Acknowledgements

Ken Frankel   Chris Neilson   Michael Blum

Acknowledgements

Ken Frankel   Chris Neilson   Michael Blum

8.3.1 PRT: Tom Alber

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Center for HIV Accessory and Regulatory Complexes
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University of California Berkeley
University of California San Francisco
National Science Foundation
University of California Campus-Laboratory Collaboration Grant
Henry Wheeler

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Elven Automation

Elves examine images and set-up data processing

Elves run...

mosflm
scala
solve
mlphare
dm
arp/warp

Holton and Alber *PNAS USA* **101** 1537-42 (2004)

Elven Automation

How often does it really work?

what are my chances?

100 s/dataset

what are my chances?

100 s/dataset

200 days/year

~150 beamlines

what are my chances?

100 s/dataset

200 days/year

~150 beamlines

~26,000,000 datasets/year

what are my chances?

100 s/dataset

200 days/year

~150 beamlines

~26,000,000 datasets/year

7000 PDBs in 2008

Turning Data into Models

35 operating US beamlines

in 2003

Turning Data into Models

35 operating US beamlines

$2x10^{13}$ ph/s

`http://biosync.sdsc.edu/`

Turning Data into Models

35 operating US beamlines

~10^{11} ph/µm^2 exposure limit

$2x10^{13}$ ph/s

`Henderson et al (1990)`

Turning Data into Models

35 operating US beamlines

~10^{11} ph/µm^2 exposure limit

2x10^9 ph/µm^2/s

http://biosync.sdsc.edu/

Turning Data into Models

35 operating US beamlines

~10^{11} ph/µm^2 exposure limit

÷ 2x10^9 ph/µm^2/s

= 400,000 datasets/year

Turning Data into Models

35 operating US beamlines

~10^{11} ph/µm^2 exposure limit

÷ 2x10^9 ph/µm^2/s

~ 200,000 datasets/year

Turning Data into Models

35 operating US beamlines

~10^{11} ph/µm^2 exposure limit

÷ 2x10^9 ph/µm^2/s

~ 100,000 datasets/year

Turning Data into Models

35 operating US beamlines

~10^{11} ph/μm^2 exposure limit

÷ $2x10^9$ ph/μm^2/s

~ 100,000 datasets/year

÷ 1324 str in 2003

Jiang & R.M. Sweet (2004)

Turning Data into Models

35 operating US beamlines

~10^{11} ph/μm^2 exposure limit

÷ $2x10^9$ ph/μm^2/s

~ 100,000 datasets/year

÷ 1324 str in 2003

~ 2% efficient

Turning data into models

Turning data into models

8.3.1 in 2003

Number	Description	Percent
	Images	

Turning data into models

8.3.1 in 2003

Number	Description	Percent
446028	Images (~7 TB)	33%

Turning data into models

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Turning data into models

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2346	Data sets	47%

Turning data into models

8.3.1 in 2003

Number	Description	Percent
446028	Images (~7 TB)	33%
2346	Data sets	47%
	MAD/SAD	

Turning data into models

8.3.1 in 2003

Number	Description	Percent
446028	Images (~7 TB)	33%
2346	Data sets	47%
449	MAD/SAD (1:2)	19%

Turning data into models

8.3.1 in 2003

Number	Description	Percent
446028	Images (~7 TB)	33%
2346	Data sets	47%
449	MAD/SAD (1:2)	19%
	Published	

Turning data into models

8.3.1 in 2003

Number	Description	Percent
446028	Images (~7 TB)	33%
2346	Data sets	47%
449	MAD/SAD (1:2)	19%
104	Published	4.4%

DVD data archive

Elven Automation

Apr 6 – 24 at ALS 8.3.1

27,686	images collected

Elven Automation

Apr 6 – 24 at ALS 8.3.1

27,686	images collected
148	datasets (15 MAD)

Elven Automation

Apr 6 – 24 at ALS 8.3.1

27,686	images collected
148	datasets (15 MAD)
31	investigators

Elven Automation

Apr 6 – 24 at ALS 8.3.1

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148	datasets (15 MAD)
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56	unique cells

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5 KDa – 23 MDa	asymmetric unit

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Apr 6 – 24 at ALS 8.3.1

27,686	images collected
148	datasets (15 MAD)
31	investigators
56	unique cells
5 KDa – 23 MDa	asymmetric unit
0.94 – 32 Å	resolution (3.2 Å)

