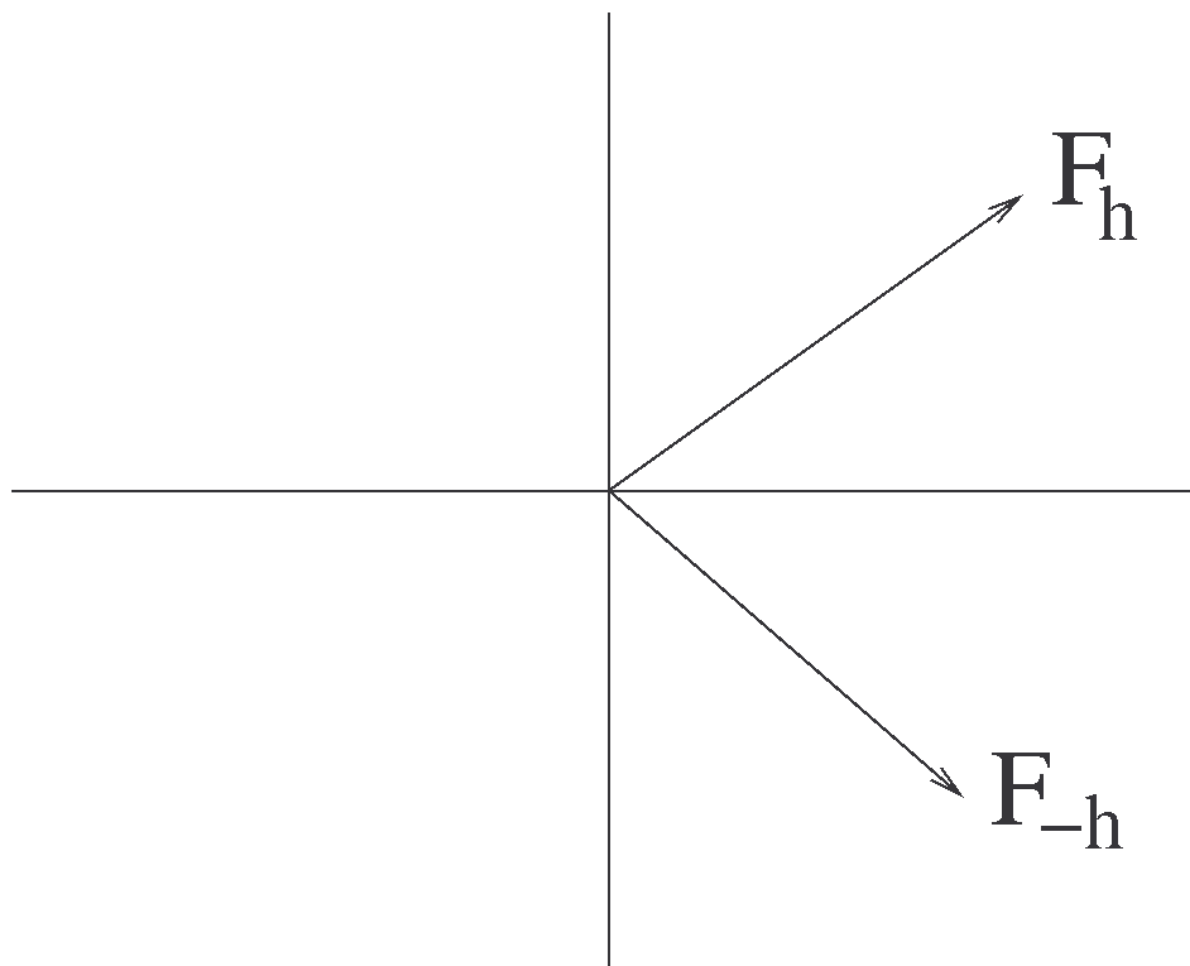


The absolute configuration of pharmaceutically interesting molecules

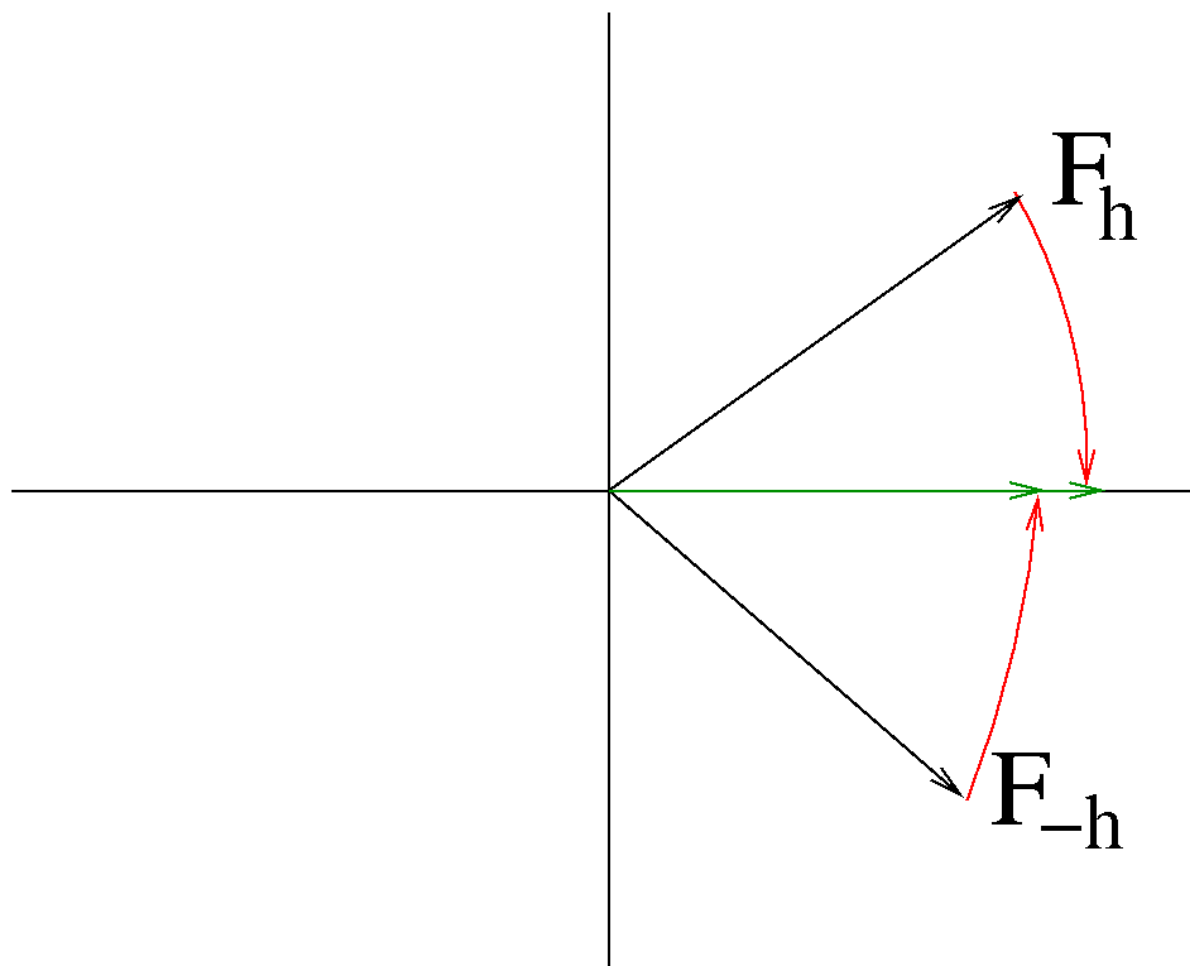
Optimal use of measured data

Rob W.W. Hooft, Bruker AXS, Delft
