PLATON/SQUEEZE

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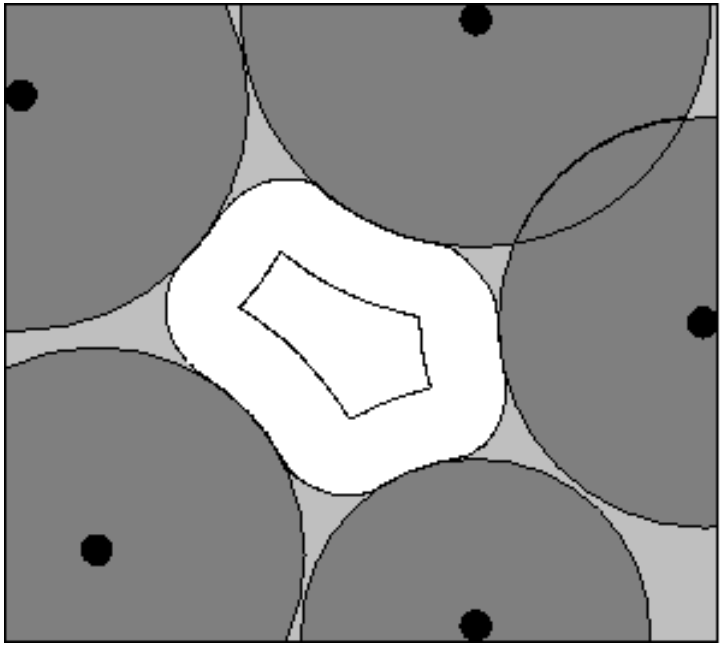


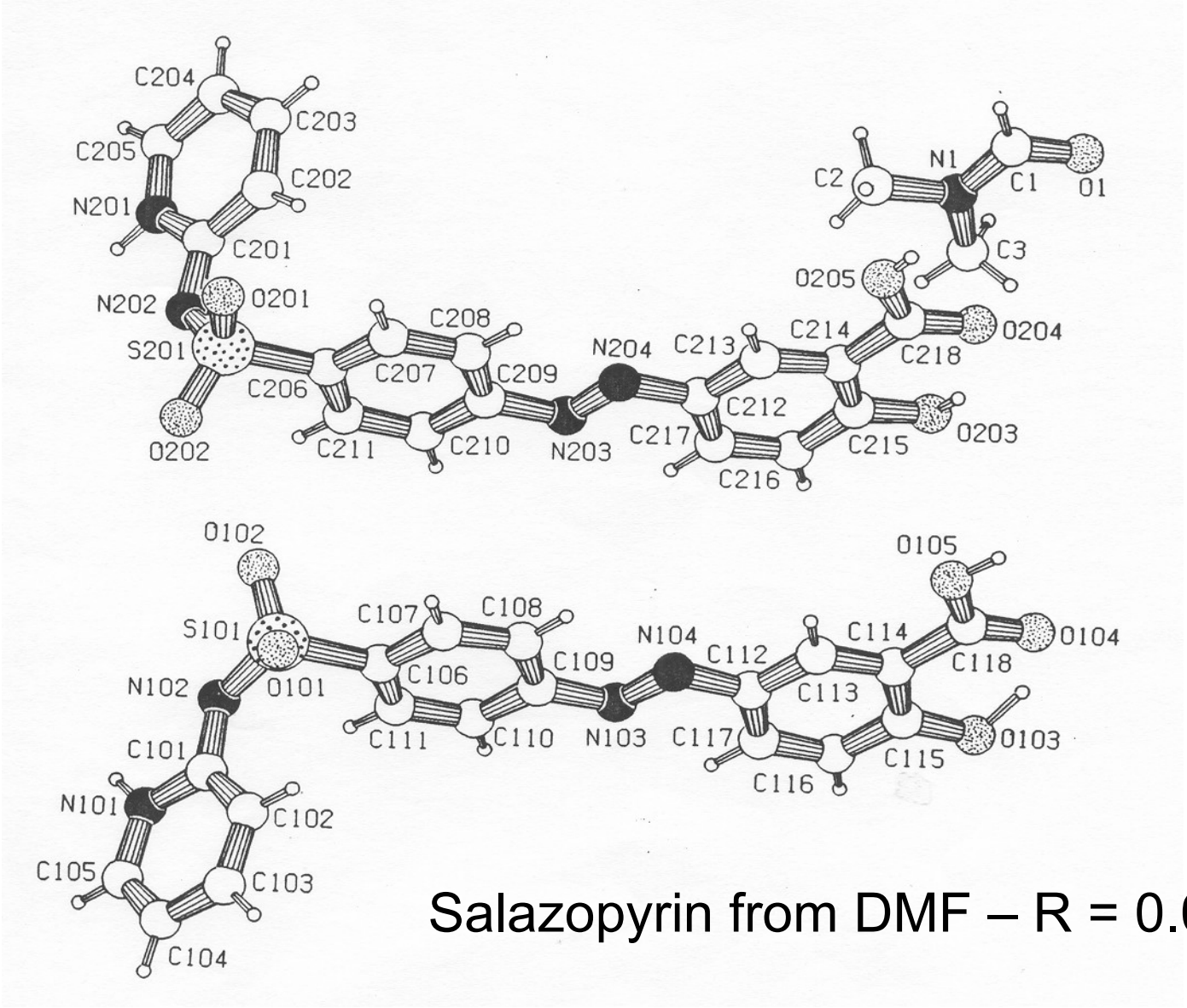
PLATON Workshop

Chicago, 24-July-2010

The Disordered Solvent Problem

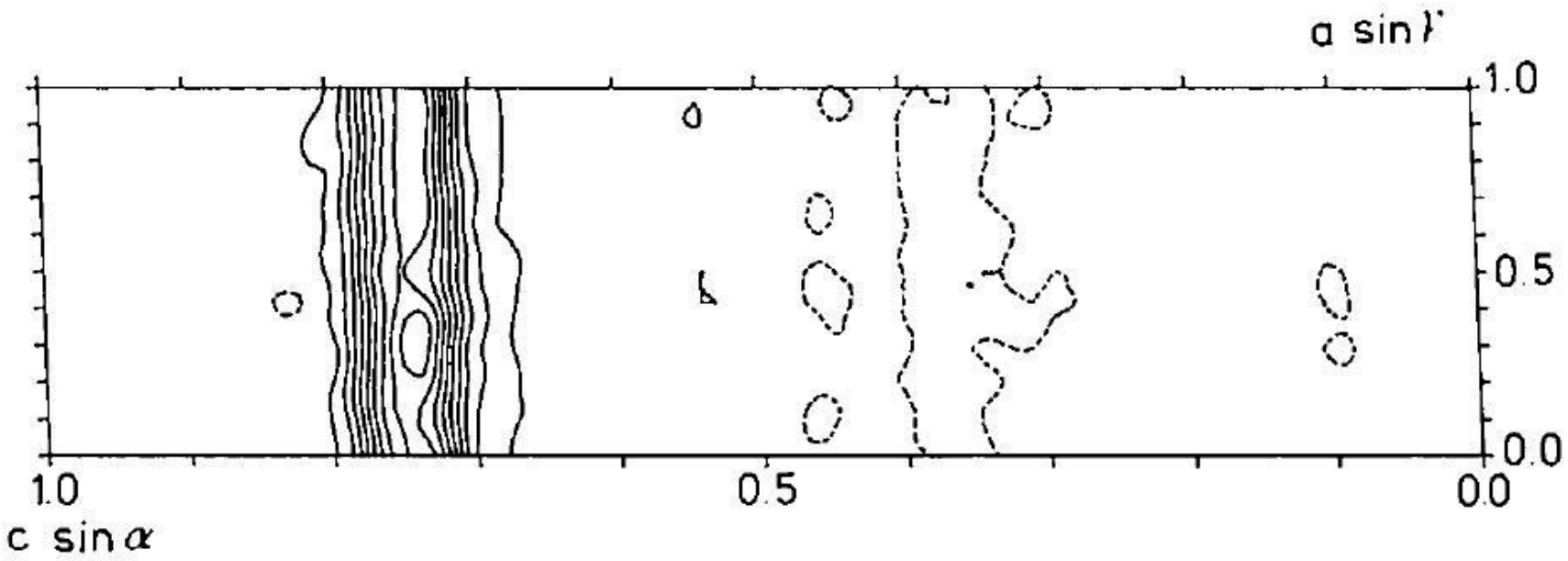
- Molecules of interest often co-crystallize (only) with the inclusion of a suitable solvent molecule.
- Solvent molecules often fill voids in a structure with little interaction and are often located on symmetry sites and with population less than 1.0
- Sometimes even the nature of the (mixture) of included solvent(s) is unclear.
- Inclusion of the scattering contribution of the solvent to the structure factors can be done either with an (elaborate) disorder model or with the SQUEEZE approach.