Elven Automation

Apr 6 – 24 at ALS 8.3.1

148	datasets

Elven Automation

Apr 6 – 24 at ALS 8.3.1

148	datasets
117	succeeded

Elven Automation

Apr 6 – 24 at ALS 8.3.1

148	datasets
117	succeeded
~3.5 (0.1-75)	hours

Elven Automation

Apr 6 – 24 at ALS 8.3.1

148	datasets
117	succeeded
~3.5 (0.1-75)	hours
31	failed

Elven Automation

Apr 6 – 24 at ALS 8.3.1

148	datasets
117	succeeded
~3.5 (0.1-75)	hours
31	failed
~61 (0-231)	hours

Elven Automation

Apr 6 – 24 at ALS 8.3.1

148	datasets
117	succeeded
~3.5 (0.1-75)	hours
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~61 (0-231)	hours
2 / 15	MAD structures

Why do structures fail?

Overlaps

Radiation Damage

Signal to noise

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Overlaps

Radiation Damage

Signal to noise

Elven Automation

Apr 6 – 24 at ALS 8.3.1

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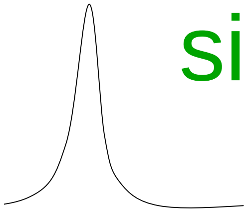
Elven Automation

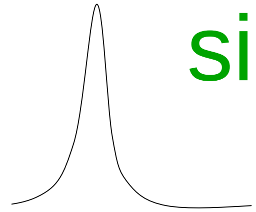
Apr 6 – 24 at ALS 8.3.1

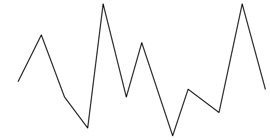
148	datasets
117	succeeded
~3.5 (0.1-75)	hours
31	failed
~61 (0-231)	hours
2 / 15	MAD structures

signal

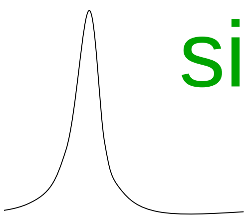


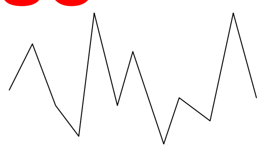
signal *vs* noise





signal *vs* noise

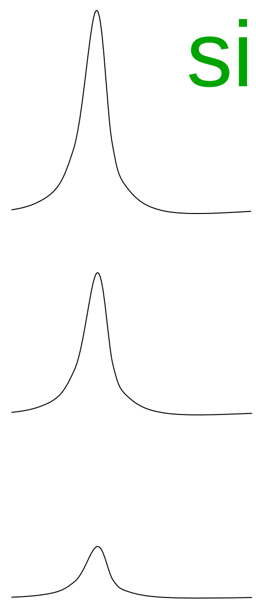




"If you don't have
good data,
then you have
no data at all."