Leo H. Straver, Bruker AXS, Delft
Anthony L. Spek, Utrecht University

A Bijvoet pair in the complex plane



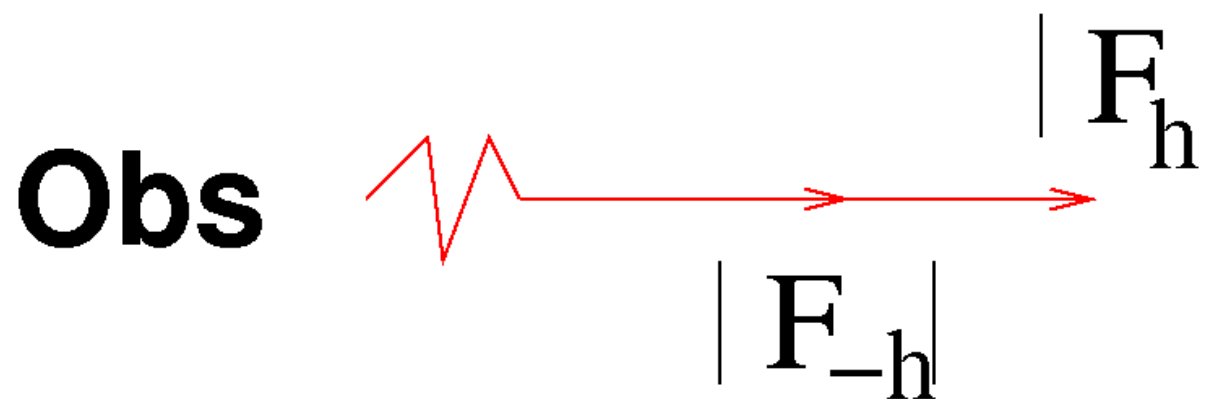
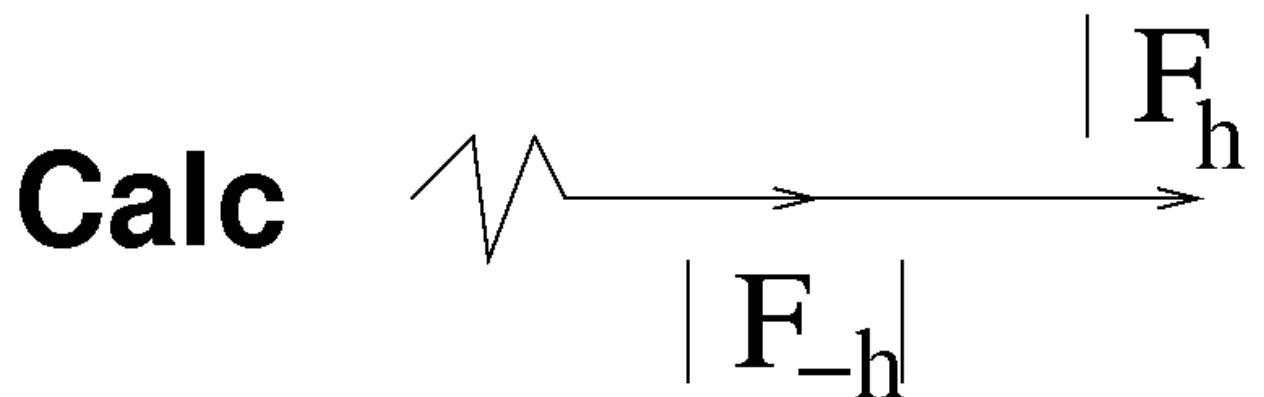
The Bijvoet difference



