

# IDEAL - Have the Cake and Eat It Too!

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# IDEAL (Invariom Derived Electron AnaLysis)



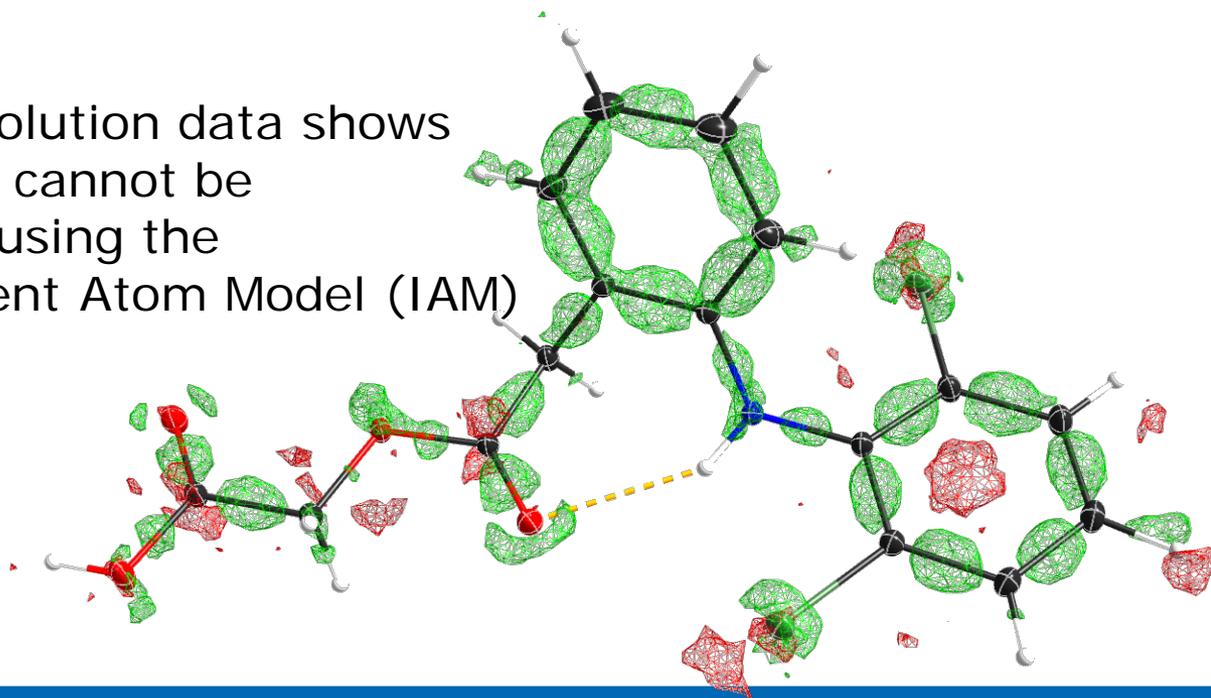
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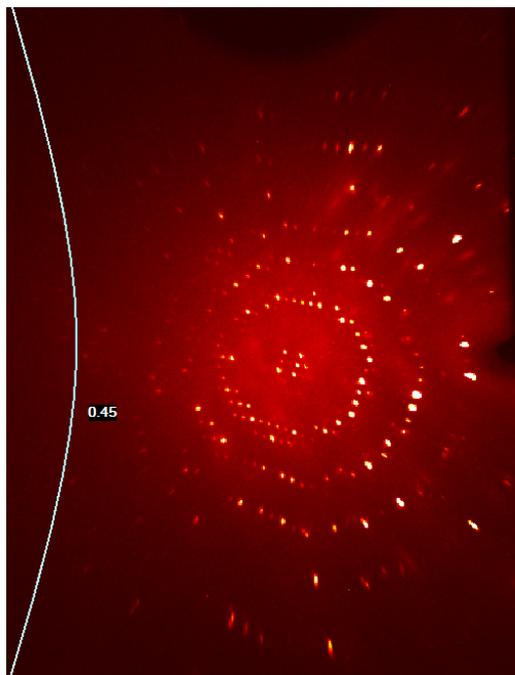
# IDEAL - The Premise

- Over the years, data quality has constantly improved with better detectors and better X-ray sources
- Large detectors like the PHOTON II provide high quality high resolution data with one detector setting and short experiment times
- High quality high resolution data shows density features that cannot be sufficiently modeled using the traditional Independent Atom Model (IAM)



# IDEAL - The Premise

- PHOTON II vs HPAD/HPC diffraction pattern
- Collect better quality data to higher resolution in one detector setting with the PHOTON II



PHOTON II

2.4 : 1 size ratio

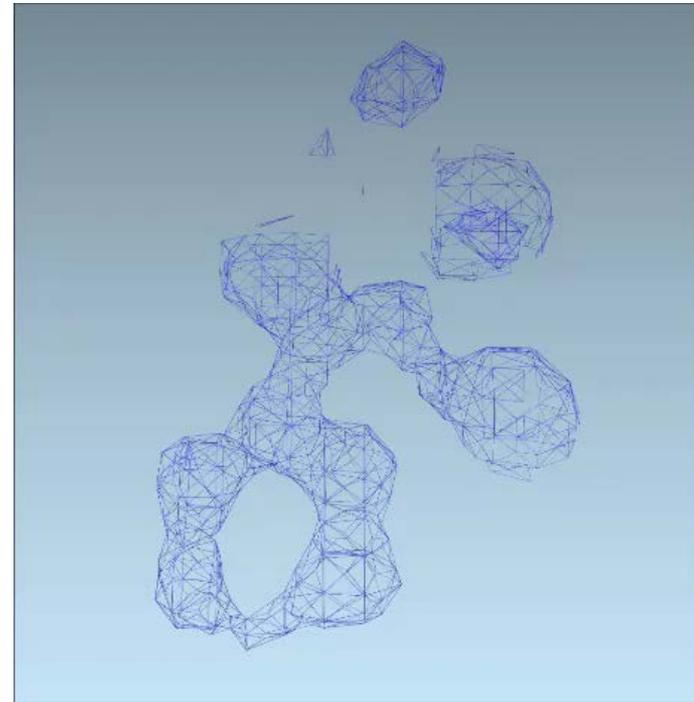
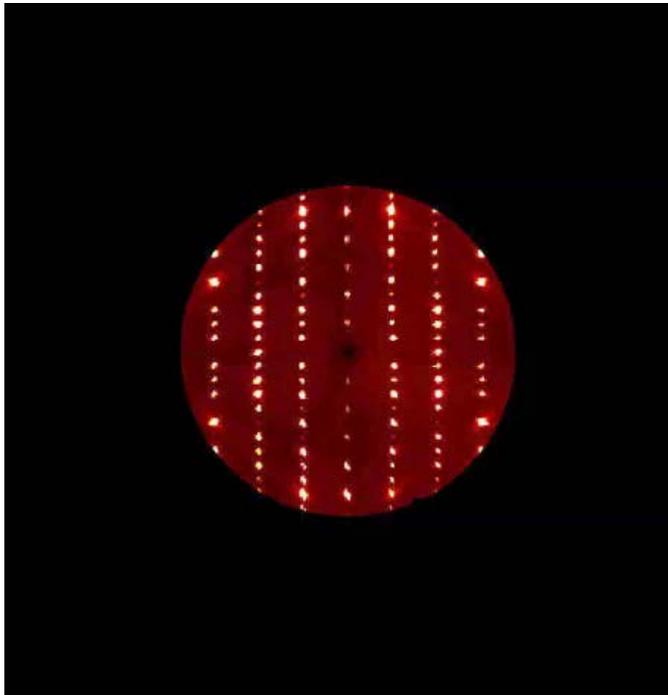


HPAD/HPC

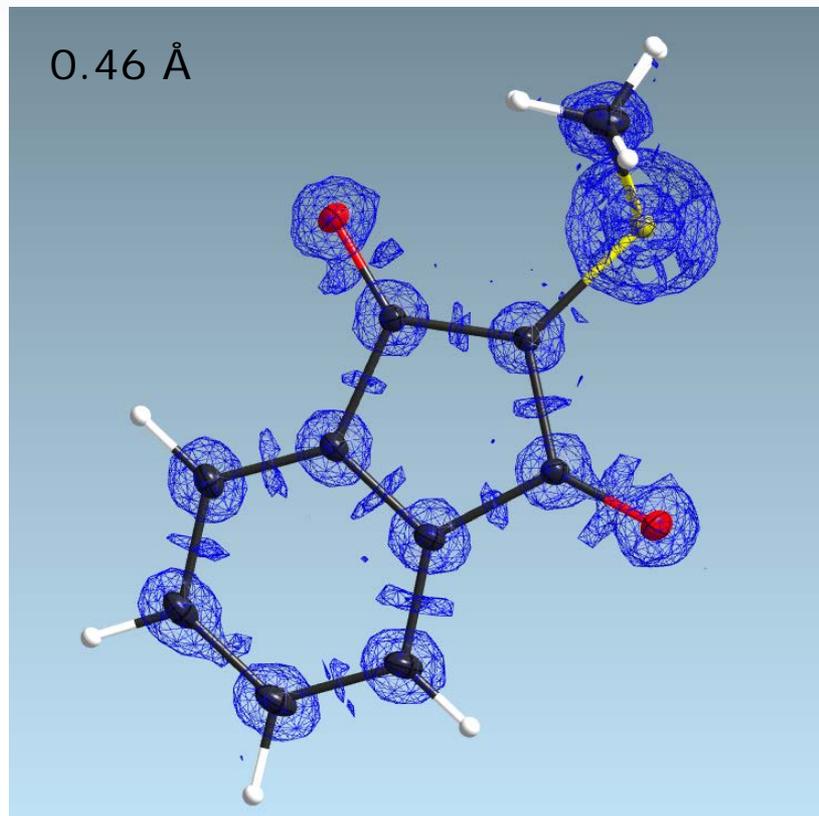
# IDEAL - Resolution: Reciprocal space vs. real space



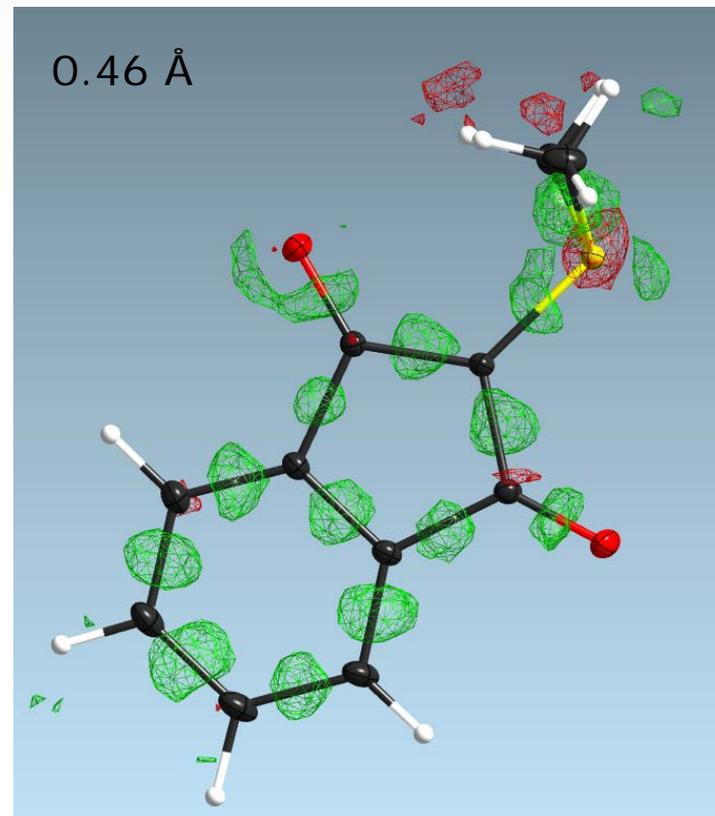
- Left: Data (reciprocal space) resolution increase in 0.1 Å steps (diffraction angle increases)
- Right: Structure (real space) resolution increases (more detail in density map)