-Sung-Hou Kim

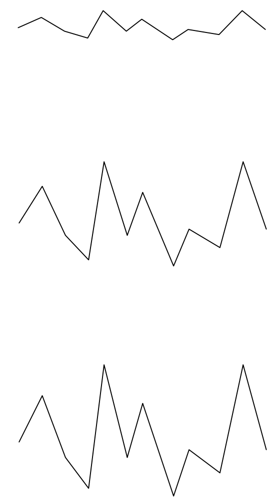
signal *vs* noise



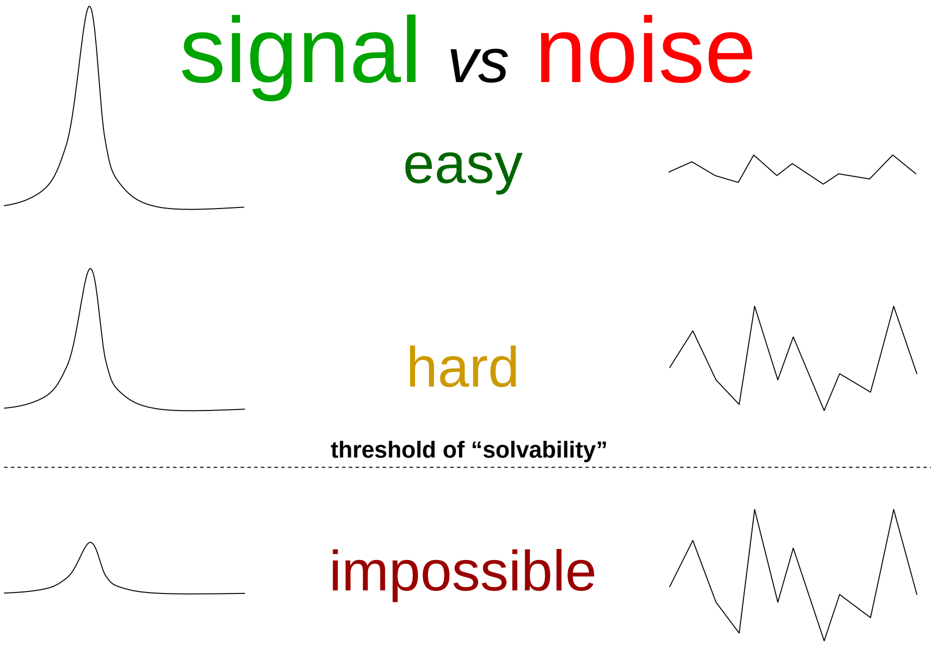
easy

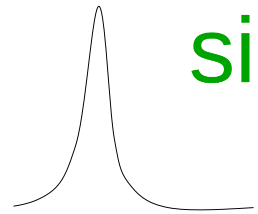
hard

impossible

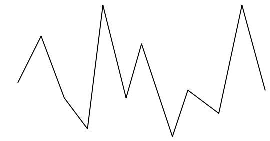


signal *vs* noise





signal *vs* noise



“If you don’t have
good data,
then you must
learn statistics.”

-James Holton

Adding noise

Adding noise

1 + 1 = 1.4

Adding noise

$1 \quad + 1 \quad = 1.4$

$\sigma_{total}^2 = \sigma_1^2 + \sigma_2^2$

Adding noise

$1^2 + 1^2 = 1.4^2$

$\sigma_{total}^2 = \sigma_1^2 + \sigma_2^2$

Adding noise

$1^2 + 1^2 = 1.4^2$

$3^2 + 1^2 = 3.2^2$

$\sigma_{total}^2 = \sigma_1^2 + \sigma_2^2$

Adding noise

$1^2 + 1^2 = 1.4^2$

$3^2 + 1^2 = 3.2^2$

$10^2 + 1^2 = 10.05^2$

Sources of noise

"photon counting"	σ(N) = sqrt(N)
Read-out noise	rms 11.5 e-/pixel
Shutter jitter	rms 0.57 ms
Beam flicker	0.15 %/√Hz
spot shape	pixels? mosaicity?
radiation damage	B/Gray?

Simulated diffraction image

Simulated diffraction image

Arndt & Wonacott (1977)

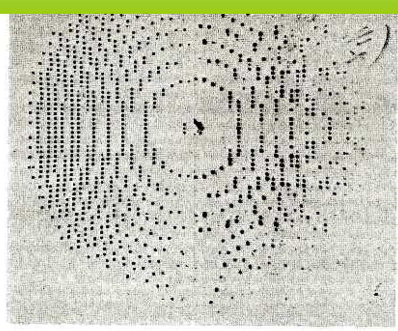


Fig. 7.12. Comparison of simulated diffraction pattern with small-angle rotation photograph.

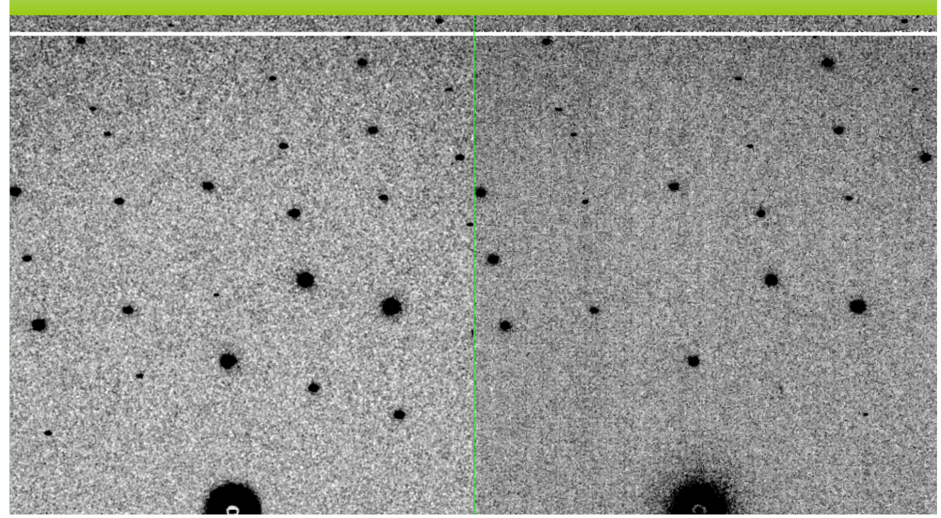
likely to occur.
The most practical means of testing for over
reflexions is to specify a minimum separation bet