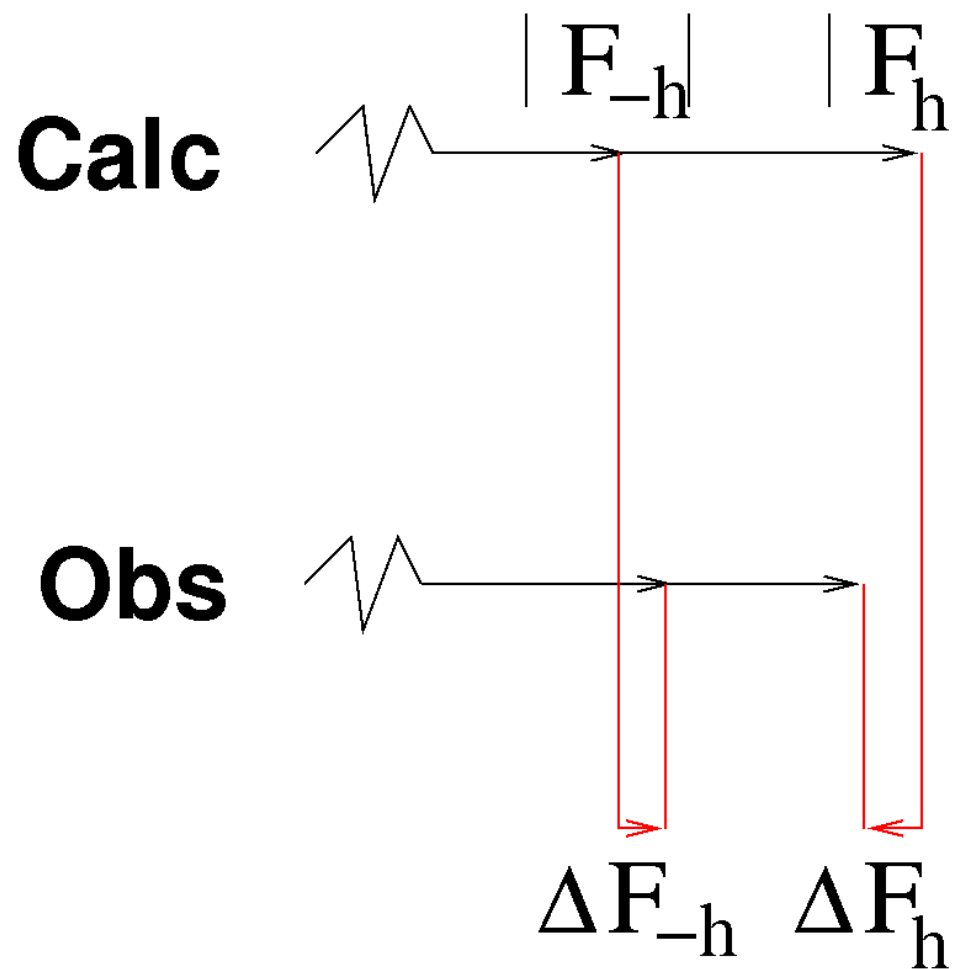
The resonant scattering signal: f''

	$f''(\text{CuK}\alpha)$	$f''(\text{MoK}\alpha)$
Se	1.14	2.23
Cl	0.70	0.16
S	0.56	0.12
O	0.032	0.006

