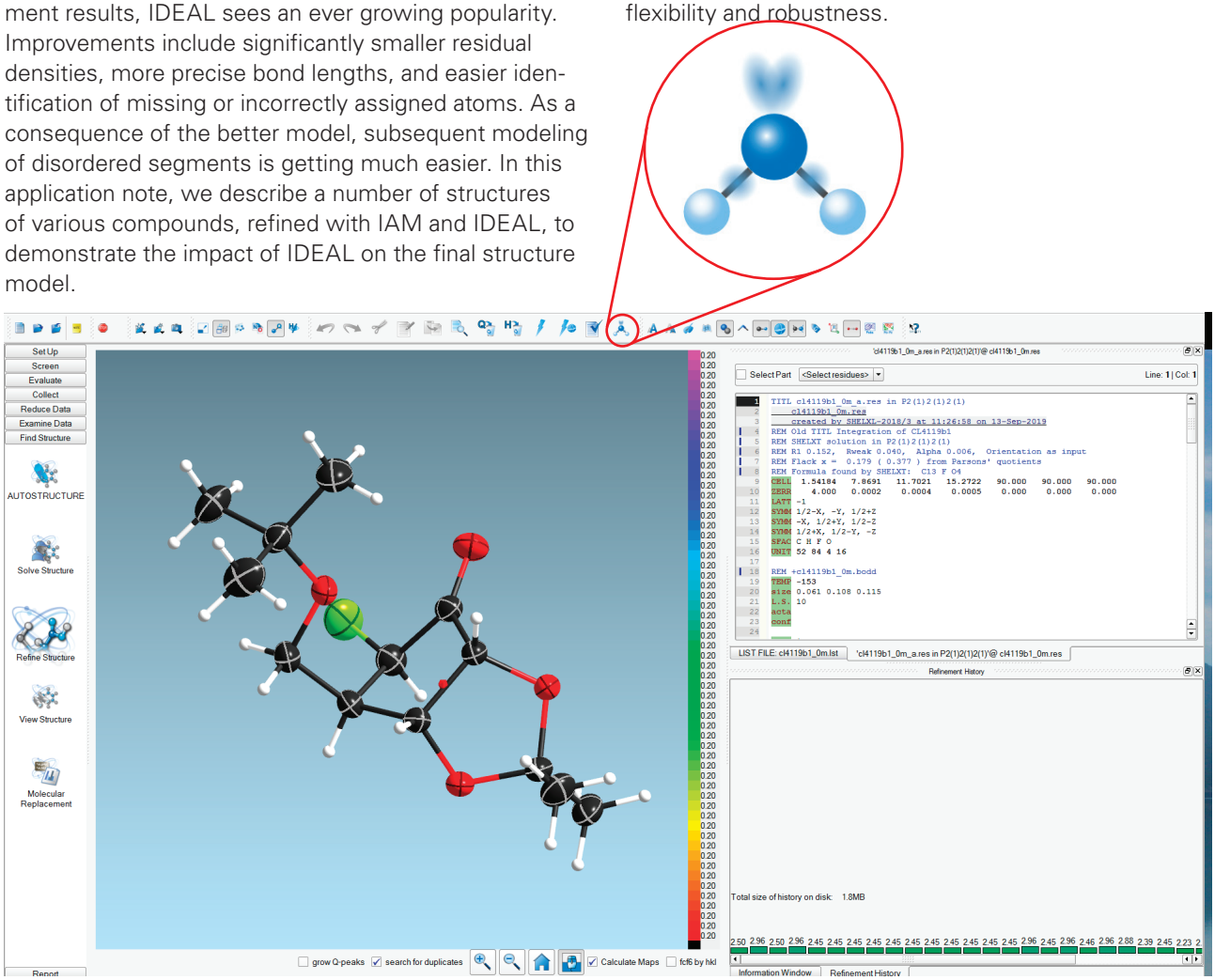


Figure 1a: IDEAL selection button in the graphical user interface of the Refinement plugin of APEX3.