# IDEAL - High Resolution Data



"Observed" electron density



Residual electron density



# The Independent Atom Model (IAM) vs The Multipole Model

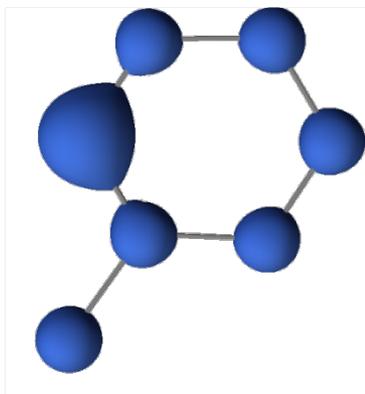


- Independent Atom Model
  - The atoms are regarded to be independent
  - The determined atom position and the displacement parameters can solely count for the right atom type at the correct lattice position with the right site occupation factor
  - It does not account for the interatomic region
  - IAM does **NOT** describe bonds, lone pairs, charges, charge transfer effects, ...
- Multipole Model
  - It models the interatomic area, the most important feature, the chemical bond
  - It assigns the gross charge density to spherical harmonics, the so-called multipoles
  - For example a dipole along the interatomic vector can account for the bond charge density

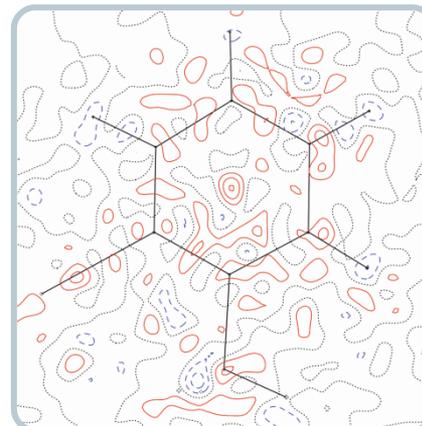
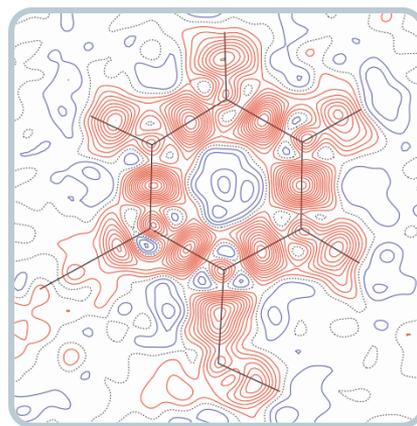
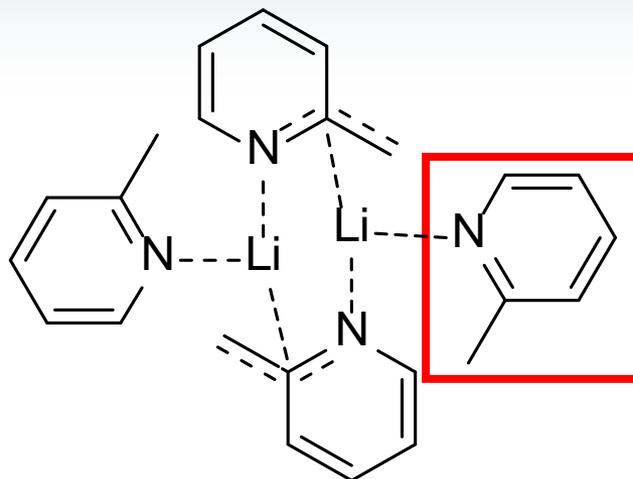
# IAM vs. MM



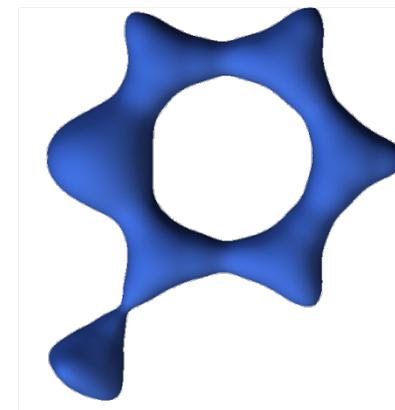
IAM



Electron Density



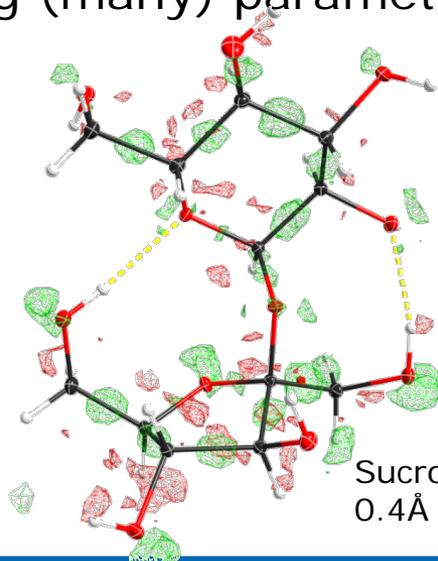
Improved Model



Electron Density

# IDEAL – The Solution

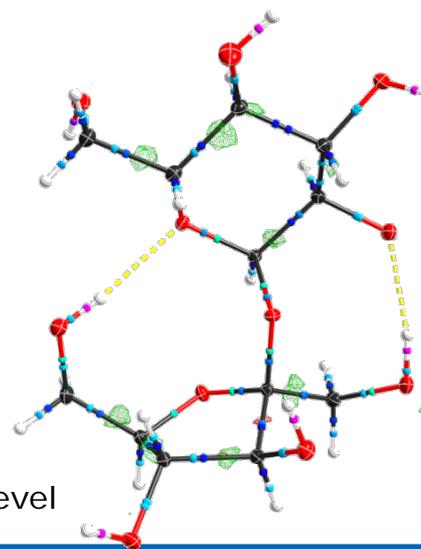
- Add bond-oriented deformation density to the Independent Atom Model (IAM) to more accurately model density
- Create a version of XL that can refine Bond Electron Density as well as Lone Pair Electron Density
- Deliver not only better data, but also better structures without adding (many) parameters



R1 = 1.84%



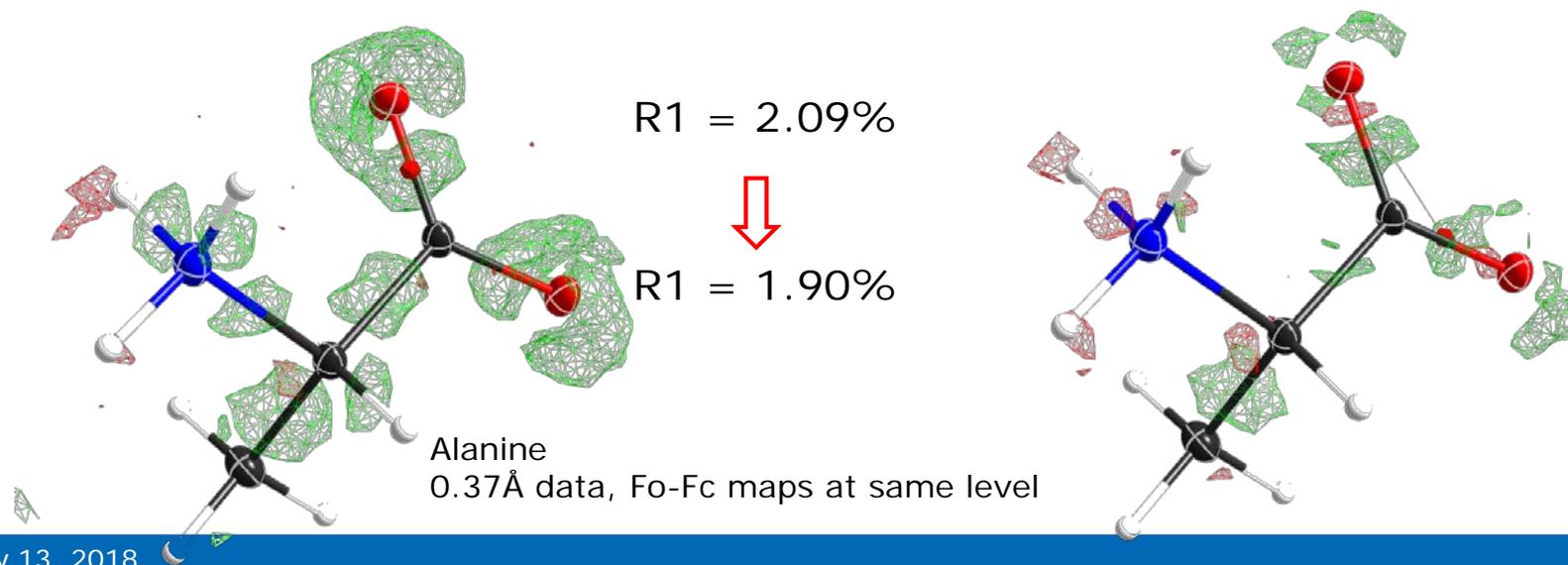
R1 = 1.43%



Sucrose  
0.4Å data, Fo-Fc maps at same level

# IDEAL – The Implementation

- BEDE and LONE instructions were added to XL. BEDE adds bond electron density and LONE adds Lone pair electron density – George Sheldrick
- Database of bond-oriented deformation density parameters from the Invariom database of *ab initio* calculations of model compounds
- GUI implementation



# IDEAL – The Implementation

- Adding Gaussian shaped densities on bonds and subtracting this density by a different Gaussian of the same height from the bonded atoms
- Adding a Gaussian shaped density at lone pair positions and subtracting the density from the atom they belong to
- Instructions with fixed values parameterized for model compounds from the Invariom database

Syntax:

BEDE            atom1 atom2 r A B1 B2

LONE    m atom1            r A B1 B2  
          m is analogous to AFIX m

For  $f(x) = \pm A e^{(-B_{1,2}(\sin(\frac{\theta}{\lambda}))^2)}$

B1 for +A, B2 for -A

# IDEAL – The Implementation



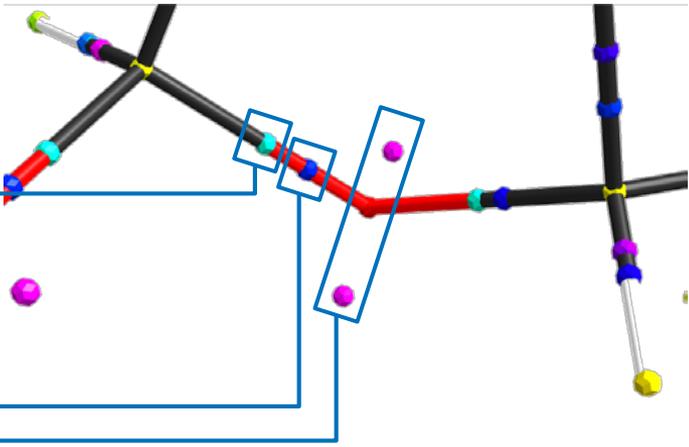
- Example

```

!ATOM C13!
!INVARIOMNAME C1o1o1c1h_0!
BEDE C13 H13 0.370 20.878 30.423 40.540
BEDE C13 O1 1.016 20.484 30.552 40.540
BEDE C13 O3 1.008 20.484 30.552 40.540
BEDE C13 C14 1.070 20.505 30.340 40.540
  