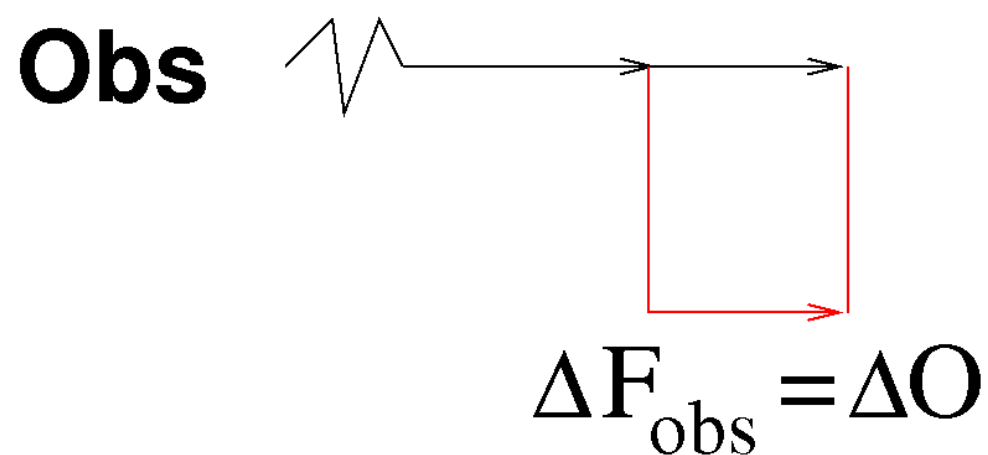
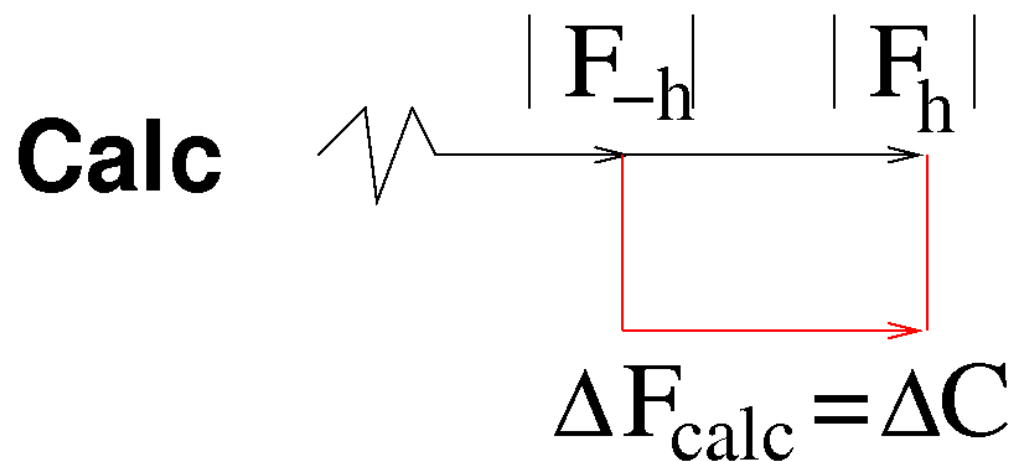
Model and observation



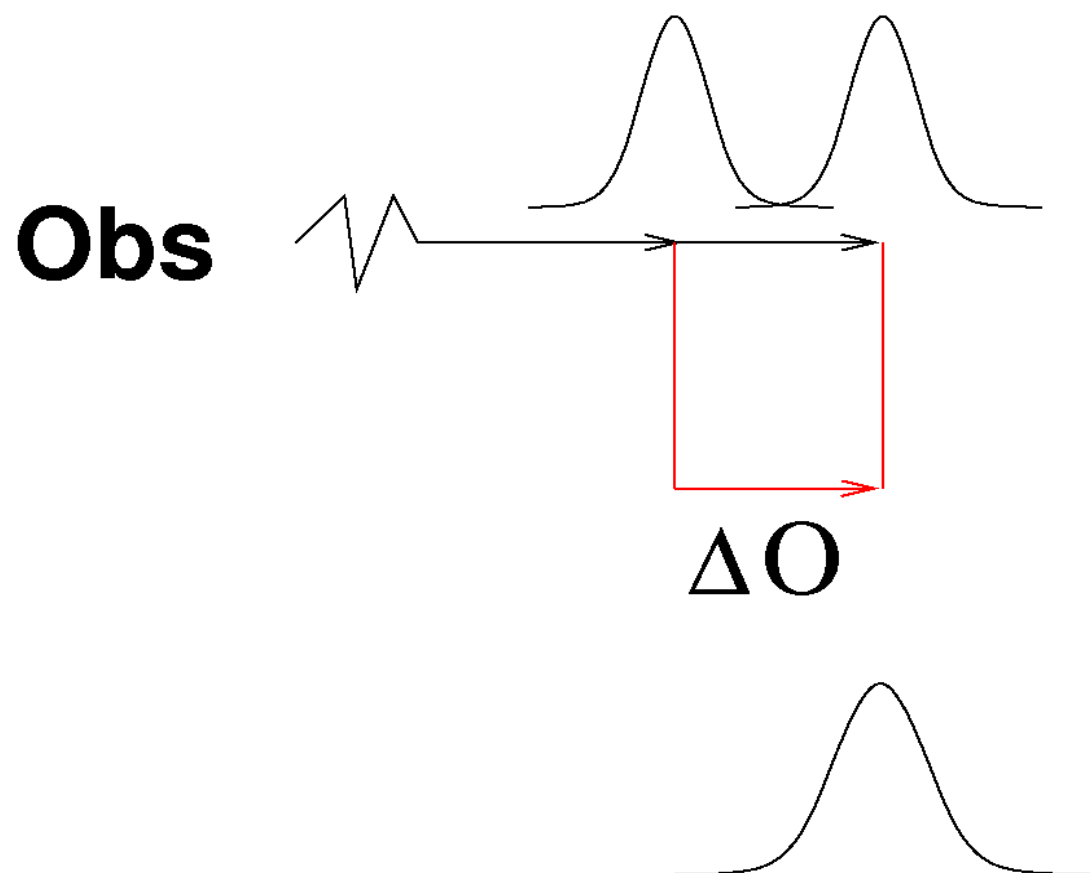
Difference between observations and model