THE MOLECULE THAT INVOKED THE BYPASS/SQUEEZE TOOL



Salazopyrin from DMF – R = 0.096

Structure Modelling and Refinement Problem for the Salazopyrin Structure

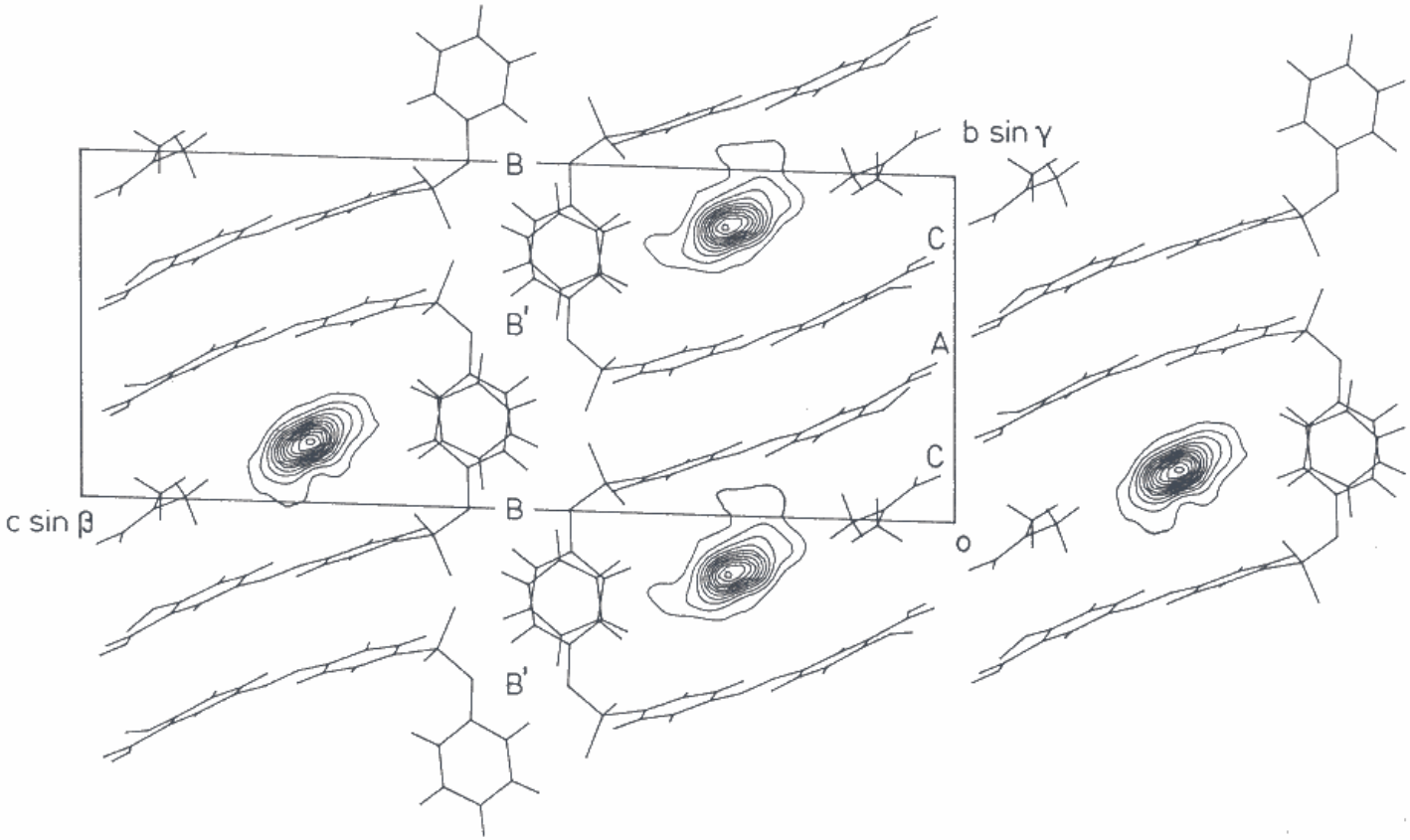


Difference Fourier map shows channels with continuous density rather than maxima

How to handle this in the Refinement ?

SQUEEZE !

Looking down the Infinite Channels in the Salazopyrin Structure

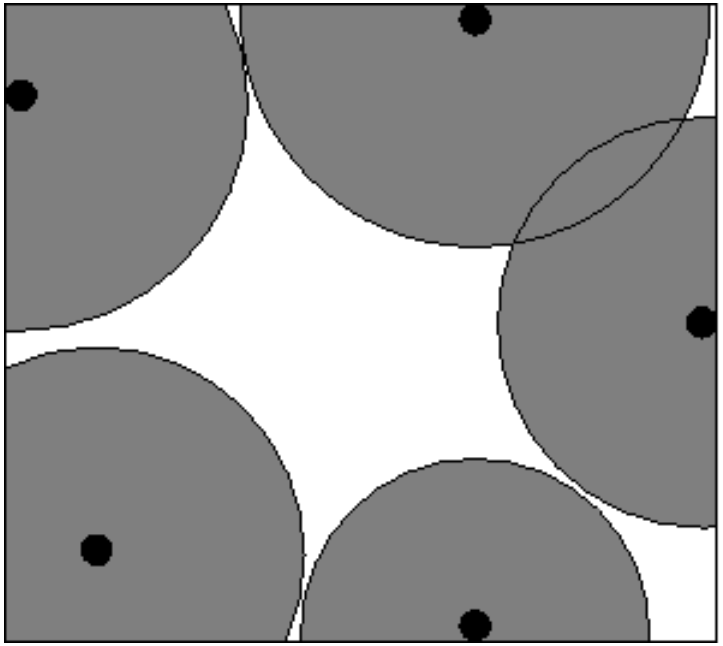


The Problem: Peak Search algorithms will not always tell about the residual density. We need special tools to detect voids in a modeled structure.