```

```

!ATOM O3!
!INVARIOMNAME 3-O#3c[#3c1c1h]#3c[#3c1c1h]_0!
BEDE O3 C13 0.672 20.108 30.442 40.558
BEDE O3 C16 0.683 20.108 30.442 40.558
LONE O3 2 21.070 30.321 40.558 0.482 137.60
  
```



# IDEAL –The Theory

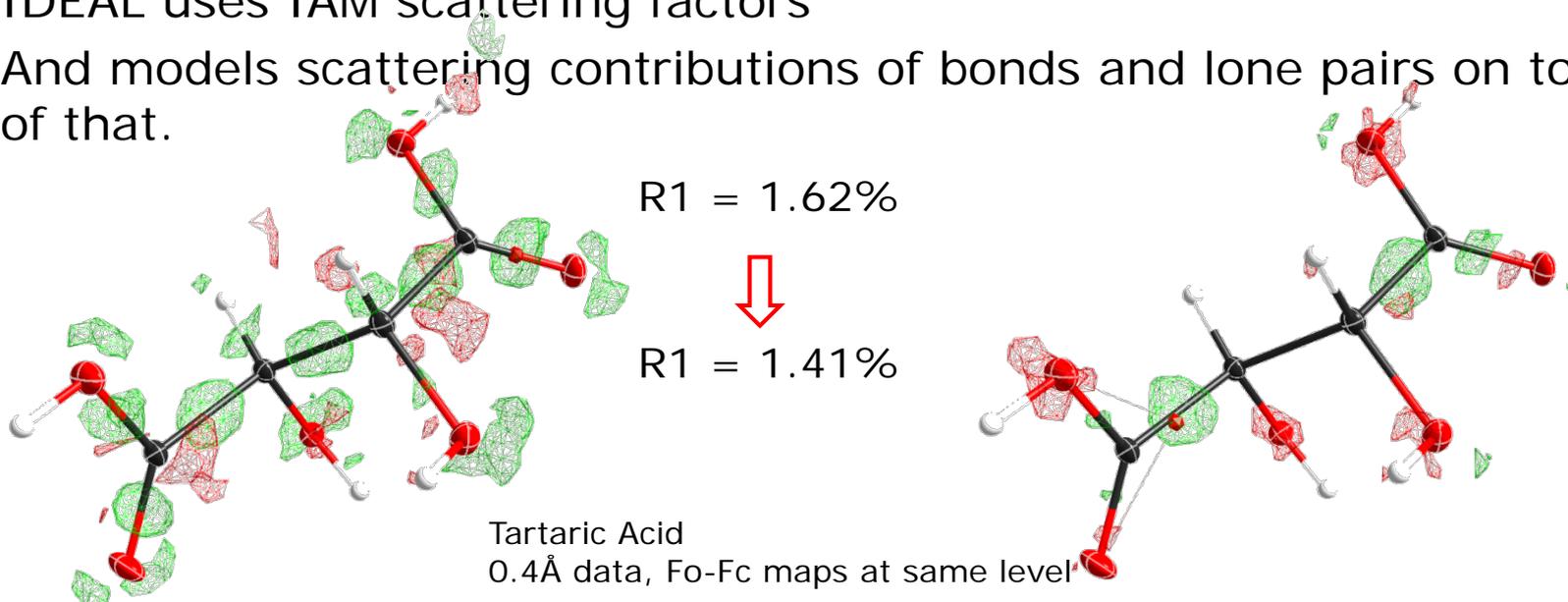
- **Invarioms** are aspherical atomic scattering factors that enable structure refinement of more accurate and more precise geometries than refinements with the conventional independent atom model (IAM).
- The use of single-crystal X-ray diffraction data of a resolution better than  $\sin \theta/\lambda = 0.6 \text{ \AA}^{-1}$  (or  $d = 0.83 \text{ \AA}$ ) is recommended.
- The invariom scattering-factor database contains transferable pseudoatom parameters of the Hansen–Coppens multipole model and associated local atomic coordinate systems.
- Parameters were derived from geometry optimizations of suitable model compounds, whose IUPAC names are also contained in the database.
- With over 2750 entries it now covers a wide sample of general organic chemistry

The generalized invariom database (GID)

B. Dittrich,<sup>a\*</sup> C. B. Hübschle,<sup>a</sup> K. Pröpper,<sup>a</sup> F. Dietrich,<sup>a</sup> T. Stolper<sup>a</sup> and J. J. Holstein<sup>a</sup>

# IDEAL –What's different

- Invarioms assemble a molecule's scattering characteristics atom by atom
- Invarioms replace IAM scattering factors and describe bonds by superimposing atomic scattering factors
- IDEAL uses IAM scattering factors
- And models scattering contributions of bonds and lone pairs on top of that.





# IDEAL –The GUI



**Invariom partitioning  
Parameter transfer  
BEDE and LONE command generation**

**Set up instruction file for refinement  
Generate .bodd file**

**It is fast! 30s for sucrose to set up all parameters**

Configuration

Ring Detection Threshold: Few Rings — Many Rings [Apply]

Free Variable Setup: Use FVARs [2] [3] [4]

Match Automatically [Clear All] [Confirm]

45 out of 45 atoms successfully matched

- H8A
- O9
- H9A
- O10
- O11
- H11
- C1 [Assign Manually]

```
C1o1o1e1h_0
  BEDE C1 H1 0.347 0.878 0.423 0.540
  BEDE C1 O1 1.013 0.484 0.552 0.540
  BEDE C1 O5 1.006 0.484 0.552 0.540
  BEDE C1 C2 1.075 0.505 0.340 0.540
```

Local Environment [Matched Environment]

Environment View

Reset rotation center  grow G peaks  search for duplicates  Calculate Maps  fcf6 by hkl

# IDEAL –The GUI

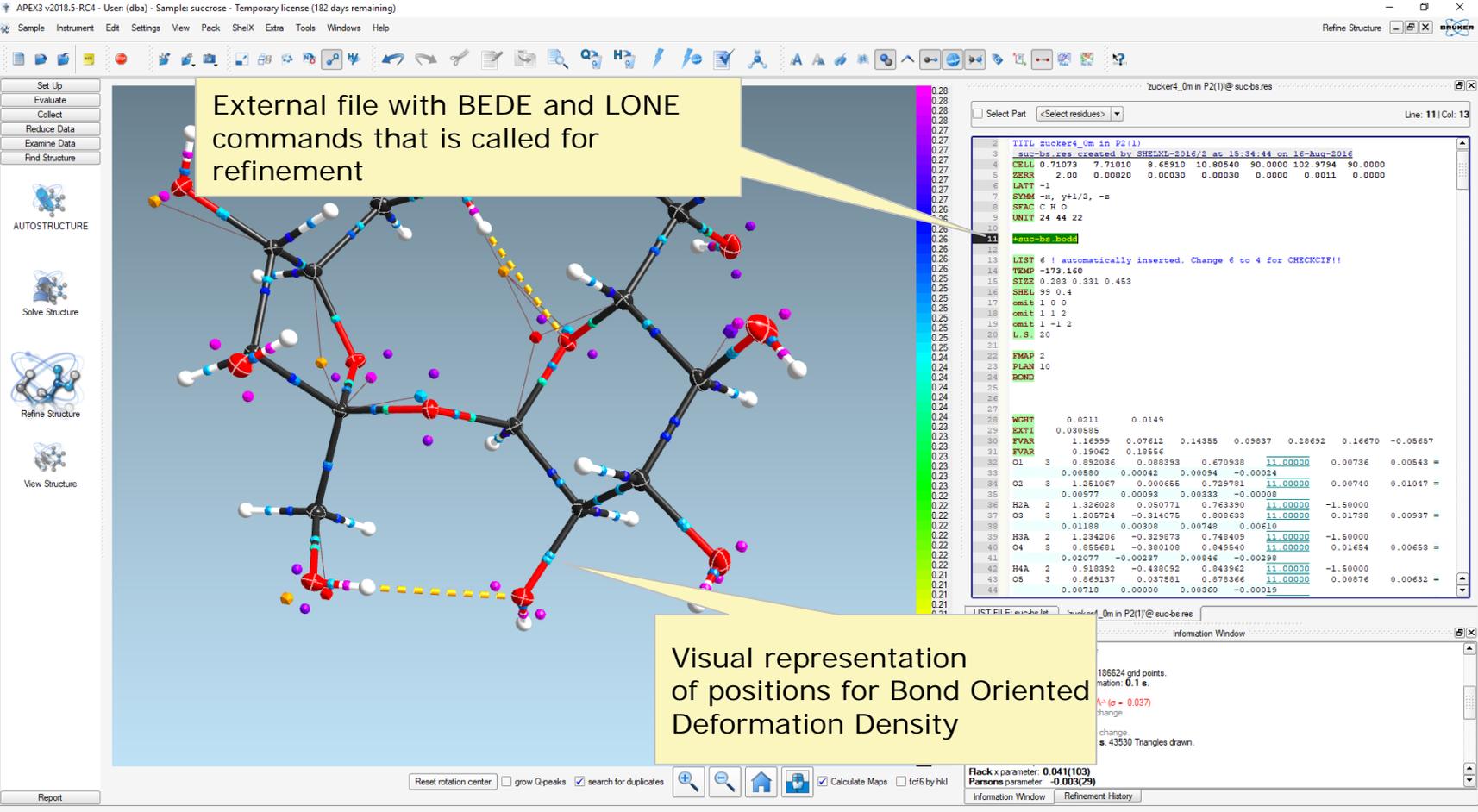


The screenshot displays the IDEAL software interface. The main window shows a 3D ball-and-stick model of a complex organic molecule. A vertical color bar on the right side of the model indicates different local environments. Three yellow callout boxes provide additional information:

- Quick configuration for challenging structures:** Points to the 'Configuration' panel on the right, which includes a 'Ring Detection Threshold' slider (set to 'Few Rings'), a 'Free Variable Setup' section (set to 'Use FVARs 2, 3, 4'), and buttons for 'Match Automatically', 'Clear All', and 'Confirm'.
- Detailed information for each atom:** Points to a list of atoms with their corresponding BEDE data. The selected atom is C1.
- Visual representation of local environments and corresponding database fragments:** Points to the 'Local Environment' and 'Matched Environment' panels at the bottom right, which show 3D models of the atom's immediate surroundings and a matching fragment from a database.