7.6. Choice of Crystal Orientation

Several factors must be considered in choosi
used for the collection of a three-dimension
depend on the individual characteristics of the
general applicability can, however, be made.
In principle, data could be collected from a
trary orientation but this creates certain practi
an appropriate oscillation range for each phot
more difficult and the total range of rotation r
asymmetric unit of reciprocal space may be grea
sary when the crystal is rotated about a particula
Recording a complete data set will, in genera
tals. In order to avoid recollecting the same da
having to use more crystals than necessary, it
crystal to within, say, one degree of the desired
azimuth from a still photograph. Then angular
for adjacent crystals need only be minimal in o

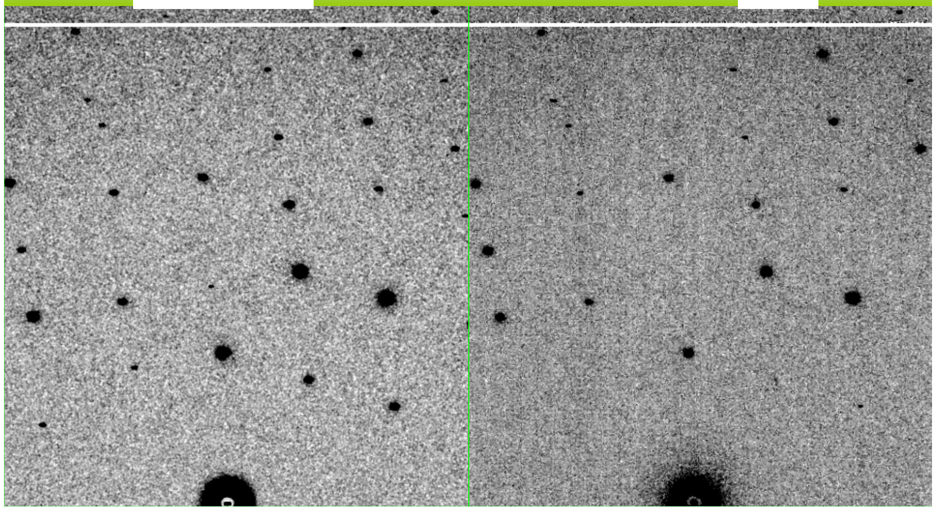
Simulated diffraction image

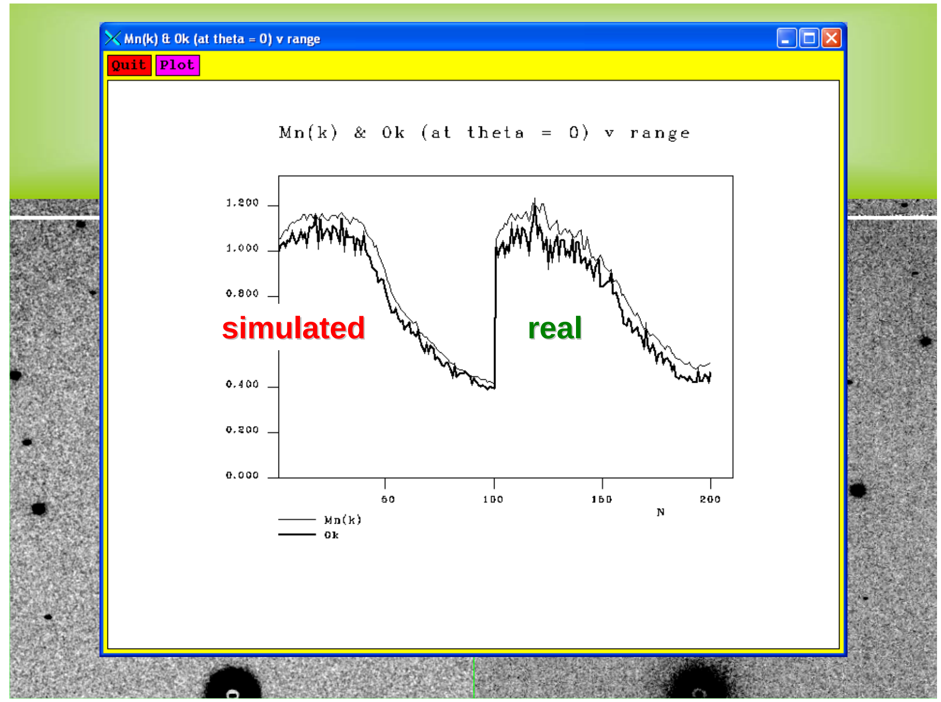
MLFSOM



Simulated diffraction image

MLFSOM





Simulated	statistic	Real
5.4%	R_{merge}	6.2%
18.9	I/sd	16.2
1.9	I/sd (1.4 Å)	1.6
1.7 4.0 0.020	SDCORR	1.0 2.2 0.065
36.8	PADFPH	31.46
3.871	mlphare f”	3.476
0.178	FOM	0.192
0.545	FOMDM	0.664
0.6270	CC(1H87)	0.6090
0.170	R_{cryst}	0.184
0.205	R_{free}	0.231

Reference experiment

Beamline:

ALS 8.3.1
0.1 s exposures
total dose = 0.47 MGy

Detector:

ADSC Quantum 315r

Crystal:

PDB id 1H87
tetragonal HEWL soaked with Gd complex (2 sites)

Gd f” at 12660 eV ~ Se

Bijvoet ratio: 3.8%

What goes into the simulation?