Automated Detection of Solvent Accessible Voids

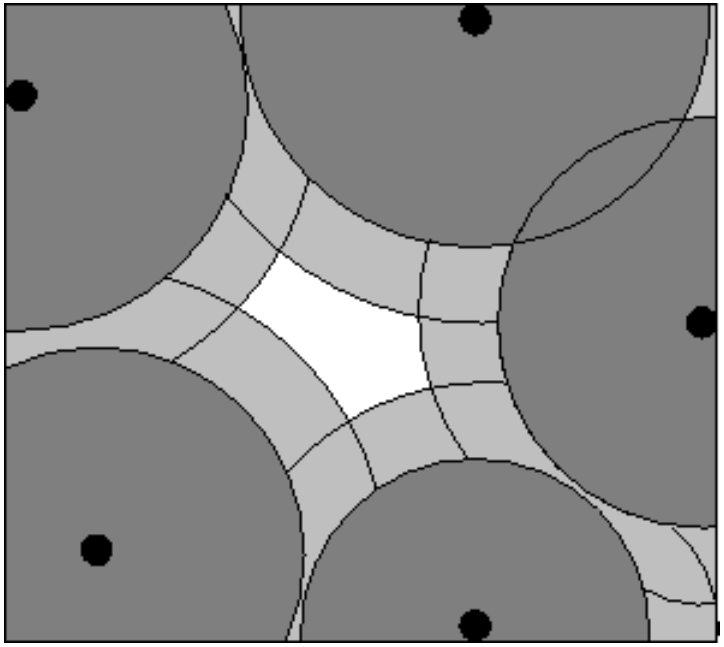
- A typical crystal structure has only in the order of 65% of the available space filled.
- The remainder volume is in voids (cusps) in-between atoms (too small to accommodate an H-atom)
- Solvent accessible voids can be defined as regions in the structure that can accommodate at least a sphere with radius 1.2 Angstrom without intersecting with any of the van der Waals spheres assigned to each atom in the structure.
- Next Slide: Void Algorithm: Cartoon Style ➔

LOCATE SOLVENT ACCESSIBLE VOID



STEP #1 – EXCLUDE VOLUME INSIDE THE VAN DER WAALS SPHERE

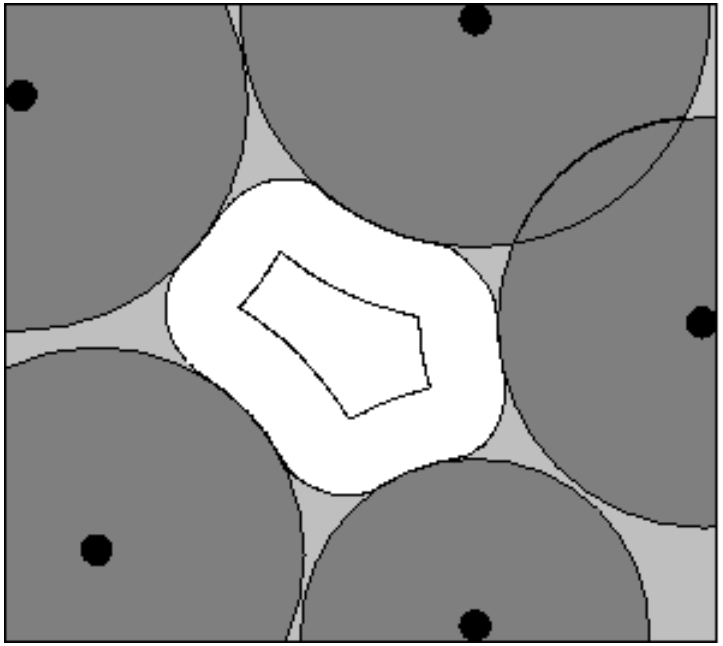
LOCATE SOLVENT ACCESSIBLE VOID



White Area:
Ohashi Volume.
Location of possible
Atom centers

STEP # 2 – EXCLUDE AN ACCESS RADIAL VOLUME TO FIND THE LOCATION OF ATOMS WITH THEIR CENTRE AT LEAST 1.2 ANGSTROM AWAY

LOCATE SOLVENT ACCESSIBLE VOID



STEP # 3 – EXTEND INNER VOLUME WITH POINTS WITHIN 1.2 ANGSTROM FROM ITS OUTER BOUNDS

VOID SEARCH ALGORITHM

- Move a probe with radius 1.2 Ang over a fine (0.2 Angstrom) grid through the unit cell.
- Start a new void when a grid point is found that is at least 1.2 Angstrom outside the van der Waals surface of all atoms.
- Expand this void with connected grid points with the same property until completed.
- Find new starting grid point for the next void until completion.
- Expand the ‘Ohashi’ volumes with grid points within 1.2 Angstrom to surface grid points.

P.L.A.T.O.N

Search for and Analysis of Solvent Accessible Voids in the Structure

Area	#GridPoint	VolPerc.	Vol(A^3)	X(av)	Y(av)	Z(av)	Eigenvector(frac)			Sig(Ang)
1	20126[4072]	4	156[31.6]	0.000	0.184	0.750	1	1.000	-0.003	0.520	1.74
							2	-0.502	-0.002	1.000	1.55
							3	-0.001	-1.000	-0.002	1.35
2	20134[4072]	4	156[31.6]	0.500	0.316	0.250	1	1.000	-0.006	0.521	1.74
							2	-0.503	0.002	1.000	1.55
							3	-0.003	-1.000	-0.001	1.35
3	20125[4072]	4	156[31.6]	0.500	0.684	0.750	1	1.000	-0.008	0.522	1.74
							2	-0.504	-0.005	1.000	1.55
							3	-0.003	-1.000	-0.004	1.35
4	20131[4072]	4	156[31.6]	0.000	0.816	0.250	1	1.000	-0.003	0.523	1.74
							2	-0.505	-0.002	1.000	1.55
							3	-0.001	-1.000	-0.002	1.35

Listing of all voids in the unit cell

The numbers in [ ] refer to the Ohashi Volume

EXAMPLE OF A VOID ANALYSIS

SOLV MENU

Stereo Opts

DotsContour

ViewX0

ViewY0

ViewZ0

Reverse-B&W

VoidAxes

UnitSymPack

Resd012..

UnitFill

Void0123...

UnitCellBox

Show-Mol

Ohashi-Vol

LabelCell

Label -Hat+

LabelSize >

<<-RotZ+>>

<<-RotY+>>

<<-RotX+>>

Color

Decoration

EPS-File

End

INSTRUCTION INPUT via KEYBOARD or LEFT-MOUSE-CLICKS (HELP with RIGHT CLICKS)

Solvent Accessible Void Found (See Listing for Details)

>> Continue (Y/N[Y])

Exit

MenuActive

VOID APPLICATIONS

- Detection of (possibly missed) Solvent Accessible Voids in a Structure
- Calculation of the Kitaigorodskii Packing Index
- Determination of the available space in solid state reactions (Ohashi)
- Determination of pore volumes, pore shapes and migration paths in micro-porous crystals
- As part of the SQUEEZE routine to handle the contribution of disordered solvents in a crystal structure refinement.

SQUEEZE

- Takes the contribution of disordered solvents to the calculated structure factors into account by back-Fourier transformation of density found in the ‘solvent accessible volume’ outside the ordered part of the structure (iterated).
- Two Options:
- Refine with SHELXL using the solvent free .hkl
- Or use CRYSTALS using the SQUEEZE solvent contribution to F(calc) and the full F(obs).
- Note:SHELXL lacks option for fixed contribution to Structure Factor Calculation.