The interface also includes a top menu bar (Sample, Instrument, Edit, Settings, View, Pack, ShellX, Extra, Tools, Windows, Help), a toolbar with various icons, and a left sidebar with buttons for 'Set Up', 'Evaluate', 'Collect', 'Reduce Data', 'Examine Data', 'Find Structure', 'AUTOSTRUCTURE', 'Solve Structure', 'Refine Structure', and 'View Structure'. The status bar at the bottom contains options like 'Reset rotation center', 'grow G peaks', 'search for duplicates', 'Calculate Maps', and 'fcf6 by hkl'.

# IDEAL—The GUI



The screenshot displays the APEX3 v2018.5-RC4 software interface. The main window shows a 3D ball-and-stick model of a sucrose molecule with a color-coded deformation density map overlaid. A yellow callout box points to the model with the text: "External file with BEDE and LONE commands that is called for refinement". Another yellow callout box points to the refinement list with the text: "Visual representation of positions for Bond Oriented Deformation Density".

The refinement list on the right side of the interface includes the following parameters:

```

TITL zucker4_0m in P2(1)@ suc-bs.res
_suc-bs.res_created_by SHELXL-2018/2 at 18:34:44 on 16-Aug-2016
CELL 0.71073 7.71010 8.65910 10.80540 90.0000 102.9794 90.0000
ZERR 2.00 0.00020 0.00030 0.00030 0.0000 0.0011 0.0000
LATT -1
SYMM -x, y+1/2, -z
SFAC C H O
UNIT 24 44 22
11
11 suc-bs.bodf
LIST 6 ! automatically inserted. Change 6 to 4 for CHECKCIF!!
TEMP -173.160
SIZE 0.283 0.331 0.453
SHEL 99 0.4
omit 1 0 0
omit 1 1 2
omit 1 -1 2
L.S 20
PLAN 2
PLAN 10
BOND
WGHT 0.0211 0.0149
EXTI 0.030595
FVAR 1.16999 0.07612 0.14355 0.09837 0.28652 0.16670 -0.06657
FVAR 0.19062 0.18564
O1 3 0.892036 0.088393 0.670938 11.00000 0.00736 0.00543 =
O2 3 0.00590 0.00042 0.00094 -0.00024
O3 3 1.261067 0.000655 0.729781 11.00000 0.00740 0.01047 =
H2A 2 1.926028 0.050771 0.763950 11.00000 -1.50000
O3 3 1.205724 -0.314075 0.808633 11.00000 0.01739 0.00937 =
O3 3 0.01188 0.00309 0.00748 0.00610
H3A 2 1.234206 -0.329873 0.749409 11.00000 -1.50000
O4 3 0.955691 -0.390109 0.849540 11.00000 0.01654 0.00653 =
O4 3 0.02077 -0.00237 0.00846 -0.00298
H4A 2 0.918392 -0.438092 0.843962 11.00000 -1.50000
O5 3 0.869137 0.037581 0.878366 11.00000 0.00876 0.00632 =
O5 3 0.00718 0.00000 0.00360 -0.00019
  
```

The bottom right corner of the interface shows the following statistics:

```

Flack x parameter: 0.041(103)
Parsons parameter: -0.003(29)
  
```

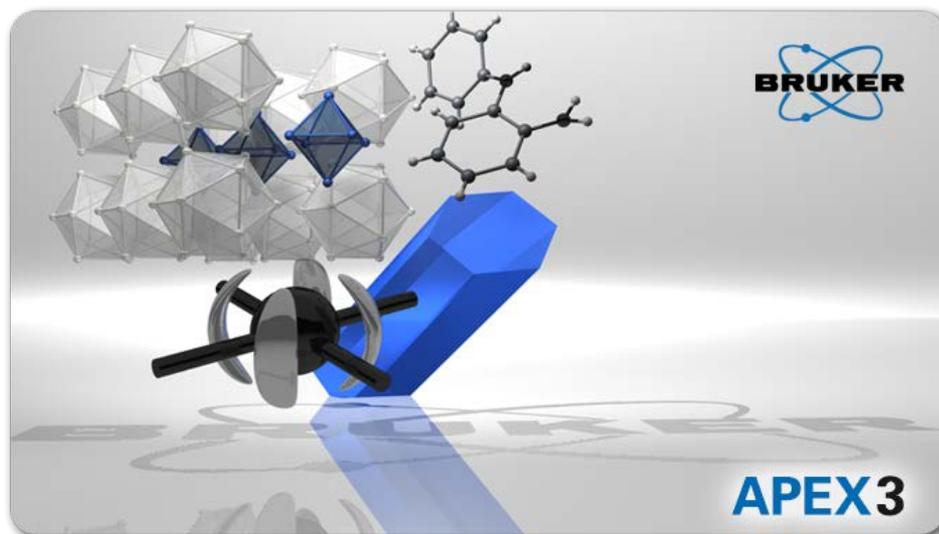
# IDEAL—The GUI

Fine tune database search by modifying input parameters with intuitive interface

BEDE C10 O10 0.732 {}0.880 {}0.359 {}0.559  
BEDE C10 H10 0.383 {}0.565 {}0.467 {}0.559  
BEDE C10 C11 0.872 {}0.600 {}0.311 {}0.559

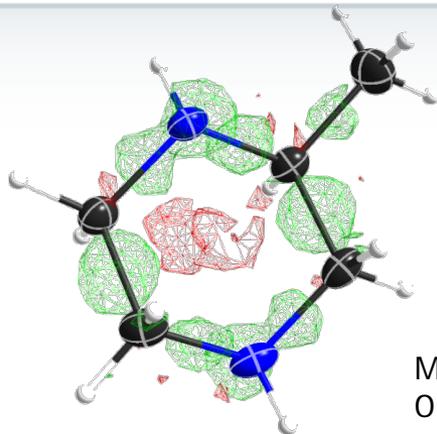
Manually select most suitable match from a sorted list of candidates

# APEX3 – Live Demo



- Live Demo of IDEAL in APEX3
- Bispyrazolone

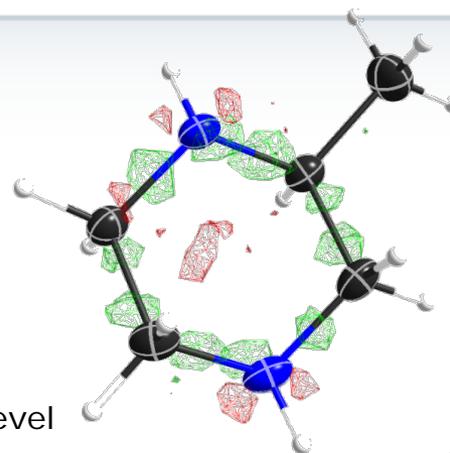
# IDEAL - More Examples 1



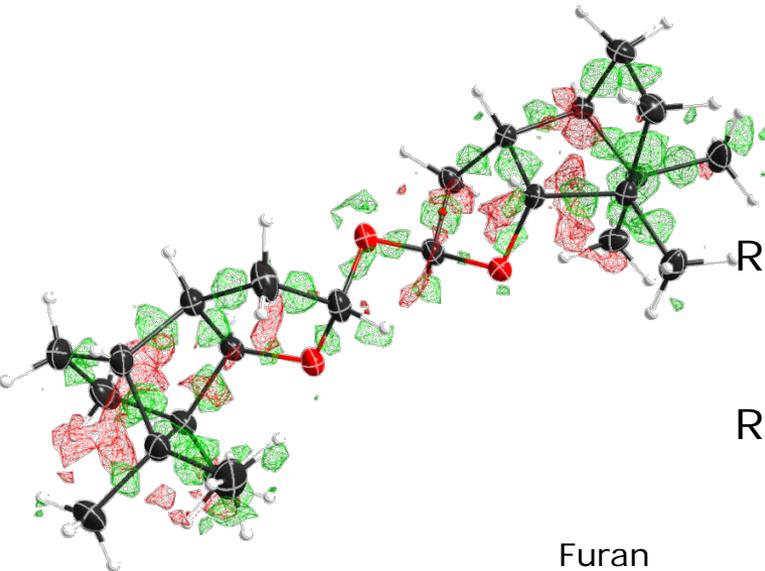
R1 = 2.72%



R1 = 2.35%



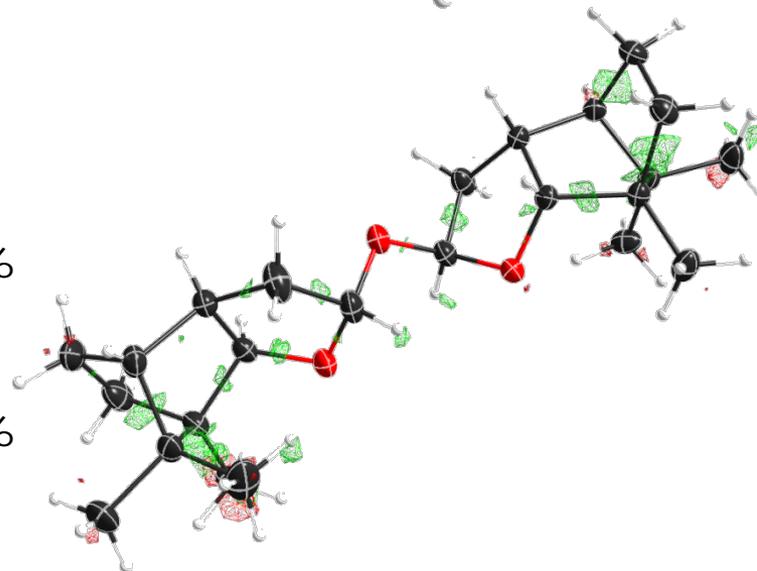
Methyl-Piperazine  
0.5Å data, Fo-Fc maps at same level