What goes into the simulation?

Crystal:
- “pristine” PDB
- “decayed” PDB
- Crystal size (μm)
- orientation matrix/angles
- mosaic spread (deg)
- absorption envelope (facet planes)

Non-crystal:
- “air” path (mm)
- cryo types & thicknesses (μm)
- ice rings

Beam:
- Flux (photons/s)
- beam size (μm)
- Wavelength (Å)
- dispersion (Δλ/λ)
- divergence (deg)
- flicker noise (%/√Hz)
- shutter jitter (ms)

Detector:
- Distance, beam center
- tilt, twist, omega (deg)
- pixels x pixels, pixel size
- E-O gain, amplifier gain
- DQE, vignette
- read noise (rms e^-/pixel)
- “ripple” noise (%)
- point-spread function
- PSF variation

What goes into the simulation?

Crystal:
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- tilt, twist, omega (deg)
- pixels x pixels, pixel size
- E-O gain, amplifier gain
- DQE, vignette
- read noise (rms e^-/pixel)
- “ripple” noise (%)
- point-spread function
- PSF variation

What does not go into the simulation?

Crystal:
- “one dimensional” (but variable)
- uniform damage
- assumed “top hat” mosaic spread
- kinematical diffraction

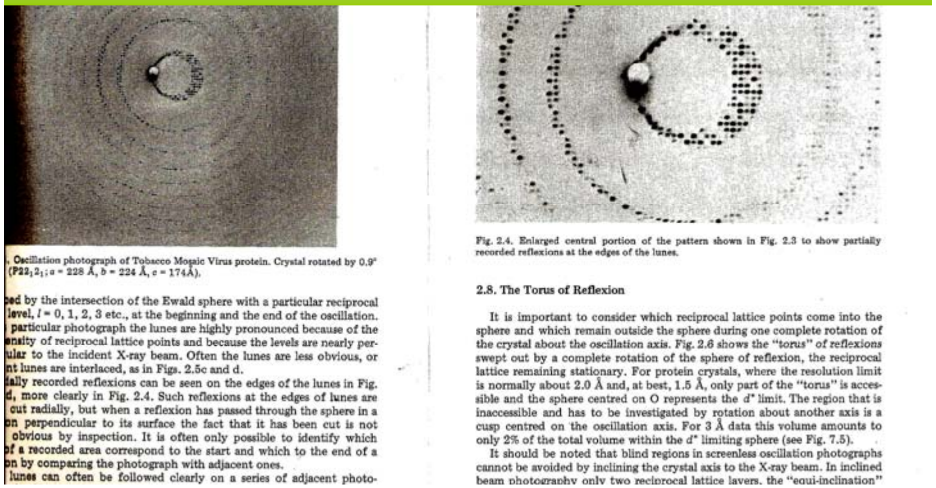
Non-crystal:
- no polarization correction
- no 2θ support

Beam:
- assumed uniform square “top hat” profiles for beam size, divergence dispersion
- flicker and jitter follow normal distribution

Detector:
- no spatial transformation
- no flood/dark correction
- no read-noise anisotropy
- no electron-counting noise

Spot Shape

Arndt & Wonacott (1977)