Informal Theory of the SQUEEZE Procedure

$$F_H = \int_V \rho(\vec{r})\, e^{2\pi i\, \vec{H}\cdot\vec{r}}\, dV$$

$$= \int_V \left(\rho^M(\vec{r}) + \rho^S(\vec{r})\right) e^{2\pi i\, \vec{H}\cdot\vec{r}}\, dV$$

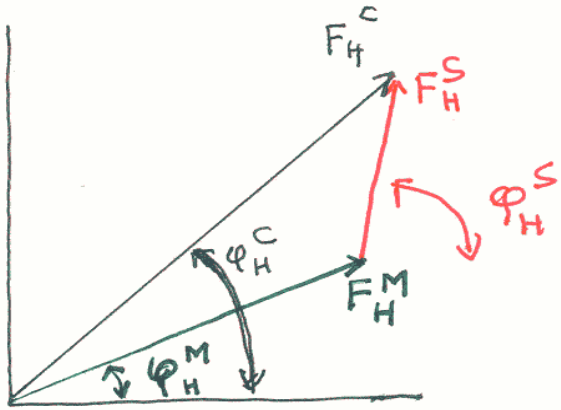
$$\rho^M(\vec{r}) = \sum_{j=1}^{N} \rho(\vec{r} - \vec{r}_j)$$

$$F_H^M = \sum_{j=1}^{N} f_j\, e^{2\pi i\, \vec{H}\cdot\vec{r}_j}$$

$$\approx \Delta\rho(\vec{r}_k) \text{ on grid}$$

$$F_H^S = V_q \sum_S \Delta\rho(\vec{r}_k)\, e^{2\pi i\, \vec{H}\cdot\vec{r}_k}$$

$$F_H^C = F_H^M + F_H^S \Longrightarrow$$



M = Ordered

S = Solvent

Iterate (Initially $\rho_H^S = \rho_H^M$)

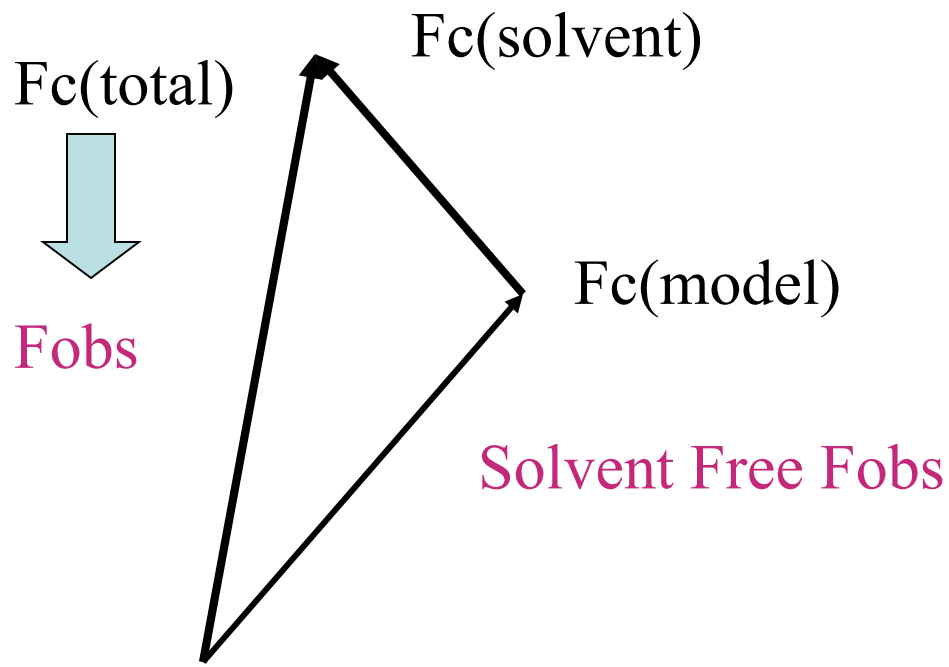
$$\Delta\rho(\vec{r}) = \frac{1}{V} \sum_H \left(s|F_H^o| e^{i\varphi_H^C} - |F_H^M| e^{i\varphi_H^M}\right) e^{-2\pi i\, \vec{H}\cdot\vec{r}} + \frac{F_o^S}{V}$$

Solvent Free ElectronCount

$$F_H^o : F_H^{o'} = |F_H^o| e^{i\varphi^C} - |F_H^S| e^{i\varphi^S}$$

$$: V_q \sum_S \Delta\rho(\vec{r}_k)$$

SQUEEZE
In the Complex Plane



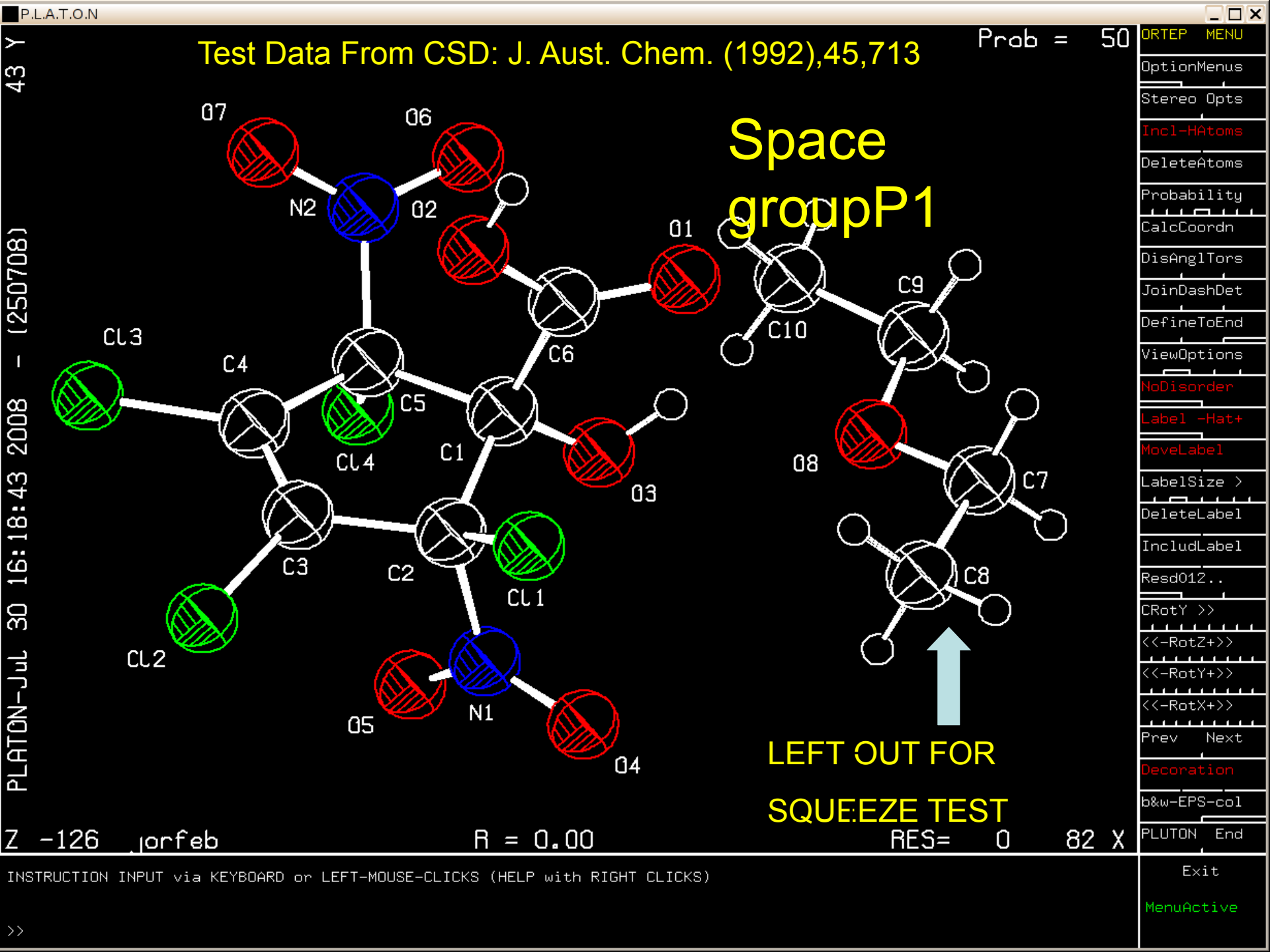
Black: Split Fc into a discrete and solvent contribution
Red: For SHELX refinement, temporarily substract recovered solvent contribution from Fobs.