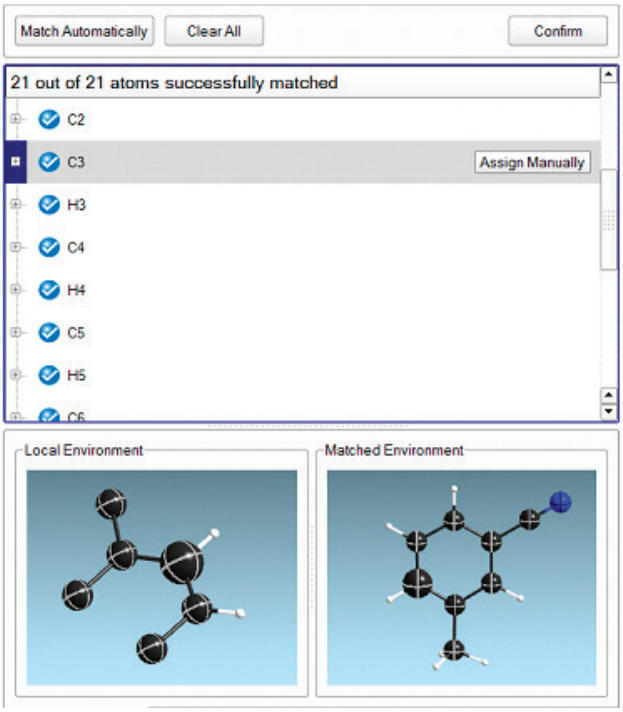


Figure 1b: IDEAL interface for automatic or manual fragment assignment including instantaneous visual feedback.

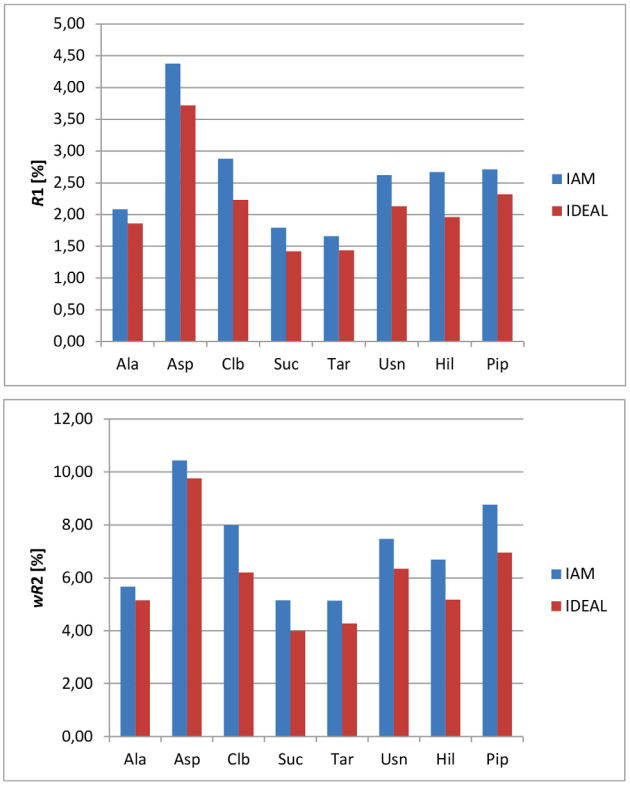


Figure 2: Improved $R1_{obs}$ and *wR2* values after IDEAL refinement compared to traditional IAM refinement.

For every atom in your structure, IDEAL derives a static bond-oriented deformation density using a model fragment. Despite this atom-oriented approach, IDEAL adds just three scaling parameters. Only these three scaling parameters are required and its number does not increase, regardless of the number of atoms or the size of the structure. Thus, IDEAL does not overfit the structure. In other words, the drop in the residual values reflects a distinct and real improvement of your crystallographic model.

For chiral compounds, the Flack parameter and Parson's Quotients method (Parsons *Q*) are slightly improved. The standard deviation of these parameters stays untouched as the data basis remains the same.

Table 1 compares final quality measures from IAM and IDEAL refinement for a variety of compounds. Structures refined with the additional IDEAL step show improved (lower) residual values (Figure 2). Also note the much more symmetrical rest electron densities, which go in line with the improved refinement.