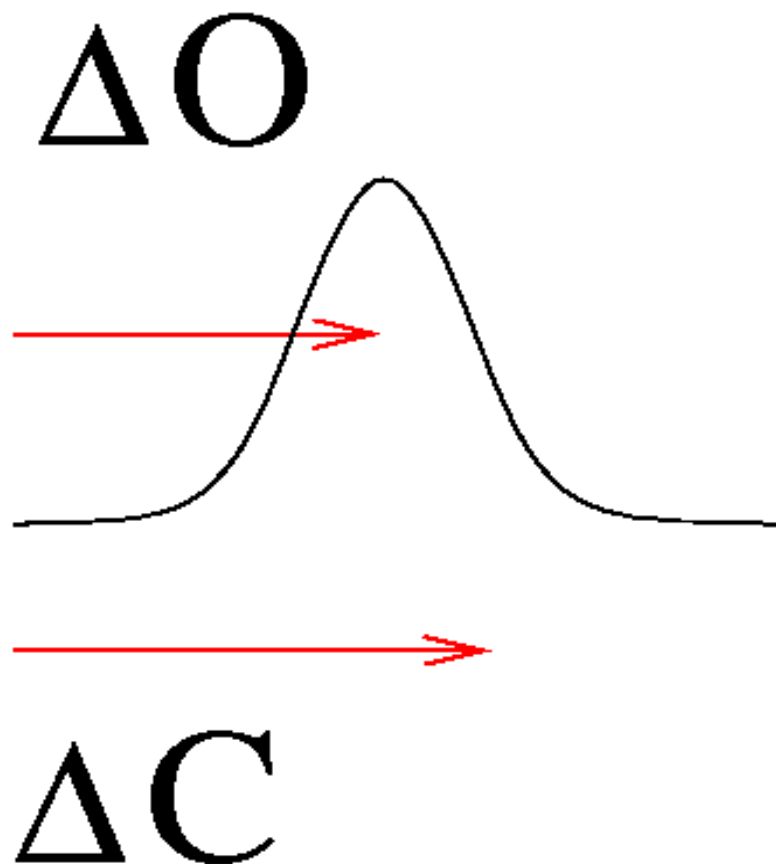
Observed and calculated differences



Standard deviations



Likelihood of correspondence



Absolute structure sensitivity

	Strong signal		Weak signal		Strong signal
$\Delta C/\sigma \gg 1$	--	--	--	-	++ or --
$\Delta C/\sigma \approx 1$	--	-	-	+	--
$\Delta C/\sigma \approx 0$	--	-	+	-	--
$\Delta C/\sigma \approx -1$	--	+	-	-	--
$\Delta C/\sigma \ll -1$	++ or --	-	--	--	--
	$\Delta O/\sigma \ll -1$	$\Delta O/\sigma \approx -1$	$\Delta O/\sigma \approx 0$	$\Delta O/\sigma \approx 1$	$\Delta O/\sigma \gg 1$

Normal distribution for a single model

$$z = \frac{\Delta C - \Delta O}{\sigma_{\Delta O}}$$

$$p(z) = \frac{1}{\sqrt{2\pi}} e^{-z^2/2}$$

Generalized model

Mix between the opposite structures at arbitrary ratios:

$$(1-y)\Delta C + y(-\Delta C) = (1-2y)\Delta C \equiv \gamma\Delta C$$

This gives:

$$x(\gamma) = \frac{\gamma\Delta C - \Delta O}{\sigma_{\Delta O}}$$

$$p(x(\gamma)) = \frac{1}{\sqrt{2\pi}} e^{-x(\gamma)^2/2}$$

What is p?

$$x(\gamma) = \frac{\gamma \Delta C - \Delta O}{\sigma_{\Delta O}} \quad p(x(\gamma)) = \frac{1}{\sqrt{2\pi}} e^{-x(\gamma)^2/2}$$

p is the chance of **observing the given intensities**, given the structural model and given the value of γ

Bayesian statistics

$$p(\gamma / \text{observations}) = \frac{p(\text{observations} / \gamma)p(\gamma)}{p(\text{observations})}$$

Delayed normalization

We **delay** normalization until we have determined the complete probability distribution:

$$p(\gamma / \text{observations}) = \frac{p(\text{observations} / \gamma)p(\gamma)}{\sum p_u(\gamma / \text{observations})}$$

Prior selection: enantiopure compound

In the case of enantiopure pharmaceuticals there are only **two** models: the proposed model and its opposite.