SQUEEZE Algorithm

1. Calculate difference Fourier map (FFT)
2. Use the VOID-map as a mask on the FFT-map to set all density outside the VOID's to zero.
3. FFT^{-1} this masked Difference map -> contribution of the disordered solvent to the structure factors
4. Calculate an improved difference map with F(obs) phases based on F(calc) including the recovered solvent contribution and F(calc) without the solvent contribution.
5. Recycle to 2 until convergence.

Test Example with Calculated Data

- ‘Observed Data’ were calculated from the published coordinates.
- The ether molecule was subsequently removed
- SQUEEZE was tested to see whether the method recovers the ether contribution to the structure factors.


P.L.A.T.O.N
Test Data From CSD: J. Aust. Chem. (1992),45,713
Prob = 50
Space groupP1
LEFT OUT FOR SQUEEZE TEST
O7
O6
N2
O2
O1
C9
C10
Cl3
C4
C6
C5
Cl4
C1
O3
O8
C7
C3
C2
Cl1
C8
Cl2
O5
N1
O4
PLATON-Jul 30 16:18:43 2008 - (250708)
43 Y
Z -126 jorfeb R = 0.00 RES= 0 82 X
ORTEP MENU
OptionMenus
Stereo Opts
Incl-HAtoms
DeleteAtoms
Probability
CalcCoordn
DisAnglTors
JoinDashDet
DefineToEnd
ViewOptions
NoDisorder
Label -Hat+
MoveLabel
LabelSize >
DeleteLabel
IncludLabel
Resd012..
CRotY >>
<<-RotZ+>>
<<-RotY+>>
<<-RotX+>>
Prev Next
Decoration
b&w-EPS-col
PLUTON End
INSTRUCTION INPUT via KEYBOARD or LEFT-MOUSE-CLICKS (HELP with RIGHT CLICKS)
>>
Exit
MenuActive

P.L.A.T.O.N

Search for and Analysis of Solvent Accessible Voids in the Structure

Area	#GridPoint	VolPerc.	Vol(A^3)	X(av)	Y(av)	Z(av)	Eigenvector(frac)			Sig(Ang)
1	21054[3308]	34	144[22.6]	0.178	0.014	0.183	1	0.120	1.000	0.235	2.32
							2	0.980	-0.903	1.000	1.37
							3	1.000	0.275	-0.605	1.27

A solvent accessible volume of 144 Ang**3 is found

This volume will be used as a mask on the difference Fourier map following the SQUEEZE recycling method

PLATON MENU
OptionMenus
NoMove
Color
Organic
Round
Parentheses
Label-Alias
R/S-Determ
Norm-H-bond
NoSymm
Join-Expand
LstARU RCel
LstCellSymm
ListAtoms
ListBonds
LstFlagRadi
Exclude H
MinQPeakHgt
MinQPeakDis
Q-Peak-Incl
KeyInstruct
Prev Next
SAVE-InstrS
ENTRY-LIST
Reset End

INSTRUCTION INPUT via KEYBOARD or LEFT-MOUSE-CLICKS (HELP with RIGHT CLICKS)

Solvent Accessible Void Found (See Listing for Details)
>> Hit RETURN to Continue

Exit
MenuActive

P.L.A.T.O.N

PLATON/SQUEEZE

Cycle	R(F)	Nref(Heml)	R(F .gt. 4Slg	Nref	El/Cell
1	0.180	1943	0.159	1938	0
2	0.085	1943	0.075	1938	27
3	0.040	1943	0.035	1938	42
4	0.031	1943	0.027	1938	43
5	0.027	1943	0.024	1938	43
6	0.024	1943	0.022	1938	43

When the SQUEEZE Recycling converges, 43 ‘electrons’ are Recovered from the difference density map.

This is close to the expected 42 electrons corresponding to Diethyl ether

PLATON MENU
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Label-Alias
R/S-Determ
Norm-H-bond
NoSymm
Join-Expand
LstARU RCel
LstCellSymm
ListAtoms
ListBonds
LstFlagRadi
Exclude H
MinQPeakHgt
MinQPeakDis
Q-Peak-Incl
KeyInstruct
Prev Next
SAVE-InstrS
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Reset End

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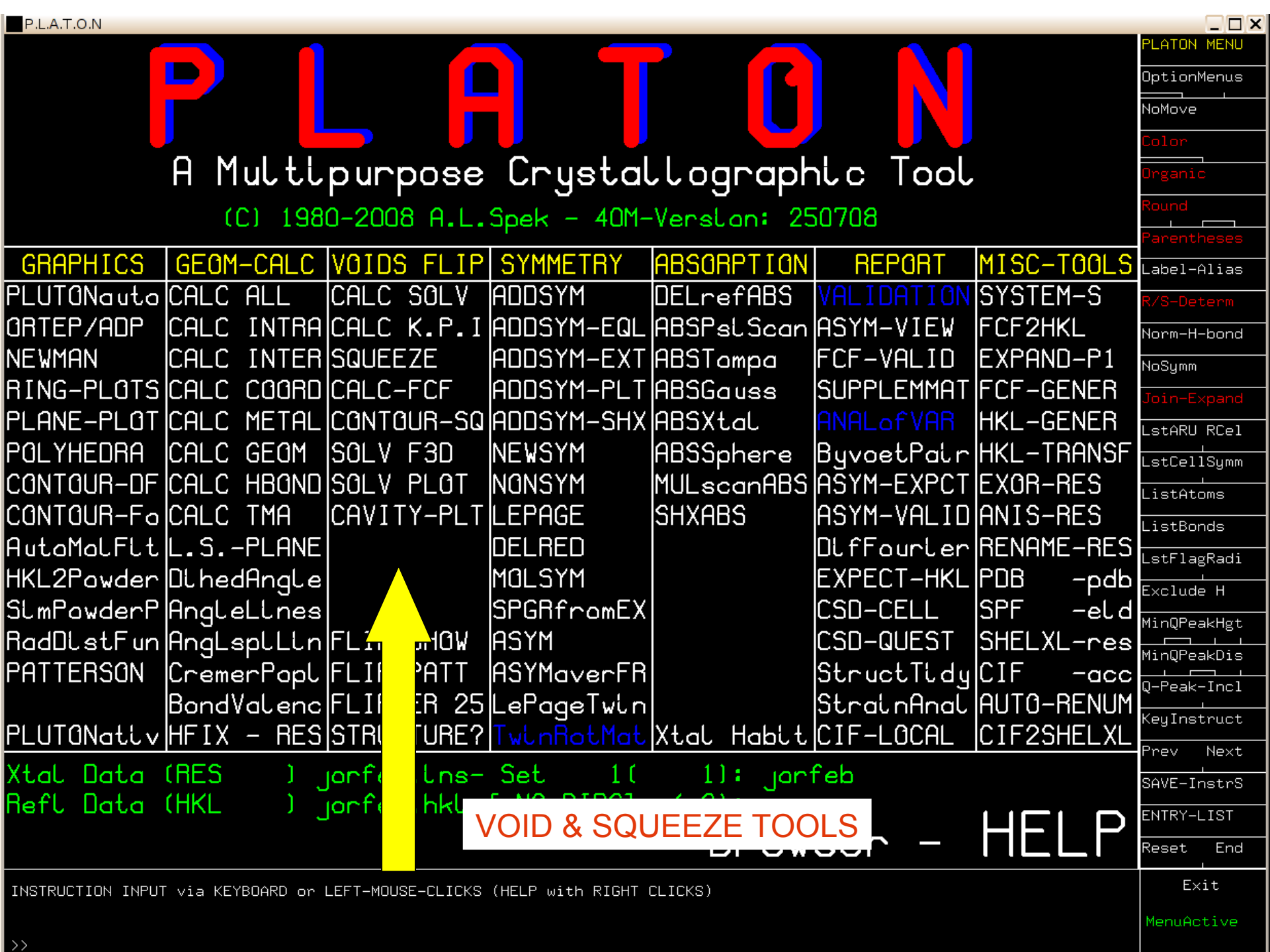
>> Hit RETURN to Continue