Compound[2]	Ala		Asp		Cl4		Suc		Tar		Usn		Hil[3]		Pip	
Method	IAM	IDEAL	IAM	IDEAL	IAM	IDEAL	IAM	IDEAL	IAM	IDEAL	IAM	IDEAL	IAM	IDEAL	IAM	IDEAL
Resolution [Å]	0.37		0.60		0.80		0.50		0.40		0.50		0.80		0.50	
*R*1(obs)	2.08	1.86	4.38%	3.72%	2.88%	2.23%	1.79%	1.42%	1.66%	1.44%	2.62%	2.13%	2.67%	1.96%	2.71%	2.32%
*R*1(all)	2.23	1.98	5.44%	4.80%	2.97%	2.34%	1.86%	1.47%	1.67%	1.44%	2.74%	2.26%	2.71%	2.07%	2.86%	2.49%
*wR*2	5.67%	5.15%	10.44%	9.76%	8.00%	6.20%	5.15%	4.00%	5.14%	4.28%	7.47%	6.34%	6.69%	5.18%	8.76%	6.96%
GooF	1.029	1.034	1.403	1.072	1.06	0.976	1.125	1.099	1.309	1.069	1.209	1.025	1.273	1.073	1.316	1.061
Residual electron density [eÅ^{-3}]	0.47/ -0.18	0.30/ -0.26	0.58/ -0.26	0.44/ -0.29	0.20/- 0.15	0.16/ -0.13	0.33/ -0.21	0.24/ -0.16	0.44/ -0.26	0.29/ -0.26	0.46/ -0.22	0.25/ -0.26	0.21/ -0.24	0.16/ -0.17	0.36/ -0.16	0.22/ -0.19
Parsons' *Q*	0.062 (51)	0.061 (51)	-	-	0.019 (22)	0.015 (22)	-0.010 (32)	-0.002 (31)	0.020 (43)	0.014 (43)	-	-	0.018 (20)	0.000 (21)	0.099 (182)	0.091 (185)

Table 1: Comparison of residual values from IAM and IDEAL refinement.

Improved Residual density

When switching from the IAM to IDEAL the improvement of the residual electron density map is undeniably most striking. Figure 3 compares the residual electron density maps from the IAM (top) and IDEAL (bottom). The IAM refinement clearly shows bonding density and the oxygen lone pairs. In the IDEAL refinement this density is nicely modelled. This is also reflected by the significantly lower and more symmetric residual density dropping from 0.47/-0.18 in the IAM refinement to 0.30/-0.26 after one round of IDEAL refinement (Table 1).

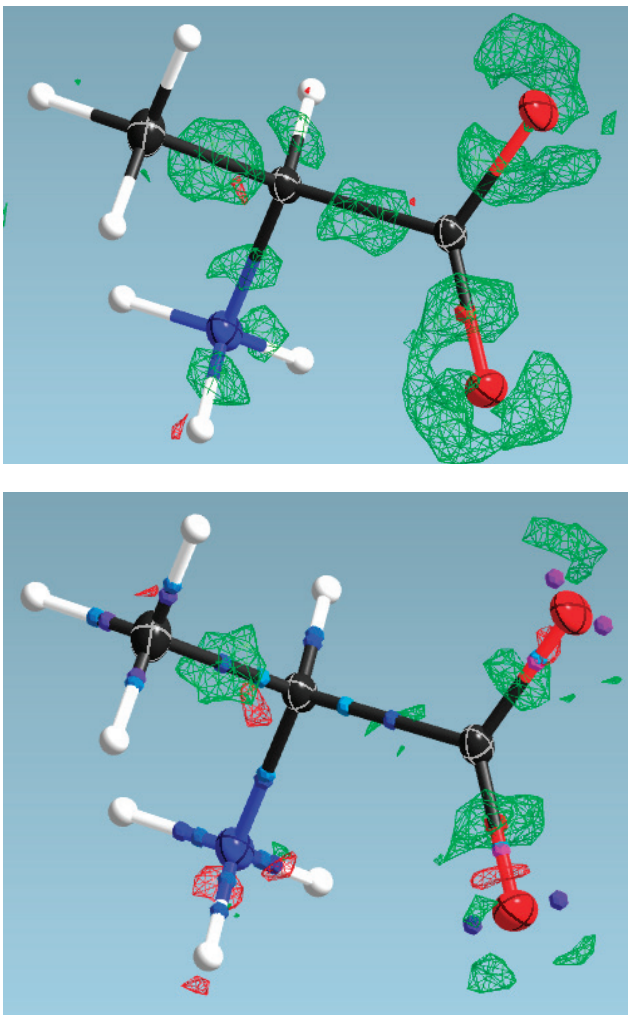
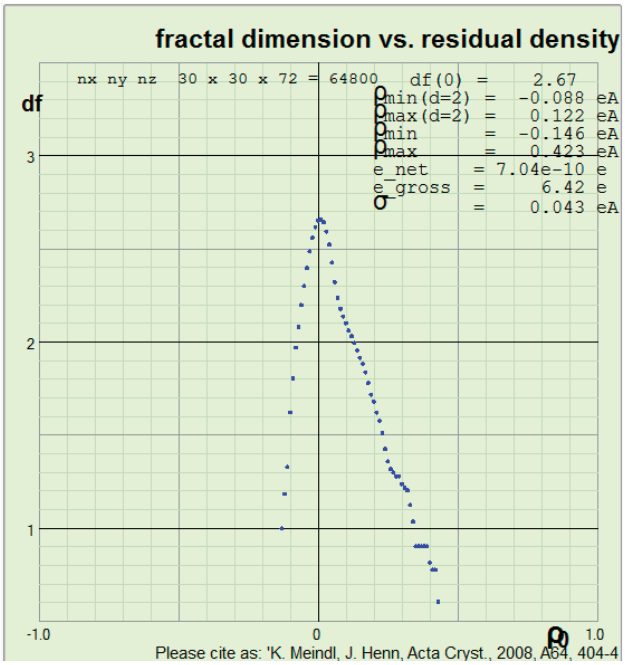