. Oscillation photograph of Tobacco Mosaic Virus protein. Crystal rotated by 0.9° ($P22_12_1$; a = 228 Å, b = 224 Å, c = 174Å).

ed by the intersection of the Ewald sphere with a particular reciprocal level, l = 0, 1, 2, 3 etc., at the beginning and the end of the oscillation. particular photograph the lunes are highly pronounced because of the nsity of reciprocal lattice points and because the levels are nearly per- ular to the incident X-ray beam. Often the lunes are less obvious, or nt lunes are interlaced, as in Figs. 2.5c and d.

ally recorded reflexions can be seen on the edges of the lunes in Fig. d, more clearly in Fig. 2.4. Such reflexions at the edges of lunes are cut radially, but when a reflexion has passed through the sphere in a n perpendicular to its surface the fact that it has been cut is not obvious by inspection. It is often only possible to identify which f a recorded area correspond to the start and which to the end of a n by comparing the photograph with adjacent ones.

lunes can often be followed clearly on a series of adjacent photo-

Fig. 2.4. Enlarged central portion of the pattern shown in Fig. 2.3 to show partially recorded reflexions at the edges of the lunes.

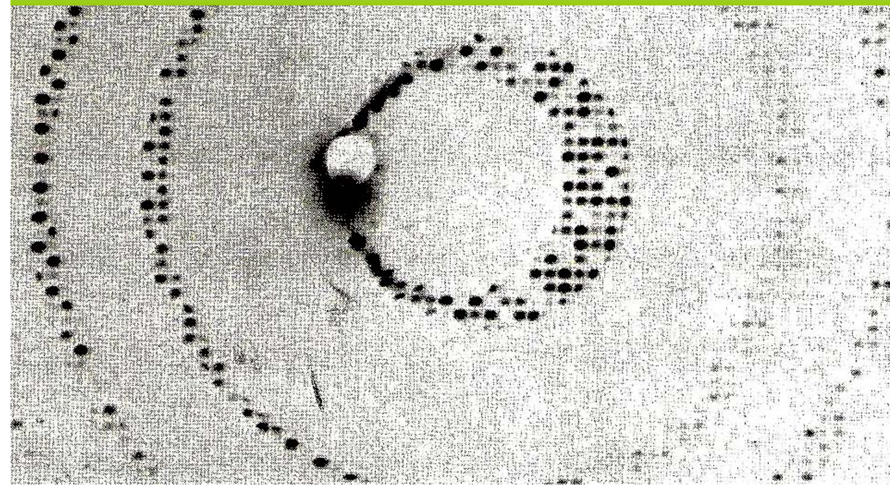
2.8. The Torus of Reflexion

It is important to consider which reciprocal lattice points come into the sphere and which remain outside the sphere during one complete rotation of the crystal about the oscillation axis. Fig. 2.6 shows the "torus" *of reflexions* swept out by a complete rotation of the sphere of reflexion, the reciprocal lattice remaining stationary. For protein crystals, where the resolution limit is normally about 2.0 Å and, at best, 1.5 Å, only part of the "torus" is accessible and the sphere centred on O represents the d^* limit. The region that is inaccessible and has to be investigated by rotation about another axis is a cusp centred on the oscillation axis. For 3 Å data this volume amounts to only 2% of the total volume within the d^* limiting sphere (see Fig. 7.5).

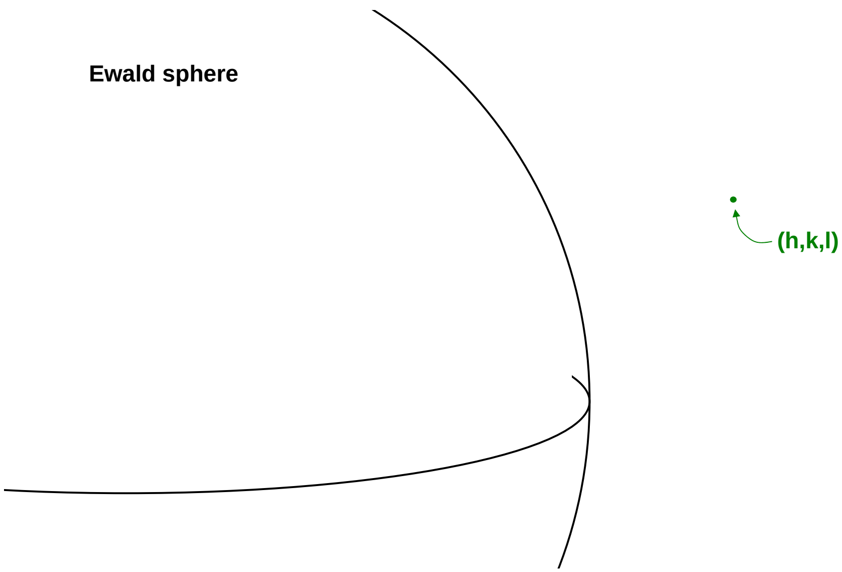
It should be noted that blind regions in screenless oscillation photographs cannot be avoided by inclining the crystal axis to the X-ray beam. In inclined beam photography only two reciprocal lattice layers, the "equi-inclination"