R1 = 3.00%

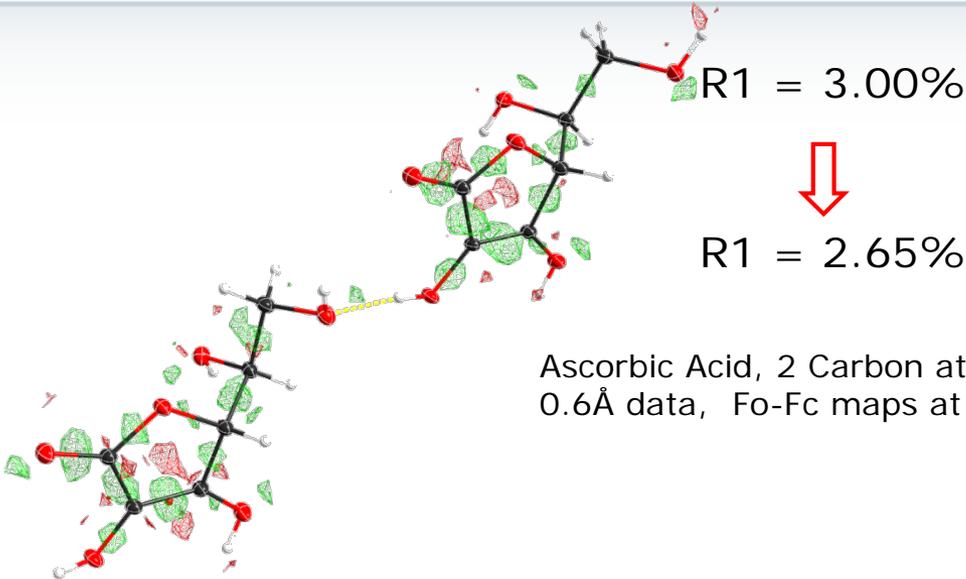


R1 = 2.51%



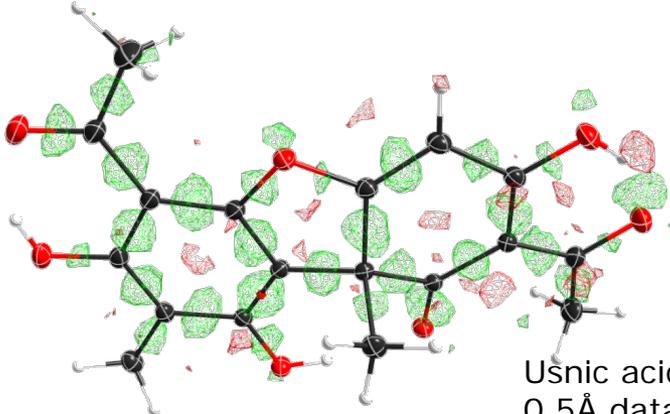
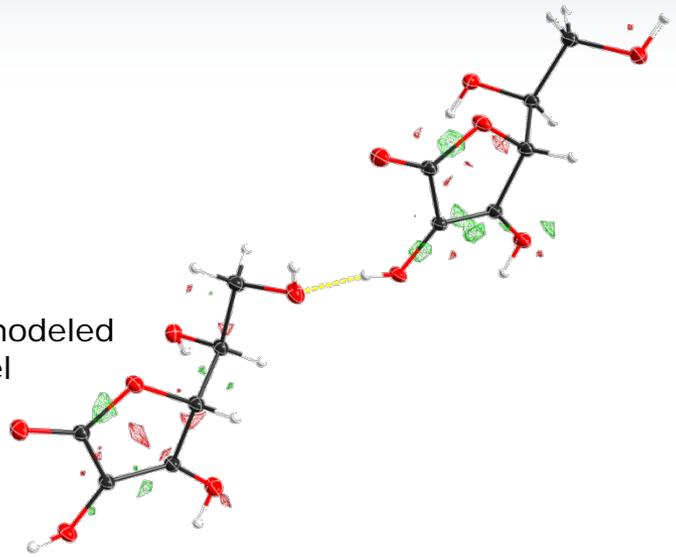
Furan  
0.55Å data, Fo-Fc maps at same level

# IDEAL - More Examples 2



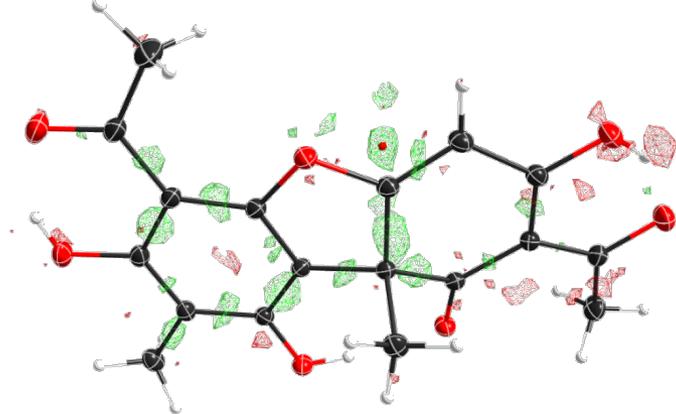
R1 = 2.65%

Ascorbic Acid, 2 Carbon atoms not modeled  
0.6Å data, Fo-Fc maps at same level

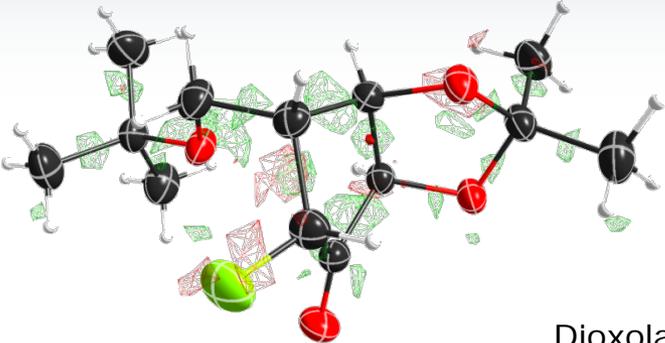


R1 = 2.29%

Usnic acid  
0.5Å data, Fo-Fc maps at same level



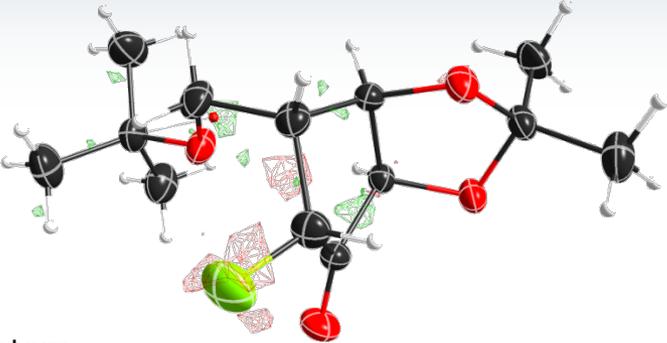
# IDEAL - More Examples 3



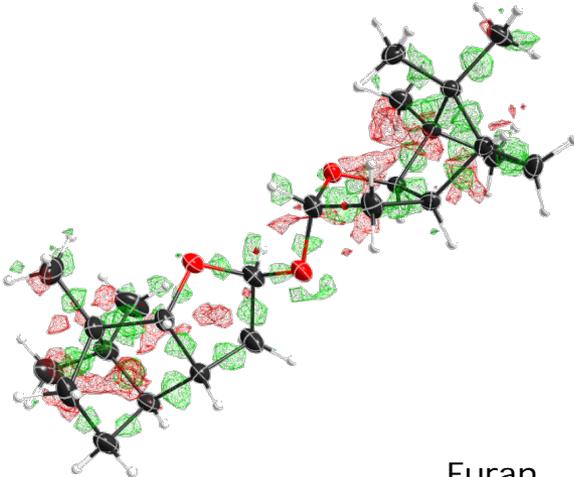
R1 = 2.95%



R1 = 2.50%



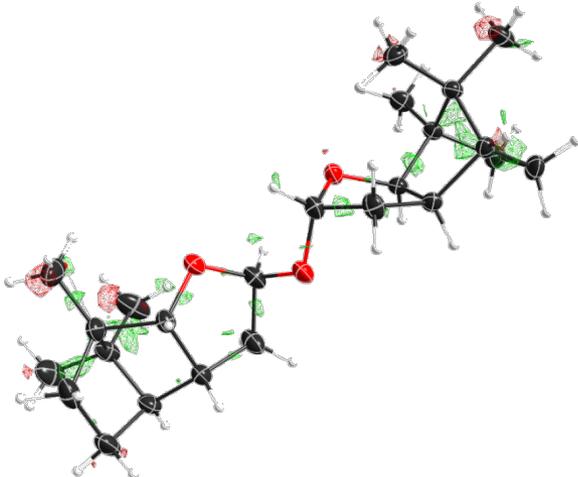
Dioxolane compound with Fluorine atom,  
0.8Å Cu data, Fo-Fc maps at same level



R1 = 2.99%

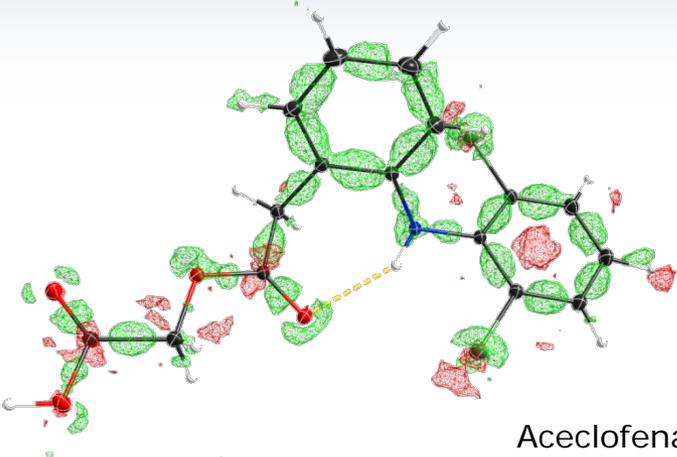


R1 = 2.51%



Furan  
0.80Å Cu data, Fo-Fc maps at same level

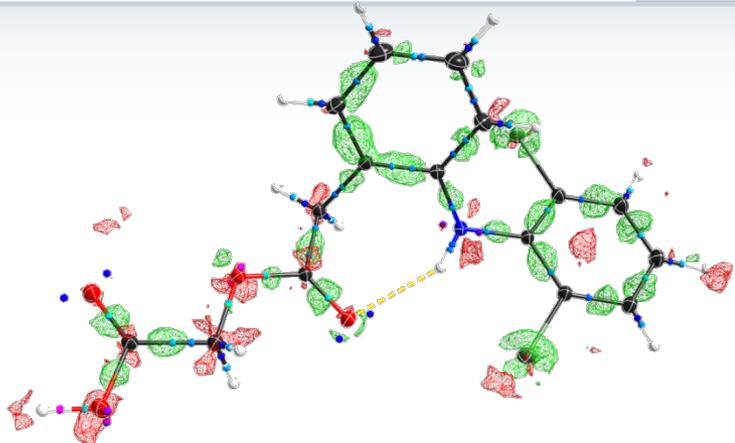
# IDEAL - More (Problematic) Examples



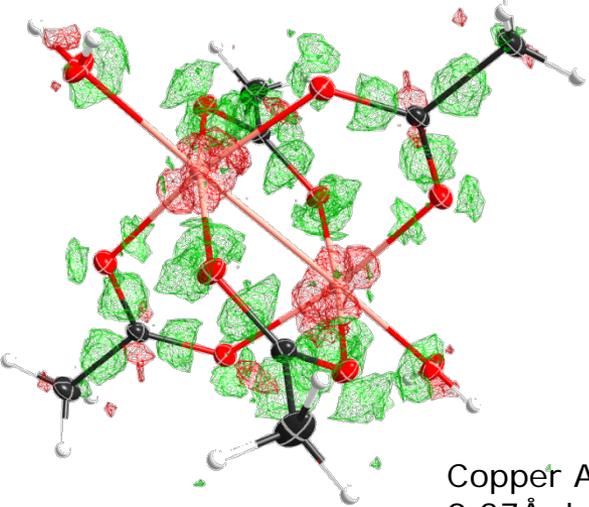
R1 = 2.33%



R1 = 2.13%



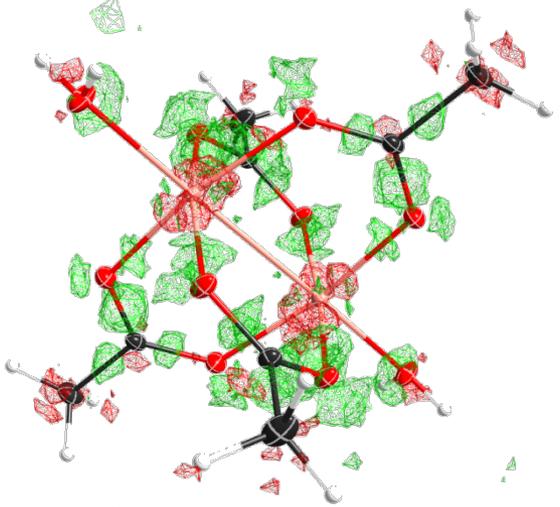
Aceclofenac, Chloride bonds not modeled  
0.37Å data, Fo-Fc maps at same level