Exit

MenuActive


P.L.A.T.O.N
P L A T O N
A Multipurpose Crystallographic Tool
(C) 1980-2008 A.L.Spek - 40M-Version: 250708
GRAPHICS
PLUTONauto
ORTEP/ADP
NEWMAN
RING-PLOTS
PLANE-PLOT
POLYHEDRA
CONTOUR-DF
CONTOUR-Fo
AutoMolFlt
HKL2Powder
SlmPowderP
RadDistFun
PATTERSON
PLUTONatlv
GEOM-CALC
CALC ALL
CALC INTRA
CALC INTER
CALC COORD
CALC METAL
CALC GEOM
CALC HBOND
CALC TMA
L.S.-PLANE
DihedAngle
AngleLines
AngLsplLln
CremerPopl
BondValenc
HFIX - RES
VOIDS FLIP
CALC SOLV
CALC K.P.I
SQUEEZE
CALC-FCF
CONTOUR-SQ
SOLV F3D
SOLV PLOT
CAVITY-PLT
SYMMETRY
ADDSYM
ADDSYM-EQL
ADDSYM-EXT
ADDSYM-PLT
ADDSYM-SHX
NEWSYM
NONSYM
LEPAGE
DELRED
MOLSYM
SPGRfromEX
ASYM
ASYMaverFR
LePageTwin
TwinRotMat
ABSORPTION
DELrefABS
ABSPslScan
ABSTompa
ABSGauss
ABSXtal
ABSSphere
MULscanABS
SHXABS
Xtal Habit
REPORT
VALIDATION
ASYM-VIEW
FCF-VALID
SUPPLEMMAT
ANALofVAR
ByvoetPair
ASYM-EXPCT
ASYM-VALID
DiffFourier
EXPECT-HKL
CSD-CELL
CSD-QUEST
StructTidy
StrainAnal
CIF-LOCAL
MISC-TOOLS
SYSTEM-S
FCF2HKL
EXPAND-P1
FCF-GENER
HKL-GENER
HKL-TRANSF
EXOR-RES
ANIS-RES
RENAME-RES
PDB -pdb
SPF -eld
SHELXL-res
CIF -acc
AUTO-RENUM
CIF2SHELXL
Xtal Data (RES) jorfeb
Refl Data (HKL) jorfeb
VOID & SQUEEZE TOOLS
HELP
INSTRUCTION INPUT via KEYBOARD or LEFT-MOUSE-CLICKS (HELP with RIGHT CLICKS)
>>
PLATON MENU
OptionMenus
NoMove
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Organic
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Parentheses
Label-Alias
R/S-Determ
Norm-H-bond
NoSymm
Join-Expand
LstARU RCel
LstCellSymm
ListAtoms
ListBonds
LstFlagRadi
Exclude H
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MinQPeakDis
Q-Peak-Incl
KeyInstruct
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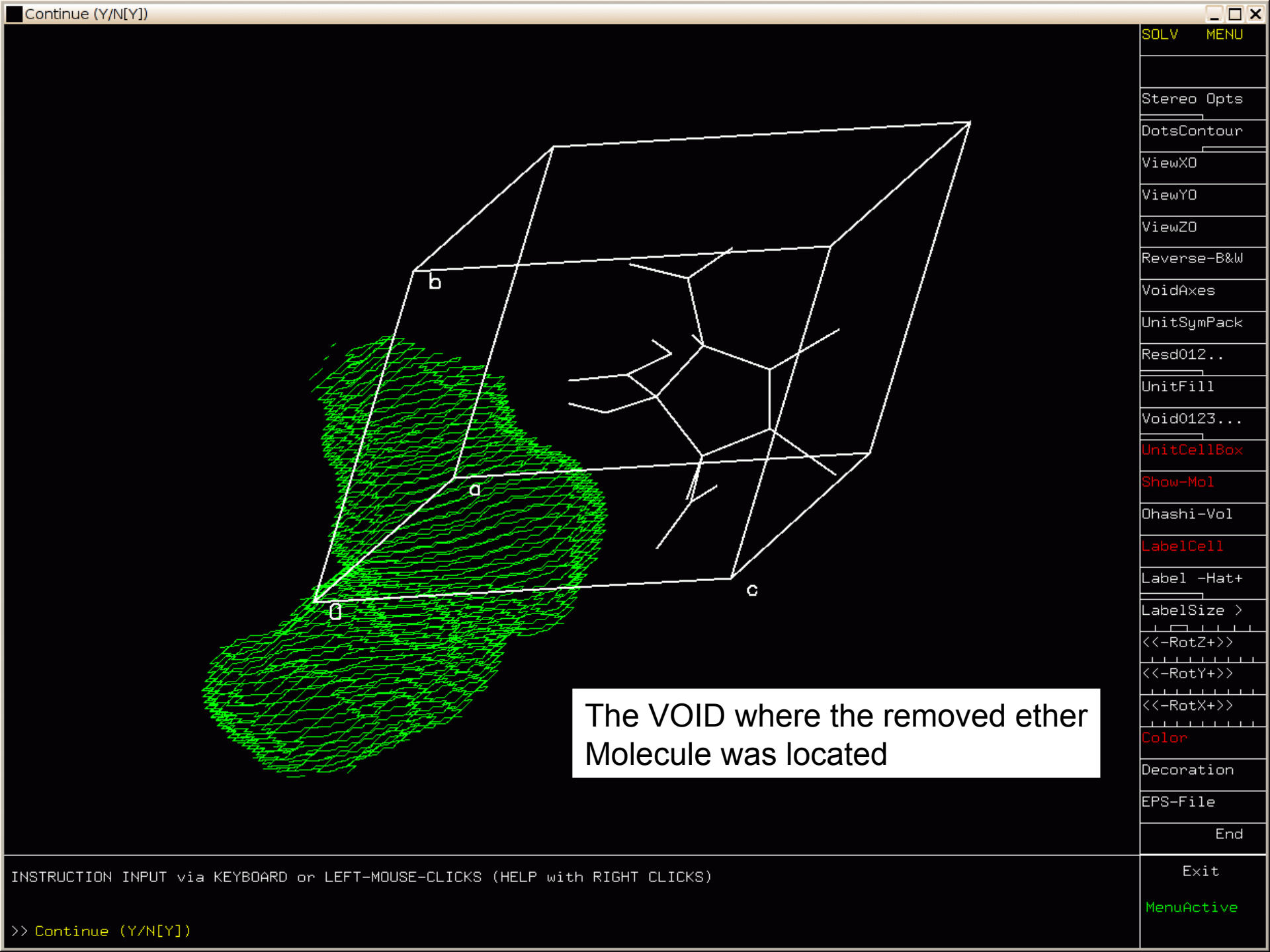
Reset End
Exit
MenuActive


Continue (Y/N[Y])
SOLV MENU
Stereo Opts
DotsContour
ViewXO
ViewYO
ViewZO
Reverse-B&W
VoidAxes
UnitSymPack
Resd012..
UnitFill
Void0123...
UnitCellBox
Show-Mol
Ohashi-Vol
LabelCell
Label -Hat+
LabelSize >
<<-RotZ+>>
<<-RotY+>>
<<-RotX+>>
Color
Decoration
EPS-File
End
b
a
c
0
The VOID where the removed ether Molecule was located
INSTRUCTION INPUT via KEYBOARD or LEFT-MOUSE-CLICKS (HELP with RIGHT CLICKS)
>> Continue (Y/N[Y])
Exit
MenuActive