Figure 3: Residual electron density map of Alanine from refinement with IAM (top) and IDEAL (bottom) refinement . Residual electron density maps are on the same scale.



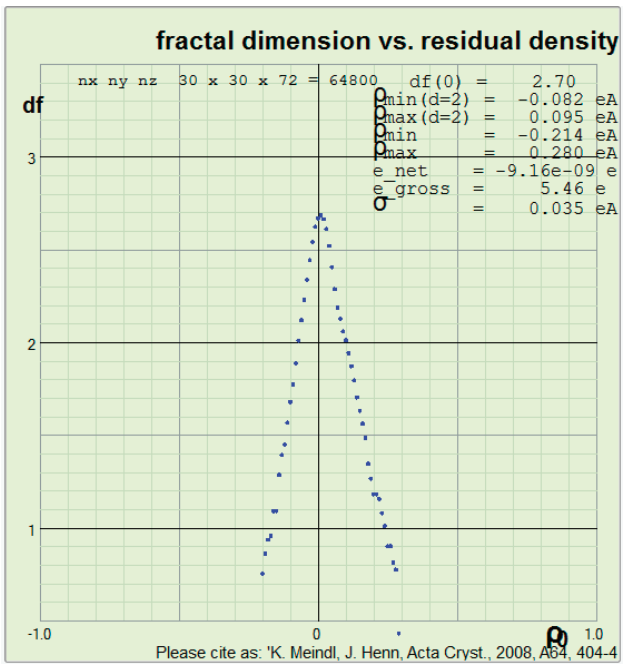


Figure 4: Fractal dimension analysis of the residual electron density from the IAM (top) and IDEAL (bottom) refinement of Alanine.

The fractal dimension analysis shown in Figure 4 allows an even more detailed analysis of the residual electron density. The ideal case would show a narrow upside down parabola with a crest at $y = 3.0$. In the IAM refinement the plot features a shoulder which reflects the positive bonding and lone pair density that is not considered. The IDEAL refinement on the other hand, accommodates the additional electron density, leading to a plot close to the ideal. The improvement is also reflected in the significantly reduced overall integrated absolute value of the residual charge *("e_gross")* of the IDEAL refinement, which drops from 6.42 to 5.46 electrons.

Figures 5 and 6 show another example where IDEAL significantly improved the residual densities.