R1 = 1.38%



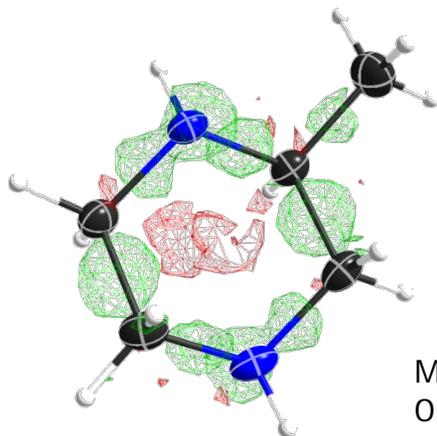
R1 = 1.36%



Copper Acetate, Cu and most Oxygen bonds not modeled  
0.37Å data, Fo-Fc maps at same level

# IDEAL - Reliability Criteria

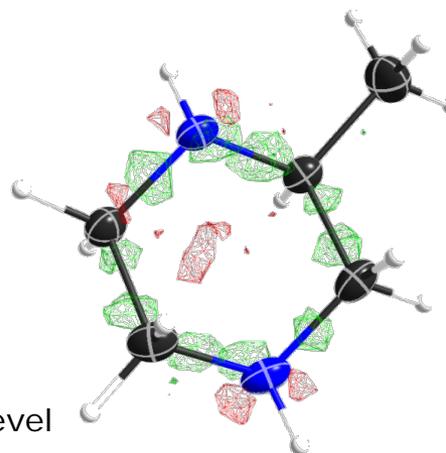
- Reduced R1
- Visual inspection of residual densities
- Can we do better?



R1 = 2.72%



R1 = 2.35%



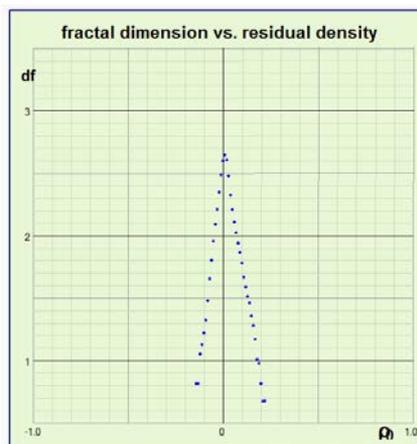
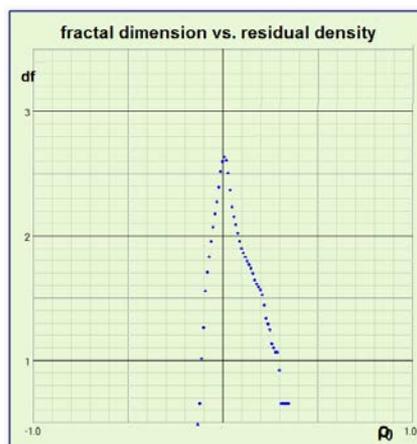
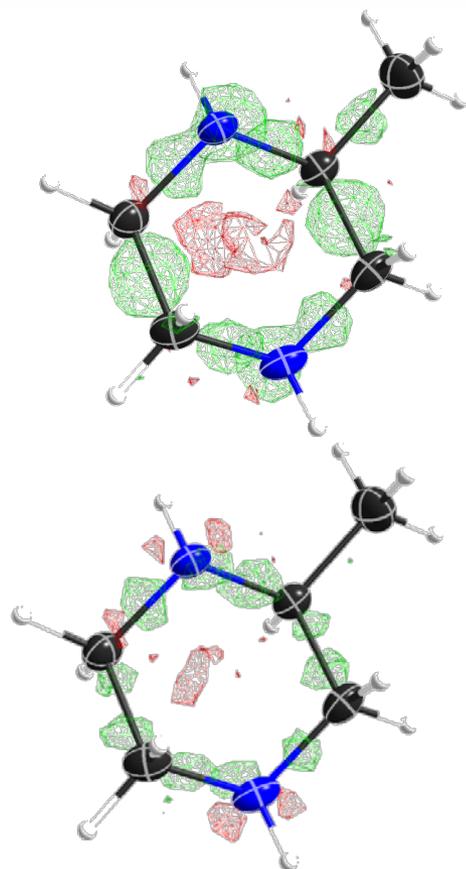
Methyl-Piperazine  
0.5Å data, Fo-Fc maps at same level

# IDEAL - Fractal dimension analysis



- Fractal dimension analysis

Foundations of residual-density analysis  
 Kathrin Meindl and Julian Henn  
 Acta Cryst. (2008). A64, 404–418



### Residual density descriptors

df0	2.65
pmin (d=2)	-0.067 eÅ <sup>-3</sup>
pmax (d=2)	0.070 eÅ <sup>-3</sup>
pmin	-0.141 eÅ <sup>-3</sup>
pmax	0.343 eÅ <sup>-3</sup>
e gross	3.59 e <sup>-</sup>
Δ ρ	0.484 e <sup>-</sup> Å <sup>-3</sup>

### Residual density descriptors

df0	2.66
pmin (d=2)	-0.051 eÅ <sup>-3</sup>
pmax (d=2)	0.064 eÅ <sup>-3</sup>
pmin	-0.154 eÅ <sup>-3</sup>
pmax	0.218 eÅ <sup>-3</sup>
e gross	3.00 e <sup>-</sup>
Δ ρ	0.372 e <sup>-</sup> Å <sup>-3</sup>

# Residual density descriptors

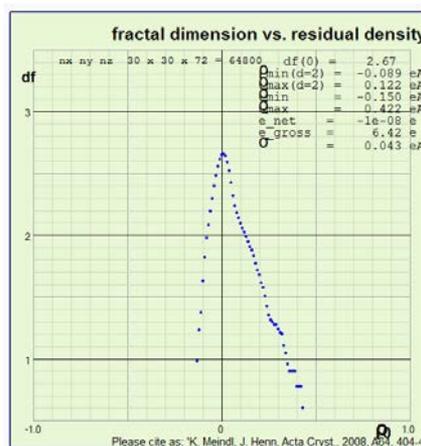
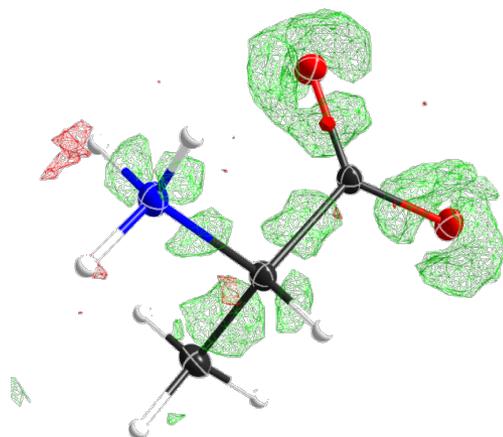
- **e gross** - The gross residual electrons describe the total inadequacies that arise from the following error:
  - Noise
  - Inadequate data processing
  - Density model errors
  - Can artificially lowered by truncating the experimental resolution
- **df0** - measure for the featurelessness of the residual density distribution
- The **shape** indicates the presence /absence of systematic errors
- **$\Delta \rho$**  - the width – indicates the flatness of the distribution

# IDEAL - Fractal dimension analysis



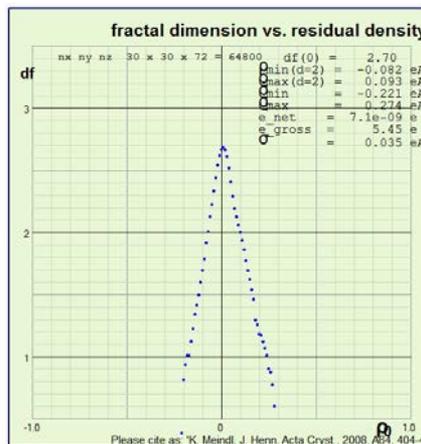
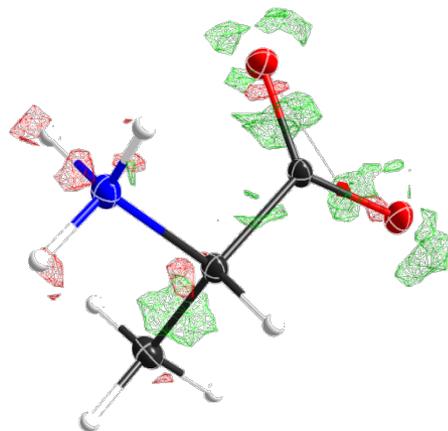
- Fractal dimension analysis

Foundations of residual-density analysis  
 Kathrin Meindl and Julian Henn  
 Acta Cryst. (2008). A64, 404–418



### Residual density descriptors

df0	2.67
$\rho_{\min}(d=2)$	-0.089 eÅ <sup>-3</sup>
$\rho_{\max}(d=2)$	0.122 eÅ <sup>-3</sup>
$\rho_{\min}$	-0.150 eÅ <sup>-3</sup>
$\rho_{\max}$	0.422 eÅ <sup>-3</sup>
e gross	6.42 e <sup>-</sup>
$\Delta \rho$	0.572 e <sup>-</sup> Å <sup>-3</sup>



### Residual density descriptors

df0	2.70
$\rho_{\min}(d=2)$	-0.082 eÅ <sup>-3</sup>
$\rho_{\max}(d=2)$	0.093 eÅ <sup>-3</sup>
$\rho_{\min}$	-0.221 eÅ <sup>-3</sup>
$\rho_{\max}$	0.274 eÅ <sup>-3</sup>
e gross	5.45 e <sup>-</sup>
$\Delta \rho$	0.495 e <sup>-</sup> Å <sup>-3</sup>

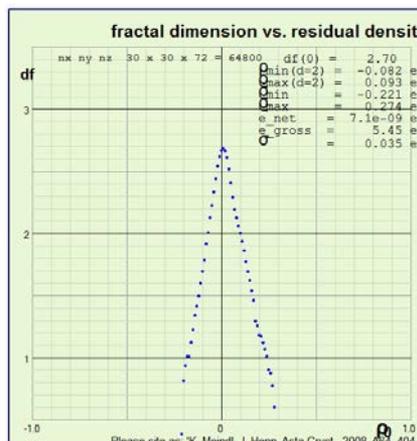
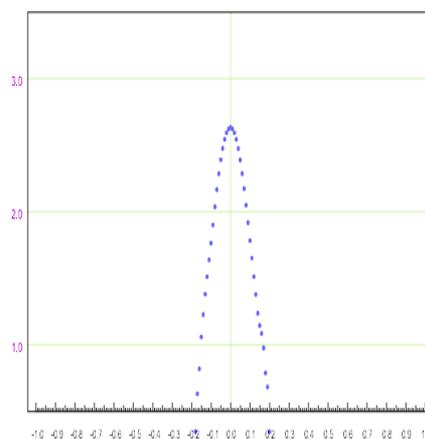
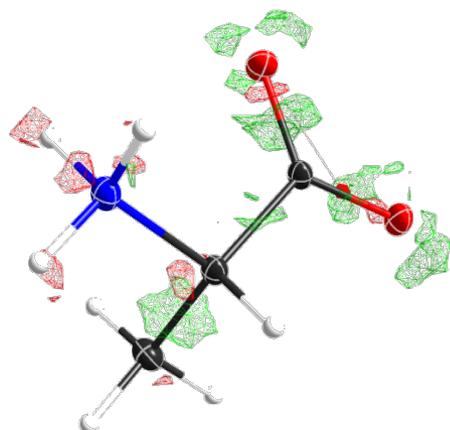
# IDEAL - Fractal dimension analysis