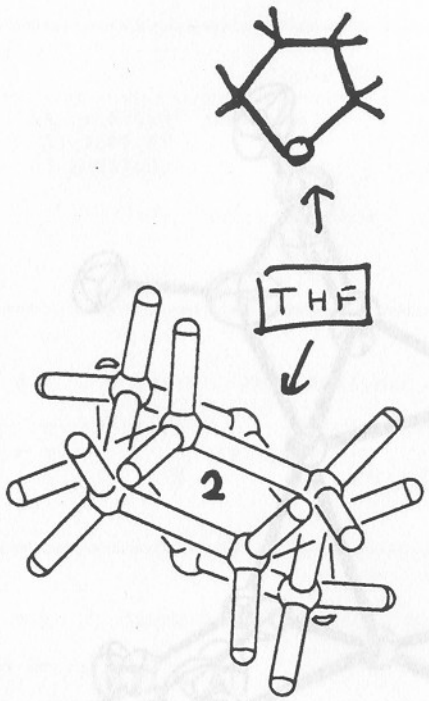
Recommended SQUEEZE Procedure in combination with SHELXL97

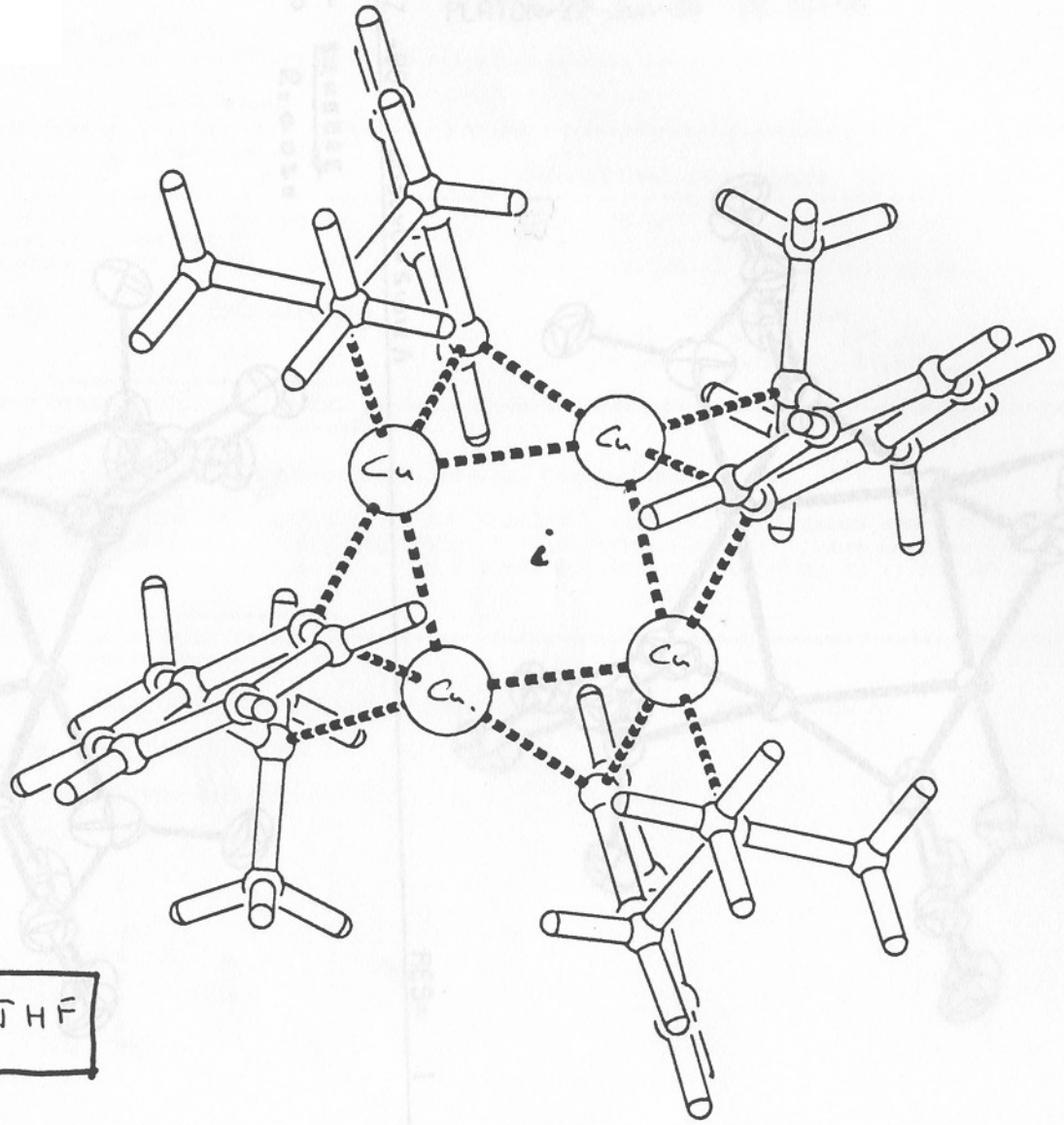
1. Refine a discrete atom model including Hydrogen atoms with SHELXL => **.res**
2. Delete (when applicable) all ‘atoms’ used to tentatively model the disordered region => **.res**
3. Do a PLATON/SQUEEZE run with **.res** (from 2) and **.hkl** (from 1)
4. Copy **.res** => **.ins** and **.hkp** => **.hkl** in a new directory
5. Refine with SHELXL (with **.ins** and **.hkl** from 4)
6. Analyze results and optionally repeat from 3 (with **.res** from 5 and original **.hkl**)
7. Do final ‘CALC FCF’ with PLATON to get proper **.fcf** (with **.res** and **.hkl** from 5 in a new directory) => **.hkp**
8. Rename **.hkp** => **.fcf**
9. Append the SQUEEZE info in **.sqf** to the **.cif** from 5

Real World Example

- THF molecule disordered over a center of inversion
- Comparison of the result of a disorder model refinement with a SQUEEZE refinement

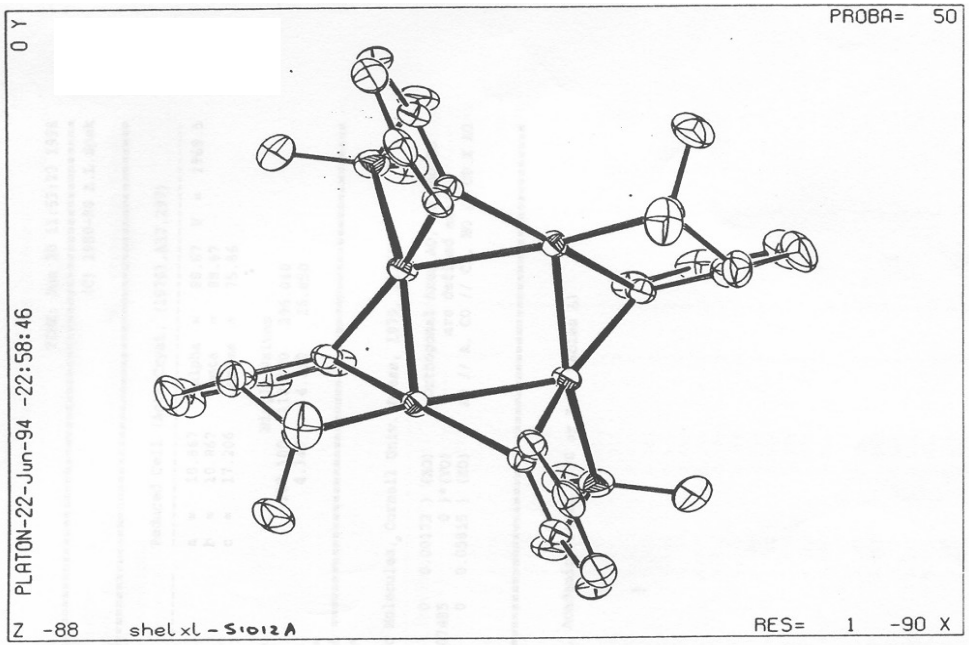
Disorder Model Refinement
Final R = 0.033