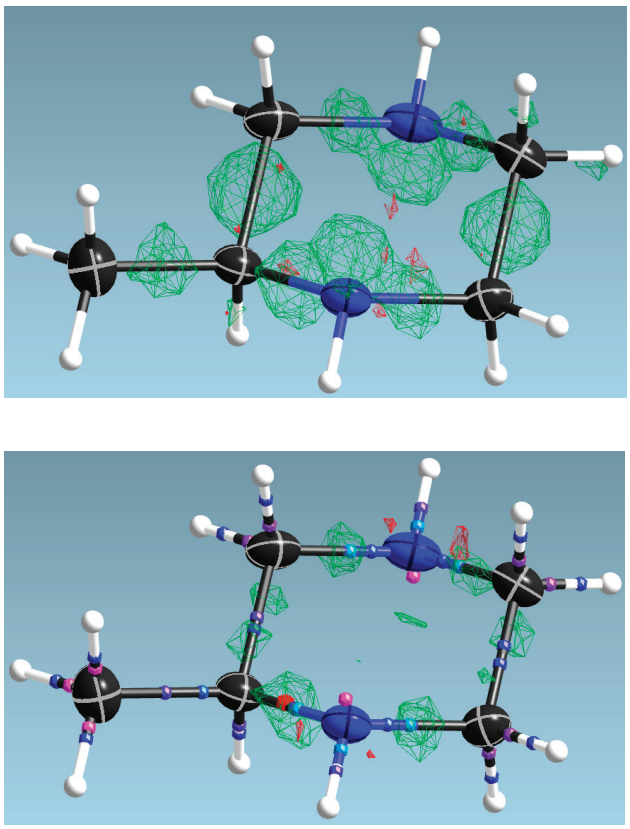
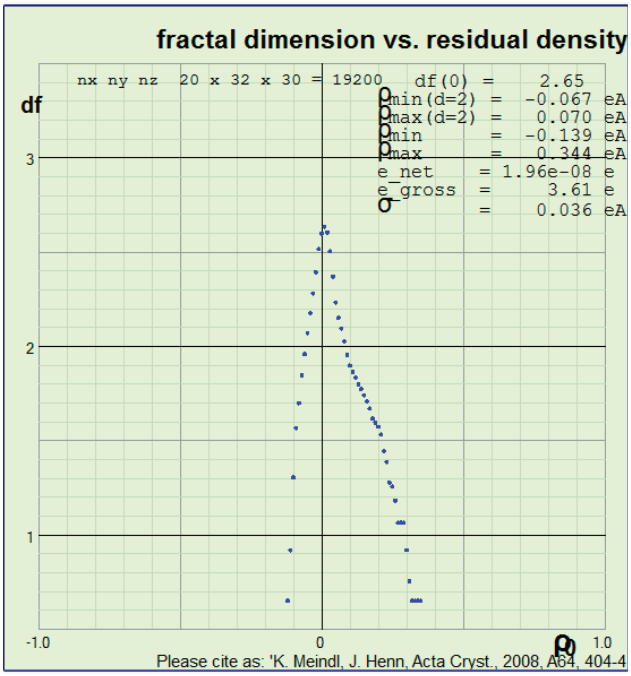


Figure 5: Residual electron density map of Pip from IAM (top) and IDEAL (bottom) refinement. Residual electron density maps are on the same scale.



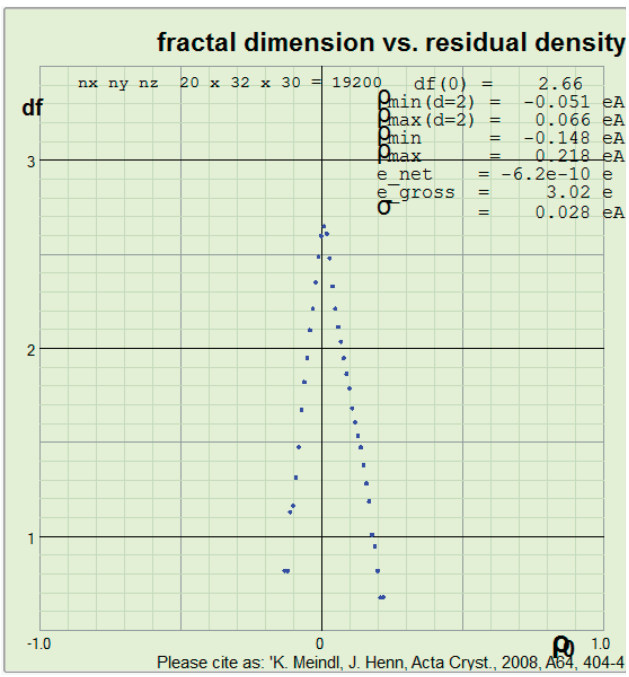


Figure 6: Fractal dimension analysis of the residual electron density from the IAM (top) and IDEAL (bottom) refinement of Pip.