## how does it compare



- Fractal dimension analysis

MoPro Multipole refinement



Foundations of residual-density analysis  
Kathrin Meindl and Julian Henn  
Acta Cryst. (2008). A64, 404–418

### Residual density descriptors

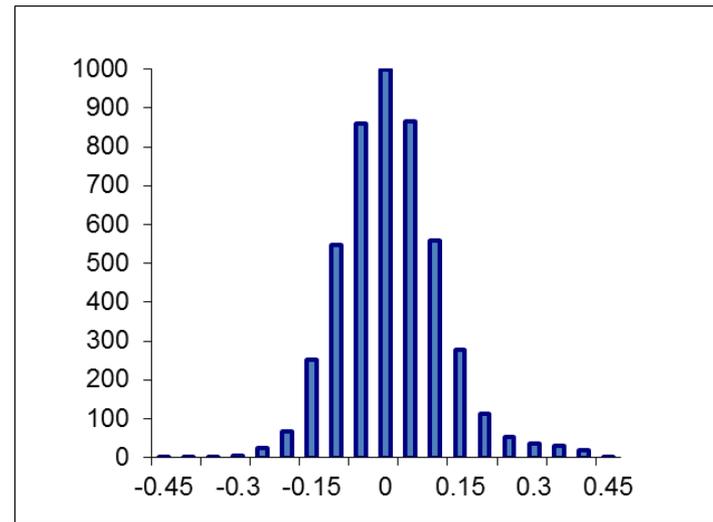
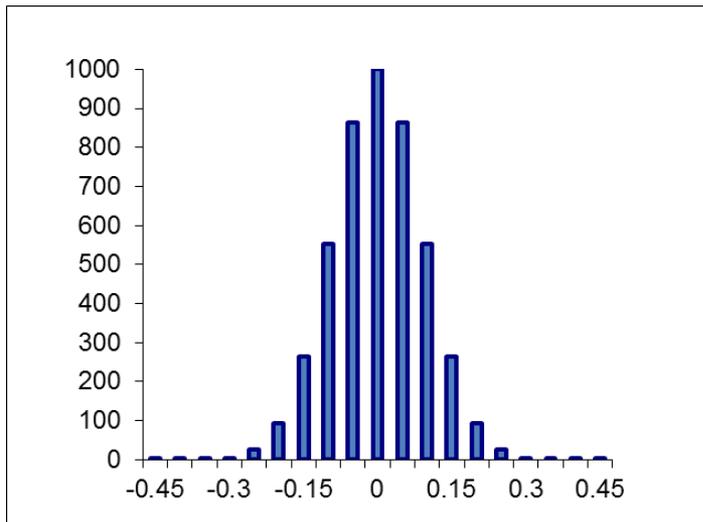
df0	2.6345
pmin (d=2)	-0.083 eÅ <sup>-3</sup>
pmax (d=2)	0.084 eÅ <sup>-3</sup>
pmin	-0.18 eÅ <sup>-3</sup>
pmax	0.21 eÅ <sup>-3</sup>
e gross	5.43 e <sup>-</sup>
Δ ρ	0.39 e <sup>-</sup> Å <sup>-3</sup>

### Residual density descriptors

df0	2.70
pmin (d=2)	-0.082 eÅ <sup>-3</sup>
pmax (d=2)	0.093 eÅ <sup>-3</sup>
pmin	-0.221 eÅ <sup>-3</sup>
pmax	0.274 eÅ <sup>-3</sup>
e gross	5.45 e <sup>-</sup>
Δ ρ	0.495 e <sup>-</sup> Å <sup>-3</sup>

# Residual density analysis

- A simple approach is to calculate a histogram of the residual density and compare it to a Gaussian distribution
- Due to the high frequency of residuals values close to zero details in the periphery cannot be observed easily

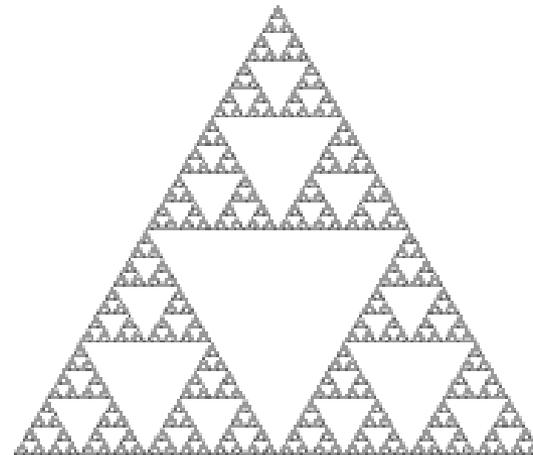


# Fractal dimension analysis

- A fractal analysis on how statistically self-similar the distribution of residual density is for a given structure
- Why fractal?



Your hand if you look closely enough



Sierpinski triangle

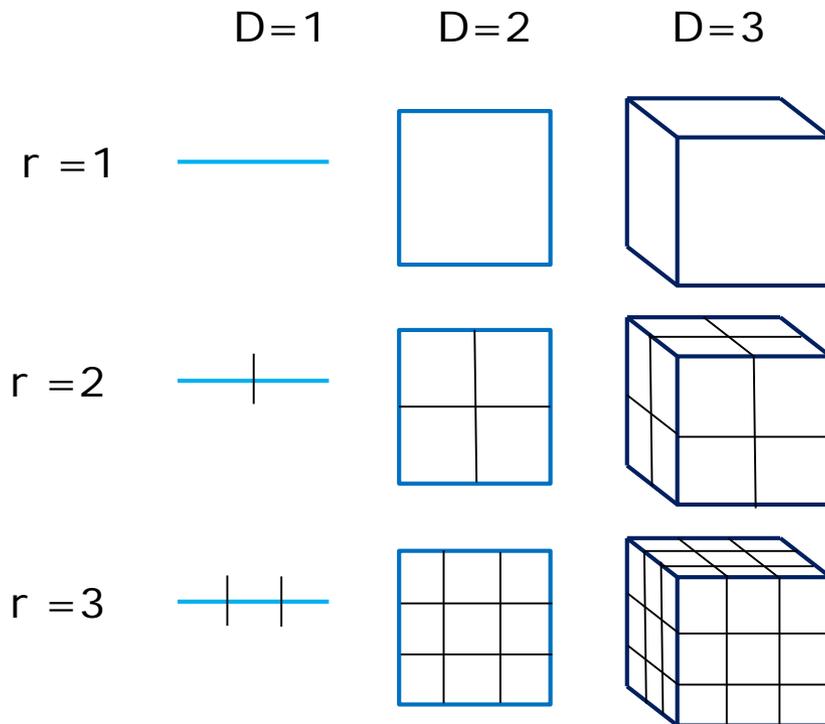
# What is a fractal dimension?

- **The Concept of Dimension**

- The three dimensions of Euclidean space ( $D=1,2,3$ )

- **The Hausdorff Dimension (or Fractal dimension)**

- Fractals, which are irregular geometric objects, require another meaning, the fractal dimension as a measure of how self-similar the object is



- Object residing in Euclidean dimension  $D$
- Reduce its linear size by  $1/r$  in each spatial direction (length, area, or volume)
- The number of objects increases to  $N=r^D$  times the original
- take the log of both sides of  $N=r^D$
- $\log(N) = D \log(r)$ .

- **$D = \log(N)/\log(r)$**

- **$D = \frac{\log(\text{number of self-similar pieces})}{\log(\text{magnification factor})}$**
- $D$  need not be an integer, as it is in Euclidean geometry
- This generalized treatment of dimension is named after the German mathematician, Felix Hausdorff
- It has proved useful for describing natural objects and for evaluating trajectories of dynamic systems

# Fractal dimension distribution of the residual density

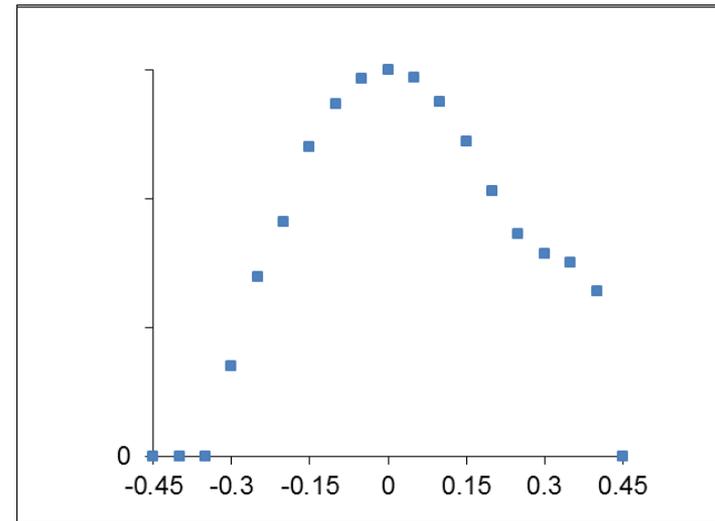
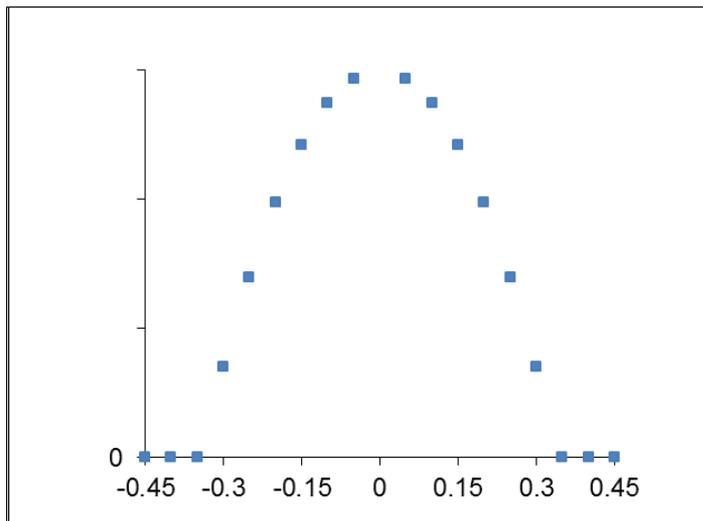


- The fractal dimension of a residual-density iso-surface of constant value  $x$  can be evaluated by a box counting algorithm using a finite grid
- If one is interested in the zero residual-density iso-surface, one just counts the number of boxes containing at least one point of zero residual density
- In the special case of a distribution containing Gaussian noise with a mean of zero and no model errors it follows that the corresponding fractal dimension distribution is of parabolic shape