Spot Shape

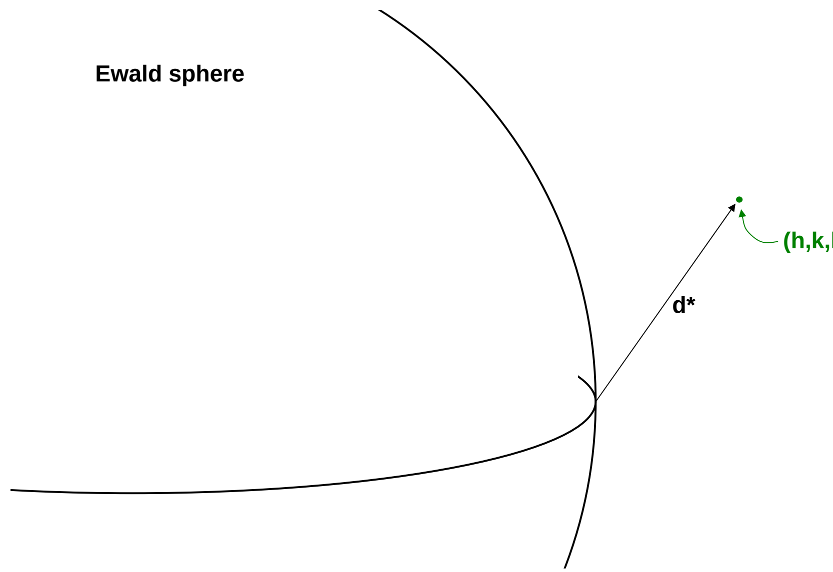
Arndt & Wonacott (1977)