Easier identification of residual peaks and disorder

Besides aesthetics, an even more important drawback of the IAM's non-modeled bonding or lone pair density is the concealment of residual electron density peaks arising from a misplaced atom or a missing hydrogen atom. Quite often, these peaks are easily overlooked in a messy residual density map. As a consequence of the improved structure model, IDEAL refined data sets show a nicely "cleaned-up" residual density map giving flaws in the structure refinement significantly better visibility. IDEAL perfectly assists you in modeling bonding and lone pair density and emphasizes real residual densities.

Figure 7 compares the residual electron density map after IAM and IDEAL refinement on the same scale.

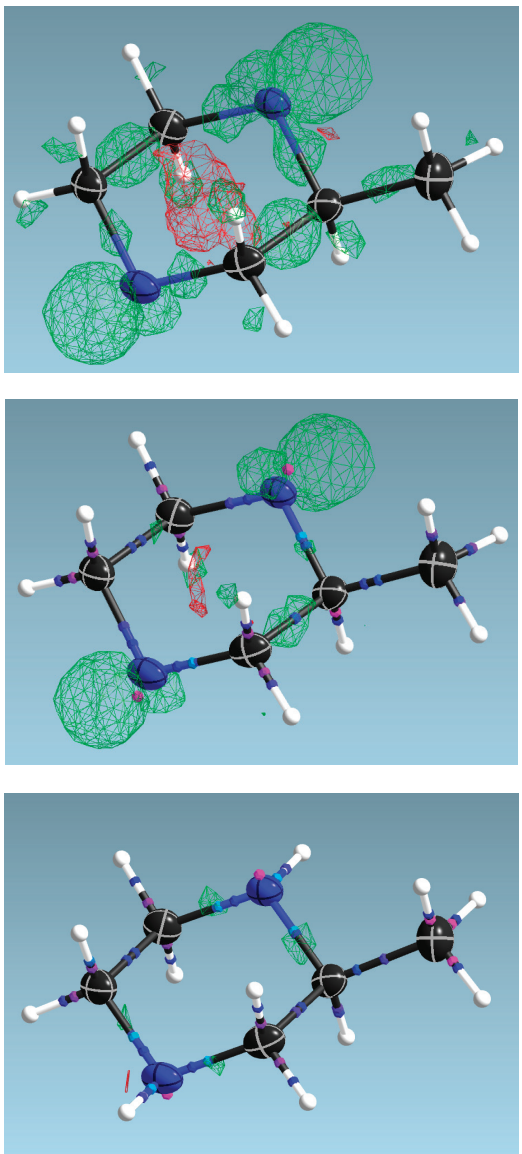


Figure 7: Residual electron density of a model with missing protons. While non-modeled bonding density in IAM refinement is distracting (top), IDEAL refinement strikingly shows missed protons (middle). The bottom image shows the IDEAL refinement after the missing hydrogen atom is added.

Improved Distances

The significance and accuracy of hydrogen bond lengths is an everlasting discussion in the structural science community. However, it is consensus that X-H distances refined from X-ray data are inherently underestimated. This is mainly due to the shortcoming of the IAM. Neutron diffraction data – yielding accurate hydrogen positions – is not easily available[4]. IDEAL offers a simple way to partially address this problem: IDEAL's bond-oriented deformation density method represents a much better description of hydrogen atoms and significantly improves the accuracy of the X-H bond length with reduced standard deviations from X-ray data. The histogram in Figure 8 compares C-H bond lengths obtained from IAM and IDEAL refinement to neutron data.