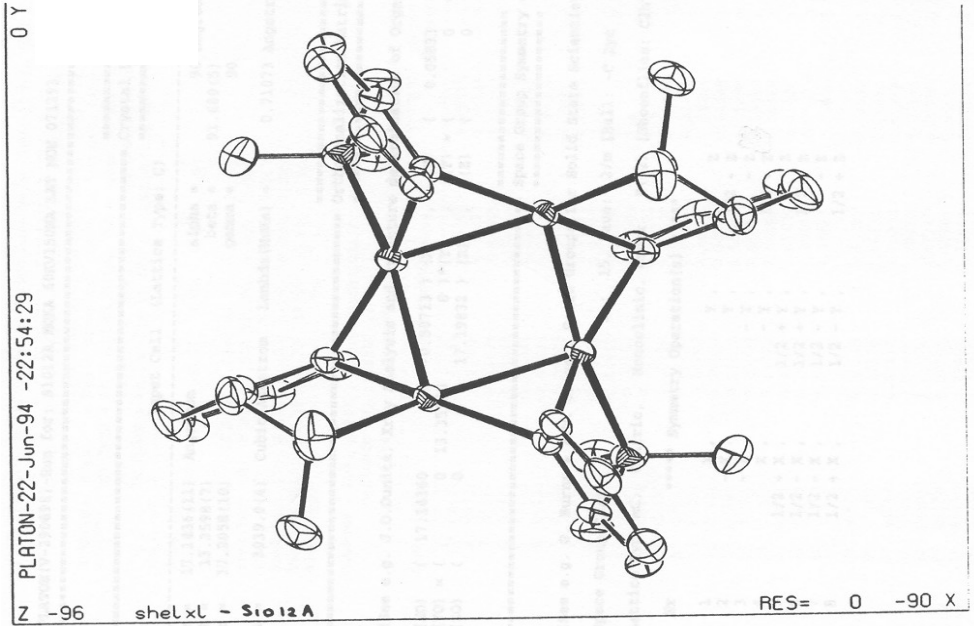


$C_{36}H_{48}Cu_4N_4 \cdot THF$

Comparison of the Results of the two Modeling Procedures



Disorder Model
R = 0.033



SQUEEZE Model
R = 0.030

LISTING OF FINAL SQUEEZE CYCLE RESULTS

```
:: Cycle =  4, R(F) = 0.04, Nref(Hemi) =  8811, R(F > 4SIGF) = 0.03 Nref =  7380

Unique Density Maxima in Enhanced  Difference Map (CutOff level =  0.50 eA-3)
=============================================================================
      x     y     z  (e/A^3)     Shortest Contacts within 3.2 Angstrom (Excl. H)
=============================================================================
  1 0.490 0.220 0.281  4.57 void
  2 0.552 0.266 0.301  4.41 void
  3 0.475 0.379 0.212  3.54 void
  4 0.441 0.356 0.252  3.39 void
  5 0.499 0.297 0.252  0.89 void
  6 0.953 0.184 0.125  0.55      C16  0.68; C11  0.75; C15  1.90; C12  1.90; Cu2
  7 0.408 0.253 0.501  0.51      C13  0.61; C12  0.90; C14  1.85; C17  1.97; C11
  8 0.358 0.170 0.717  0.50      Cu1  1.11; C21  1.53; C22  2.11; C27  2.37; Cu2
  9 0.283 0.085 0.613  0.50      C18  0.77; N1   1.75; C19  2.46; Cu1  2.82; C17

VOID   Volume Ang^3 Electron-Count (e-) Volume per electron Vol/Atom
=============================================================================
    A          155              43          3.6                    29
    B          155              43          3.6                    29
    C          155              43          3.6                    29
    D          155              43          3.6                    29

Total (Positive) Electron Count in Voids/Cell =   172

Total (Fo-Fc)map Electron Count in  Unit Cell =   171

VOID-Fo-Fc-Map:     Rho(min) =   -0.28, Rho(max) =    4.57, RhoCutOff =    0.00
PeaksCloseToAtoms: Rho(min) =   -0.63, Rho(max) =    0.55, RhoCutOff =    0.50

:: Fo-scale =0.210538E+01 - SinT/L-Min = 0.20 for Fo/Fc-Scaling


:: Cycle =  5, R(F) = 0.04, Nref(Hemi) =  8811, R(F > 4SIGF) = 0.03 Nref =  7380
```

ANALYSIS OF R-VALUE IMPROVEMENT WITH RESOLUTION

ANALYSIS

SQUEEZE Statistics on the Difference Map Phasing

FcMod = Average contribution to Fc from discrete model
FcSolv = Average contribution to Fc from solvent region
FcTot = Average Fc total (= model + solvent contrib.)
DelMS = Average Phase difference between model and solvent contrib.
DelMT = Average Phase difference between model and combined contrib.
N = Number of reflections in Sin(Theta)/Lambda range
R(Mod) = SIGMA(ABS(ABS(FcMod) - Fo)) / SIGMA(Fo)
R(Tot) = SIGMA(ABS(ABS(FcTot) - Fo)) / SIGMA(Fo)

SinT/L	<FcMod>	<FcSolv>	<FcTot>	<Fo>	<DelMS>	<DelMT>	N	R(Mod)	R(Tot)
0.05	269.40	95.86	278.98	275.37	100.00	0.01	18.	0.336	0.033
0.10	143.62	47.76	157.32	160.98	77.17	12.87	56.	0.281	0.043
0.15	105.09	16.83	107.15	110.76	86.51	8.88	122.	0.155	0.048
0.20	114.13	8.59	115.03	116.75	87.75	3.38	210.	0.090	0.041
0.25	116.69	8.11	116.64	117.74	87.17	1.18	322.	0.080	0.038
0.30	88.12	6.28	88.18	88.41	91.33	2.29	480.	0.083	0.037
0.35	71.70	4.12	71.60	71.80	91.11	3.11	632.	0.070	0.039
0.40	60.71	3.18	60.94	60.76	87.13	1.15	842.	0.074	0.047
0.45	53.95	2.79	54.11	53.87	88.69	2.19	1036.	0.075	0.051
0.50	49.89	2.26	49.87	49.59	92.77	1.79	1262.	0.071	0.055
0.55	40.11	1.61	40.15	39.83	88.48	1.11	1138.	0.075	0.063
0.60	30.62	1.02	30.62	30.91	89.65	1.57	917.	0.089	0.078
0.65	28.65	0.86	28.69	28.90	87.74	0.51	481.	0.098	0.086

SQUEEZE REQUIREMENTS

- A Complete data set, including non-zero intensity low order reflections for the estimation of the number of electrons in the void region.
- No significant residual unresolved density excursions in the difference map for the ordered part of the structure

Limitations of SQUEEZE

- SQUEEZE can currently not handle properly most cases of main molecule disorder that is coupled with the solvent disorder.
- SQUEEZE is currently incompatible with twinning
- SQUEEZE needs a sufficient data resolution to give meaningful results

Concluding Remarks

- The CSD includes now in the order of 1000 entries where SQUEEZE was used.
- Care should be taken with issues such as charge balance that effects the chemistry involved.
- The use of the SQUEEZE procedure should be detailed in the experimental section of a paper based on its use.

Additional Info

http://www.cryst.chem.uu.nl/platon/PLATON-MANUAL.pdf

The Bypass Paper:

P. van der Sluis & A.L.Spek (1990).Acta Cryst., A46, 194-201.