- P for the proposed model we call **P2(OK)**
- P for the opposite model we call **P2(wrong)**
- The prior $p(\gamma)$ is $\frac{1}{2}$ if $\gamma=1$ or $\gamma=-1$, and 0 otherwise.

Prior selection: racemic twinning

In the case of a potential racemic twin, γ becomes a continuous function

- Physics restrains values to $\gamma \geq -1$ and $\gamma \leq 1$
- Prior: $p(\gamma)=1$ if $\gamma \geq -1$ and $\gamma \leq 1$, $p(\gamma)=0$ elsewhere

This makes sense from a statistical point of view, but it does not give any warning if there would be a serious aberration

Alternative:

- Prior definition $p(\gamma)=1$ everywhere
- i.e. **no prior** knowledge is used

Prior selection: racemic twinning (2)

Prior definition $p(\gamma)=1$ everywhere, i.e. **no prior** knowledge
 $p_u(\gamma|\text{observations})$ looks like a Gaussian. We can calculate a mean, G ,
and associated standard deviation:

$$G = \frac{\int \gamma p_u(\gamma) d\gamma}{\int p_u(\gamma) d\gamma} \qquad \sigma^2(G) = \frac{\int (\gamma - G)^2 p_u(\gamma) d\gamma}{\int p_u(\gamma) d\gamma}$$

Example

P L A T O N

A Multipurpose Crystallographic Tool

(C) 1980-2006 A.L.Spek - 4QM-Version: 170706

GRAPHICS	GEOM-CALC	VOIDS TWIN	SYMMETRY	ABSORPTION	REPORT	MISC-TOOLS
PLUTONauto	CALC ALL	CALC SOLV	ADDSYM	DELrefABS	VALIDATION	PATTERSON
ORTEP/ADP	CALC INTRA	CALC K.P.I	ADDSYM-EQL	ABSPeScan	ASYM-VIEW	FCF2HKL
NEWMAN	CALC INTER	SQUEEZE	ADDSYM-EXT	ABSTampa	FCF-VALID	EXPAND-P1
RING-PLOTS	CALC COORD	CALC-FCF	ADDSYM-PLT	ABSGauss	SUPPLEMMAT	FCF-GENER
PLANE-PLOT	CALC METAL	CONTOUR-SQ	ADDSYM-SHX	ABSXtal	ANALofVAR	HKL-GENER
POLYHEDRA	CALC GEOM	SOLV F3D	NEWSYM	ABSSphere	ByvoetPatr	HKL-TRANSF
CONTOUR-DF	CALC HBOND	SOLV PLOT	NONSYM	MULscanABS	ASYM-EXPCT	EXOR-RES
CONTOUR-Fo	CALC TMA	CAVITY-PLT	LEPAGE	SHXABS	ASYM-VALID	ANIS-RES
AutoMolFlt	L.S.-PLANE		DELAED			RENAME-RES
HKL2Powder	DihedAngle		MOLSYM		EXPECT-HKL	PDB -pdb
SLmPowderP	AngleLines				CSD-CELL	SPF -eld
RadDlstFun	AngLspLLLn		ASYM		CSD-QUEST	SHELXL-res
	CremerPopl		ASYMaverFR			CIF -acc
	BondValenc	LePageTwln	SPGRfromEX		CALC OMEGA	AUTO-RENUM
PLUTONativ	HFIX - RES	TwlnRotMat	StructTldy	Xtal Hablt	CIF-LOCAL	SYSTEM-S

Xtal Data (CIF) ambl.cif- Set 1(1): ambl

RefL Data (SHELXL) ambl.fcf [NO-DIRC] (1): ambl

No check.def fclle found for CIF-Validation

Browser - HELP

PLATON MENU

OptionMenus

NoMove

NoDisorder

Organic

Round

Parentheses

Label-Alias

R/S-Determ

Norm-H-bond

NoSymm

Join-Expand

LstARU RCell

LstCellSymm

ListAtoms

ListBonds

LstFlagRadi

MinQPeakHgt

MinQPeakDis

Q-Peak-Incl

KeyInstruct

Prev Next

SAVE-InstrS

ENTRY-LIST

Reset End

Exit

MenuActive

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

>>

Bruker **AXS**

PLATON-JUL 20 13:54:17 2006 - (170706)