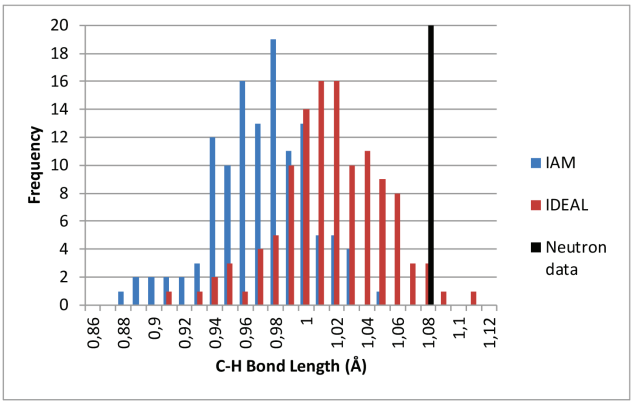


Figure 8: C-H bond length histogram.

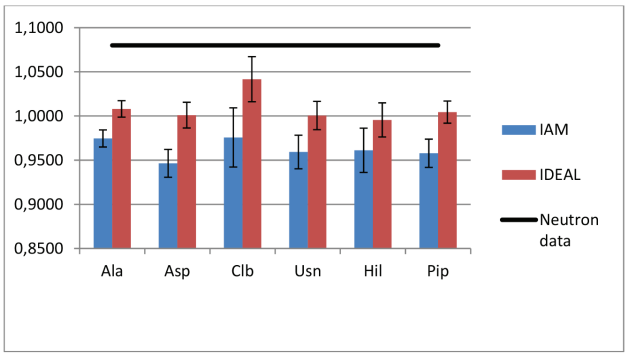


Figure 9: C-H bond length and standard deviation in methyl moiety as determined by IAM and IDEAL refinement.

Although the improvement and accuracy in bond lengths is most pronounced for X-H bonds (Figure 9, Table 2, Table 3), the IDEAL refinement also improves bond accuracies in general[5]. As an example, the improvement of the precision of C-C bonds after IDEAL refinement is shown in Figure 11.

Compound[2]	Method	CH3	CH2	CH(sp3)	CH(sp2)	NH	OH
Ala	IAM	0.9746(97)	-	0.9702(74)	-	0.9206(96)	-
	IDEAL	1.008(93)	-	0.9988(69)	-	0.9394(89)	-
Asp	IAM	0.9464(158)	-	-	0.9665(136)	-	0.8759(153)
	IDEAL	1.0010(146)	-	-	1.0028(126)	-	0.9118(142)
Clb	IAM	0.9819(219)	1.0040(245)	0.9757(335)	-	-	-
	IDEAL	1.0522(166)	1.0913(186)	1.0417(255)	-	-	-
Suc	IAM	-	0.9737(138)	0.9127(152)	-	-	0.8396(170)
	IDEAL	-	1.0198(101)	0.9600(96)	-	-	0.8882(89)
Tar	IAM	-	-	0.9491(95)	-	-	0.8490(101)
	IDEAL	-	-	0.9849(79)	-	-	0.8383(83)
Usn	IAM	0.9593(190)	-	-	0.9556(156)	-	0.8620(187)
	IDEAL	1.0005(160)	-	-	1.0038(127)	-	0.9087(135)
Hil[3]	IAM	0.9612(251)	0.9734(219)	0.9649(218)	-	-	0.8002(255)
	IDEAL	0.9956(193)	1.0297(169)	1.0016(116)	-	-	0.8700(196)
Pip	IAM	0.9578(160)	0.9820(128)	0.9962(113)	-	0.8834(129)	-
	IDEAL	1.0044(125)	1.0142(109)	1.0468(95)	-	0.8942(98)	-

Table 2: Average hydrogen bond length [Å] as determined by IAM and IDEAL refinement.

Compound[2]	Method	C-C	C-N	C-O
Ala	IAM	0.0002	0.0002	0.0002
	IDEAL	0.0002	0.0002	0.0002
Asp	IAM	0.0012	-	0.001
	IDEAL	0.0011	-	0.0009
Clb	IAM	0.0023	-	0.0018
	IDEAL	0.0017	-	0.0014
Suc	IAM	0.0006	-	0.0005
	IDEAL	0.0004	-	0.0004
Tar	IAM	0.0003	-	0.0003
	IDEAL	0.0002	-	0.0002
Usn	IAM	0.0007	-	0.0007
	IDEAL	0.0006	-	0.0006
Hil[3]	IAM	0.002	-	0.0019
	IDEAL	0.0015	-	0.0015
Pip	IAM	0.0007	0.0006	-
	IDEAL	0.0006	0.0005	-

Table 3: Average standard deviations on bond length [Å] as determined by IAM and IDEAL refinement.