# Fractal dimension in residual density analysis



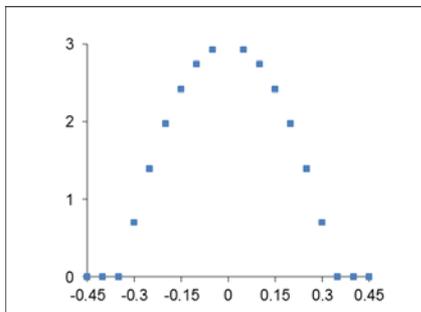
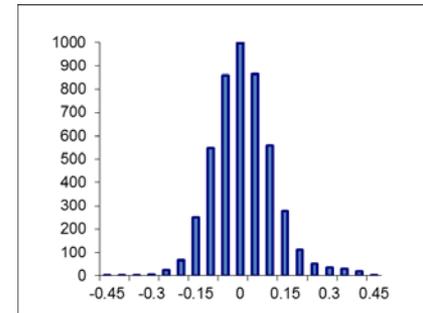
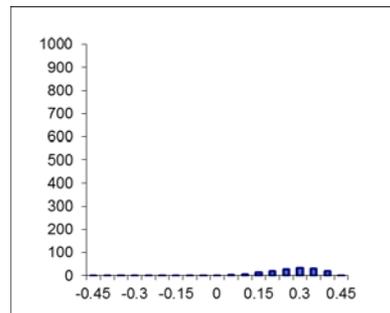
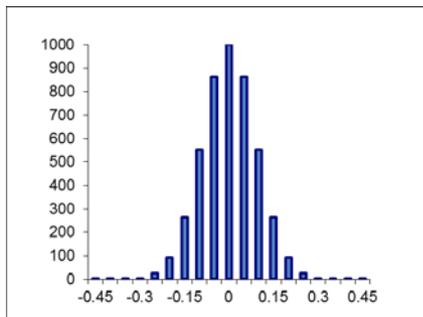
- In the special case of a of a distribution containing Gaussian noise with a mean of zero and no model errors the corresponding fractal dimension distribution is of parabolic shape
- The max value of  $df_0$  is 3



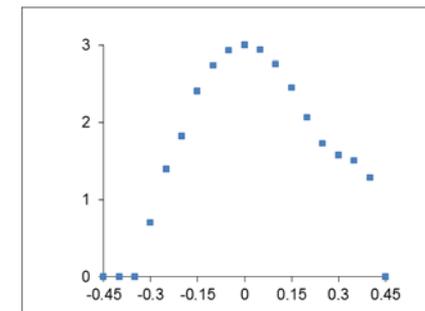
# Fractal dimension in residual density analysis



- So where does the shoulder come from?



Adding some  
positive residuals  
causes a shoulder  
to appear on the  
parabola



# IDEAL - Fractal dimension analysis



- Fractal dimension analysis

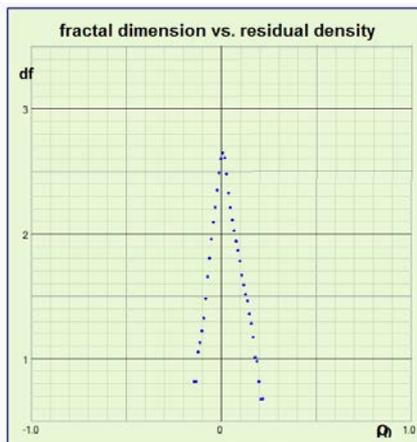
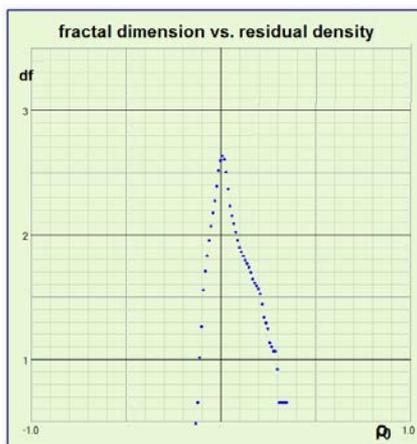
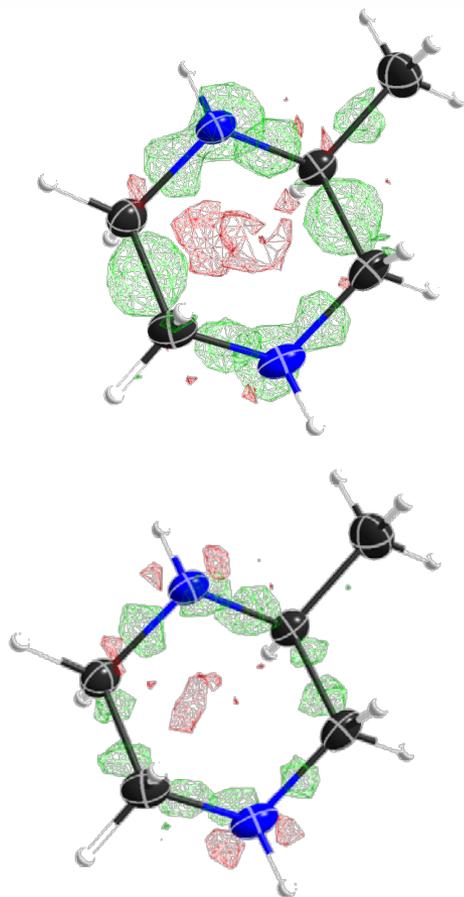
Foundations of residual-density analysis  
Kathrin Meindl and Julian Henn  
Acta Cryst. (2008). A64, 404–418

### Residual density descriptors

df0	2.65
pmin	-0.141 eÅ <sup>-3</sup>
pmax	0.343 eÅ <sup>-3</sup>
e gross	3.59 e <sup>-</sup>
Δ ρ	0.484 e <sup>-</sup> Å <sup>-3</sup>

### Residual density descriptors

df0	2.66
pmin	-0.154 eÅ <sup>-3</sup>
pmax	0.218 eÅ <sup>-3</sup>
e gross	3.00 e <sup>-</sup>
Δ ρ	0.372 e <sup>-</sup> Å <sup>-3</sup>



# IDEAL–The Value Proposition

- Better structure description – better R values
  - Increased model accuracy
  - Access to more detailed model properties
  - Easy to use
  - Fully automated - Interactivity optional
  - Seamless integration into APEX3
  - Compatibility with checkcif
- 
- IDEAL is proprietary to Bruker
  - XL with BEDE and LONE functionality will be exclusive to Bruker for 5 years

# Questions and Answers



Any questions?

Please type any questions you may have for our speakers in the [Q&A panel](#) and click Send.

Thank you!





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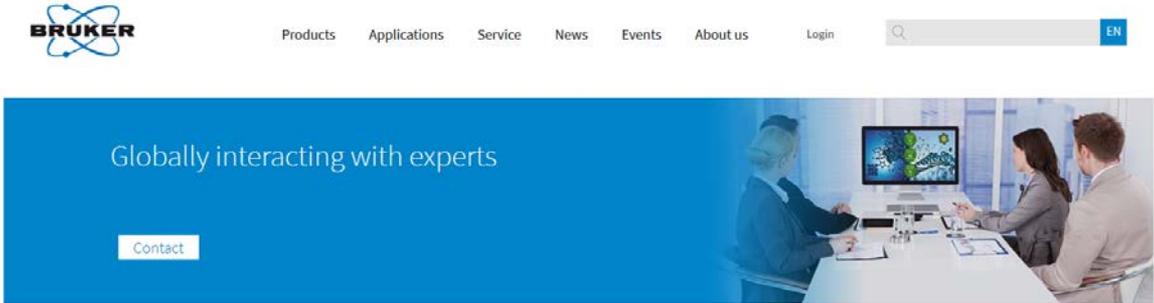
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Webinar	Content
Jul 10, 2018	In this 45-minute webinar Jens Lubben and Michael Ruf will talk about a new addition to Bruker's APEX3 software for structure analysis: IDEAL - Invarium Derived Electron Analysis. Jens will introduce you to the theory of IDEAL, while Michael will focus on its practical application and implementation in APEX3.
IDEAL - Invarium Derived Electron Analysis: Have the Cake and Eat It Too!	<a href="#">Register now!</a>

単結晶線構造解析の測定において一つの反射強度をできるだけ正確にS/Nよく測定することは、言うまでもなく最重要課題です。装置は年々進化し、そのパフォーマンスはどんどんよくなっています。同じ測定方法で測定し、より高いS/Nを得るには、

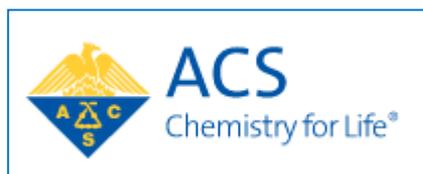
Webinar	Content
Dec 12, 2016	In this 45-minute webinar, Przemyslaw Dera and Michael Ruf will talk about high-pressure crystallography performed on a Bruker home-lab instrument. Przemek's will start with a brief introduction to high-pressure crystallography.
High-pressure X-ray Crystallography for the Home Lab	<a href="#">View recording or download slides</a>

Oct 25, 2016	In this 40-minute webinar, Matt Benning will discuss the current trends in Native SAD phasing. This webinar will focus on the basic theory and experimental practices involved in SAD phasing as well as sub-structure determination and phasing using the SHELX suite.
Protein X-ray Crystallography: Native SAD	

Meet us at these upcoming events



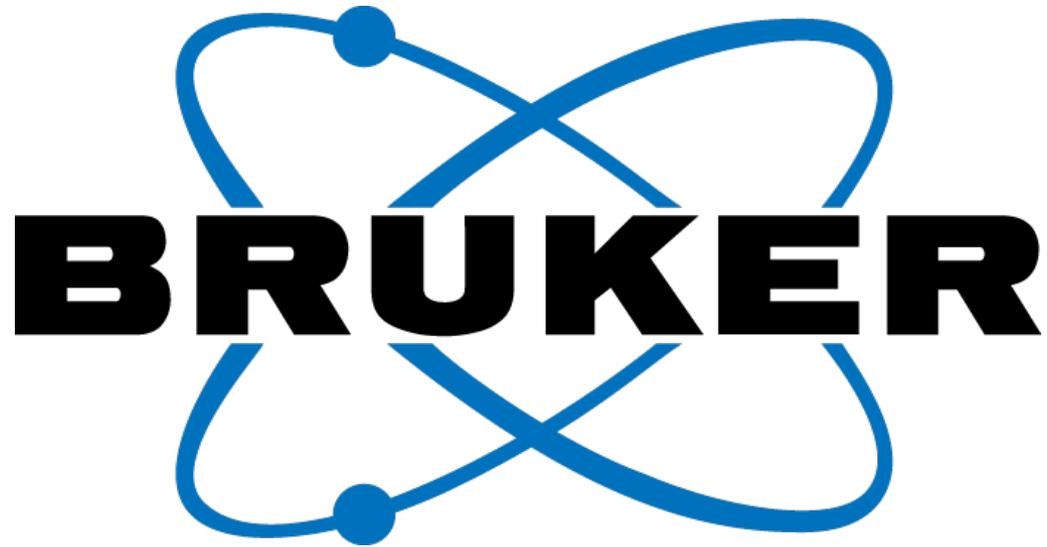
**ACA Annual Meeting**  
July 20 to 24, 2018  
Toronto, Canada



**ACS Fall Meeting**  
Aug 19 to 23, 2018  
Boston, Massachusetts, USA



**ECM31, European Crystallographic Meeting**  
Aug 20 to 27, 2018  
Oviedo, Spain



Innovation with Integrity