NGMOVE FORCED RES=0

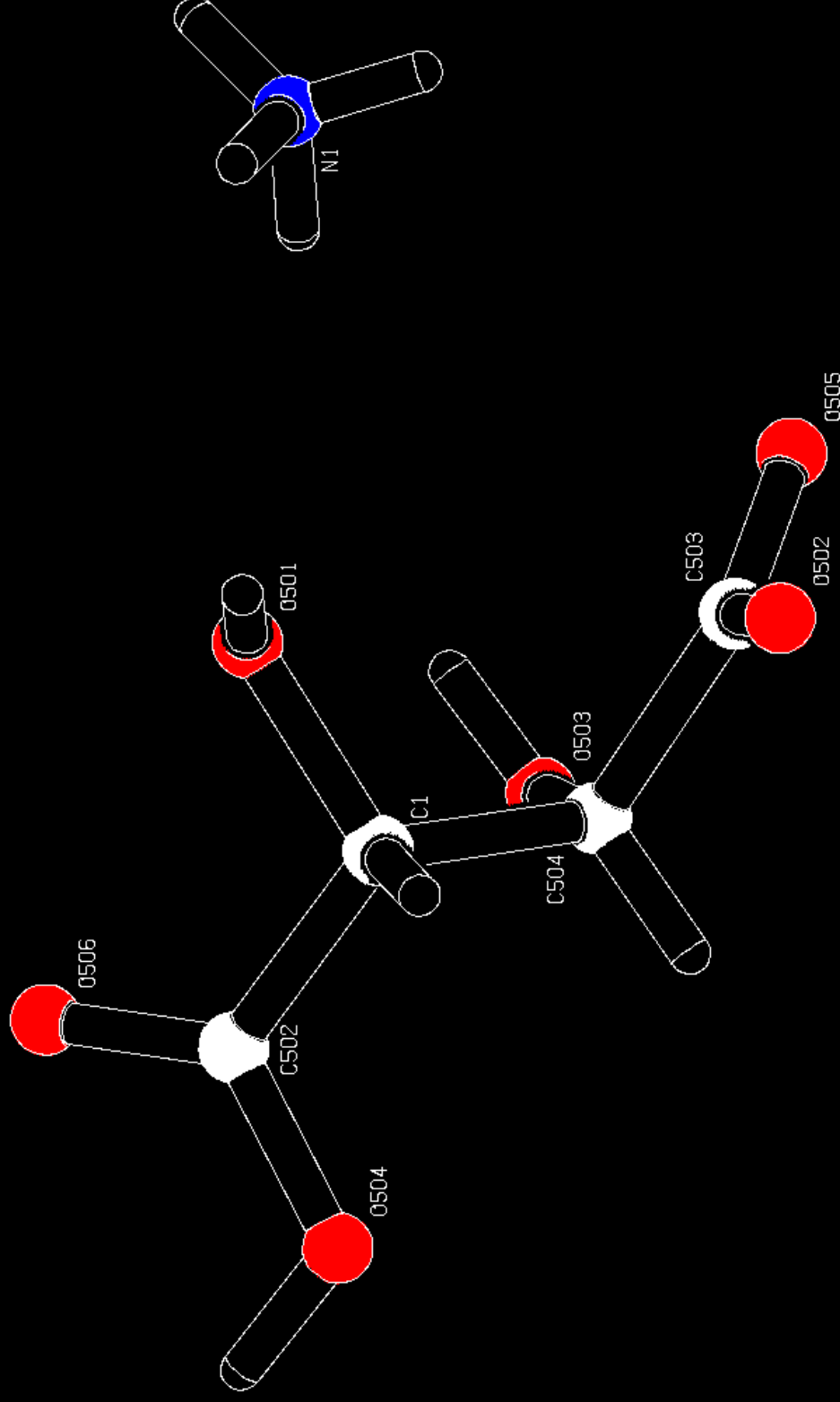
PLUTON MENU

- OptionMenu
- Stereo Opts
- Incl-HAtoms
- Solid-Style
- Rod -Style
- CPK +Stick
- Straw-Style
- Stick-Style
- BWC Res ARU
- ViewOptions
- GeomCalc
- LabelSize >
- UnitCellBox
- Resd012...
- H-Bonds-X
- PackRange
- Label -Hat+
- CRotY >>
- <<-RotZ+>>
- <<-RotY+>>
- <<-RotX+>>
- Col Res ARU
- Decoration
- EPS Pov Ras
- Reset End