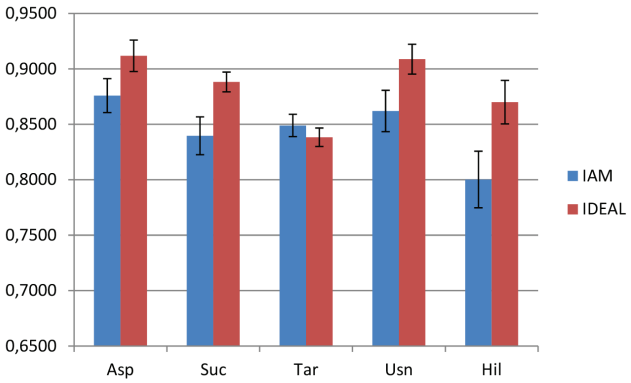


Figure 10:O-H bond length and standard deviation as determined by IAM and IDEAL refinement.

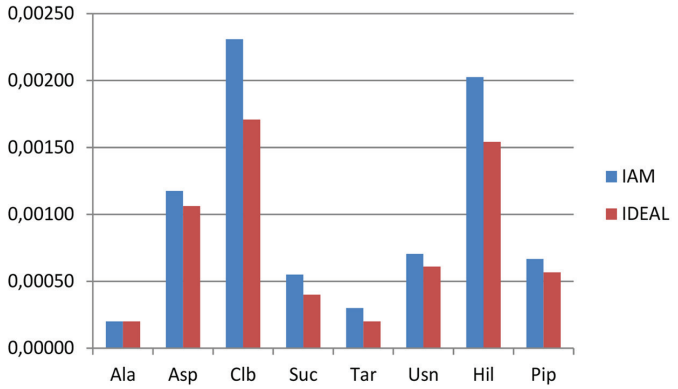


Figure 11: C-C Bond precision as determined by IAM and IDEAL refinement.

Conclusion

IDEAL extends the traditionally used IAM to aspherical atom models, which allows for modeling of bond and lone-pair density. More accurate structure models with significantly improved bond precision are obtained, resulting in distinctly reduced residual densities. Applying the advanced IDEAL refinedmodels highlights and helps to identify incorrect atom assignments and missed atoms or disorder. Detailed investigations on the significance of IDEAL refinements demonstrate its capability to identify incorrect atom assignments even in metal complexes[6]. This also makes IDEAL a potential tool for future structure validation. IDEAL is seamlessly integrated into APEX3, and is intuitive and easy-to-use. No additional software or expertise are required.

IDEAL goes beyond traditional structure refinement. Make full use of your superior Bruker data and IDEALize your structures.

Author

Dr. Tobias Stuerzer, Senior Application Scientist, Bruker AXS GmbH, Karlsruhe, Germany.

We are grateful for Clb crystals kindly provided by S. W. Schneller, C. Liu, Auburn University, Auburn, AL, USA.

References

[1] J. Lübben *et al.*, *Acta Crystallogr., Sect. A* **2017**, *75*, 50-62.
[2] Ala = Alanine, Asp = Aspirin, Clb = 6-(t-butoxymethyl)-5-fluoro-2,2-dimethyltetrahydro-2H,4H-cyclopenta[d][1,3] dioxol-4-one, Suc = Sucrose, Tar = Tartaric acid, Usn = Usnic acid, Hil = Withanolide, Pip = Piperazine.
[3] M. Sangern, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2755-2759.
[4] F. H. Allen, *Acta Crystallogr., Sect. B.* **1986**, *42*, 515
[5] C. Wandtke, Dissertation, Göttingen 2017.
[6] C. Wandtke et al., *Acta Crystallogr., Sect. B* **2017**, *73*, 794–804.

Bruker AXS GmbH

info.baxs@bruker.com

www.bruker.com

Worldwide offices

bruker.com/baxs-offices

Online information

bruker.com/sc-xrd