Z -148 ambt

R = 0.02

-90 X



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

Exit

MenuActive

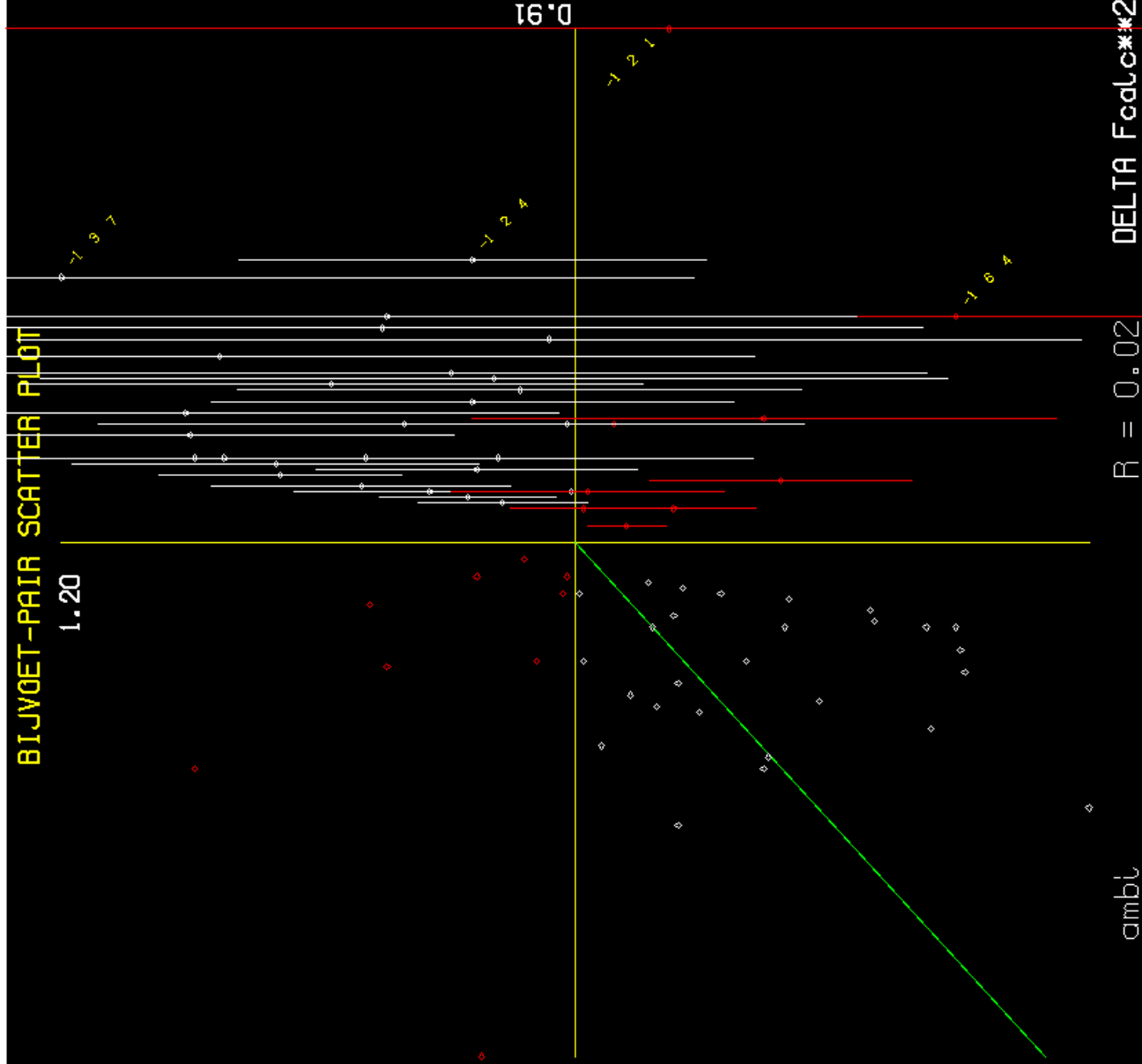
>>

BIJVOET-PAIR SCATTER PLOT

1.20

DELTA Fobs**2

PLATON-JUL 20 13:49:10 2006 - (1170706)



DELTA Fobs**2

R = 0.02

ambt

Space Group P212121
Wavelength 0.71073
Flack Param -0.100
Flack S.U. 0.900
Bl_jvoet Pairs:
Sigma Crlt... 0.25
Selected ... 38
Out of 612
Number Plus 29
Number Minus 9
Aver. RatLo 1.391
RC 1.206
Normal Prob. Plot
Corr. Coeff. 0.991
Intercept .. -0.022
Slope 0.840
Bayesian Statistics
Bl_jvoet Pairs 612
P2(true).... 1.000
P3(true).... 0.998
P3(rac-twln) 0.002
P3(false) .. 0.2E-09
G 1.0936
G S.U. 0.3116
FLEQ -0.047
FLEQ S.U. .. 0.156

BIJVOETMENU
SigmaCriter
ApplySlope
EPS-File
End

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

Exit

MenuActive

>>

Experiences

σ_y is about half of σ_x sometimes even less

y clusters very well around 0.0

absolute structure of $C_xH_yO_z$ can be determined reliably using $CuK\alpha$ radiation

....sometimes even using $MoK\alpha$ radiation

When Bijvoet pairs are measured explicitly, the least-squares refinement of the Flack x parameter is not correlated with atomic coordinates

Conclusions

A new method to determine absolute structure

Pharmaceutical compounds, known to be enantiopure.

Explicit calculation of the likelihood of an inversion (P2) without assumption about the Gaussian shape of the probability curve

The method can be used for very weak anomalous scatterers

But:

Bijvoet pairs must be measured explicitly

This absolute structure determination can not take place inside the full matrix refinement.