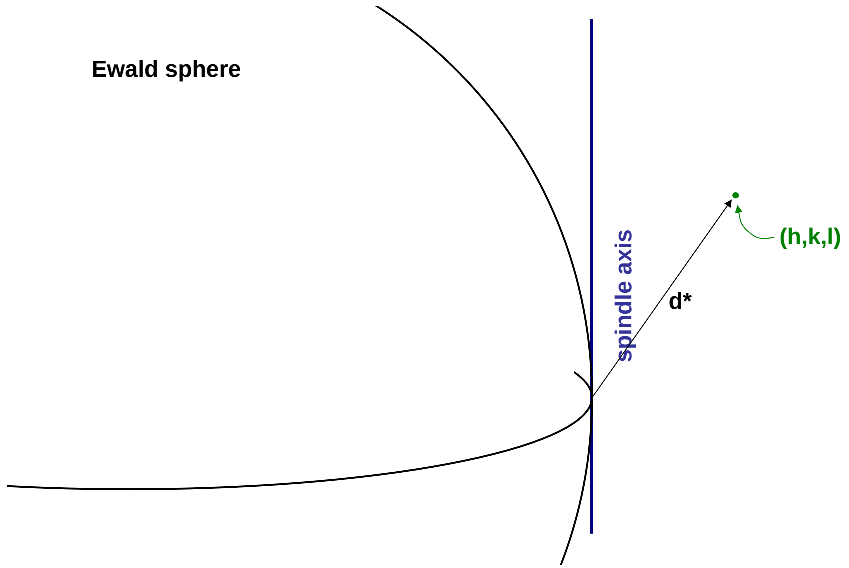
Spot shape



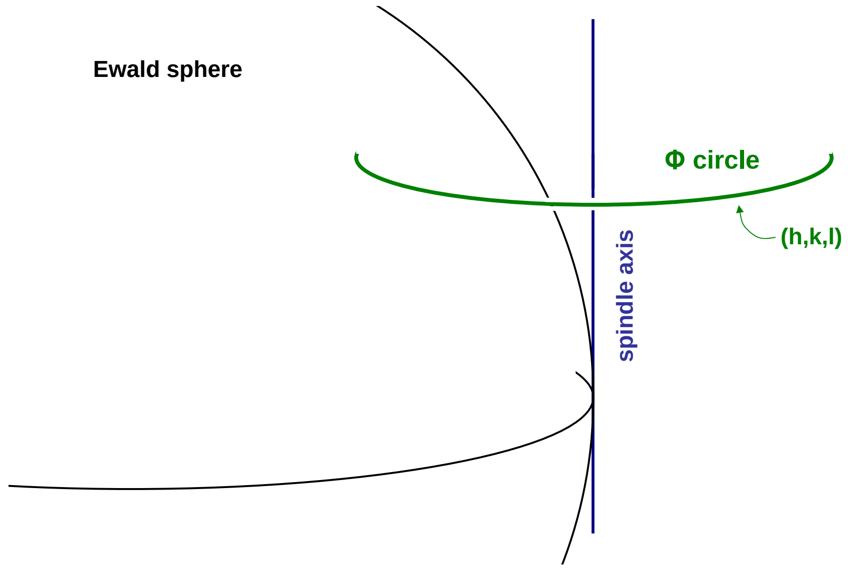
Spot shape



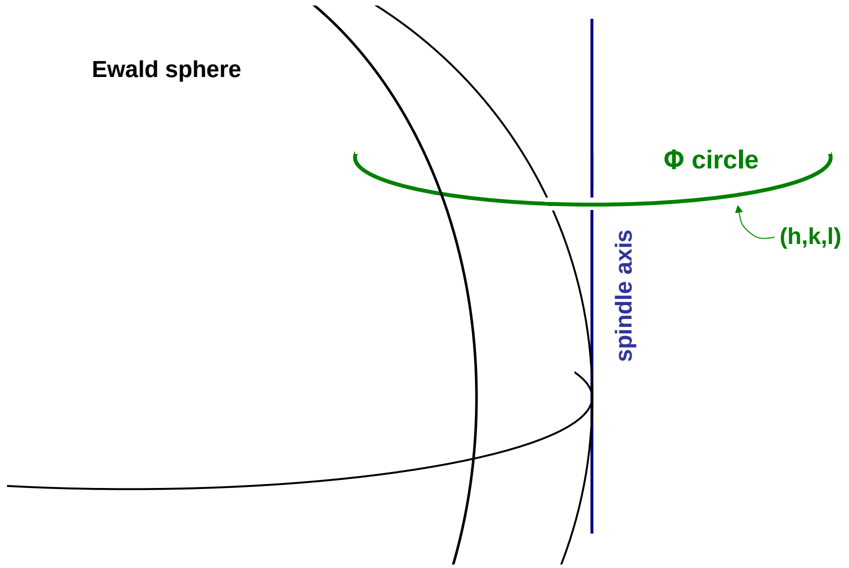
Spot shape



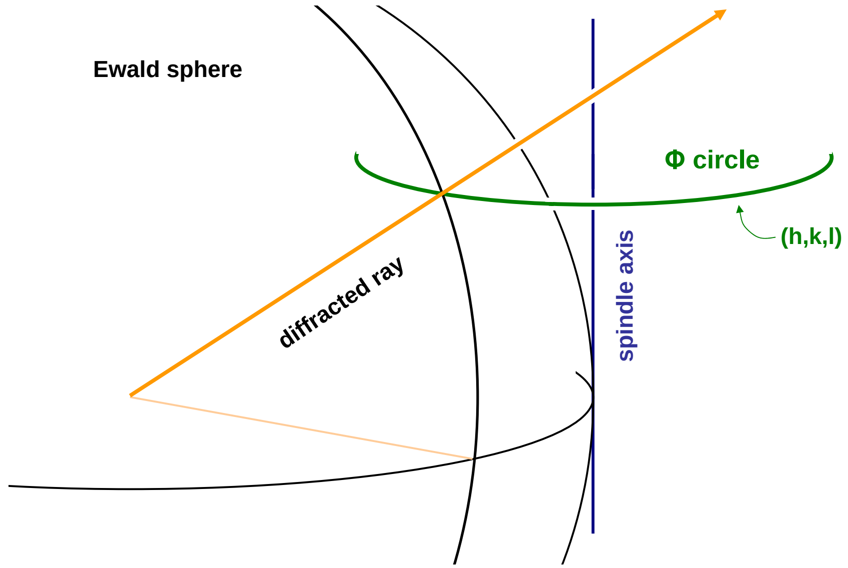
Spot shape



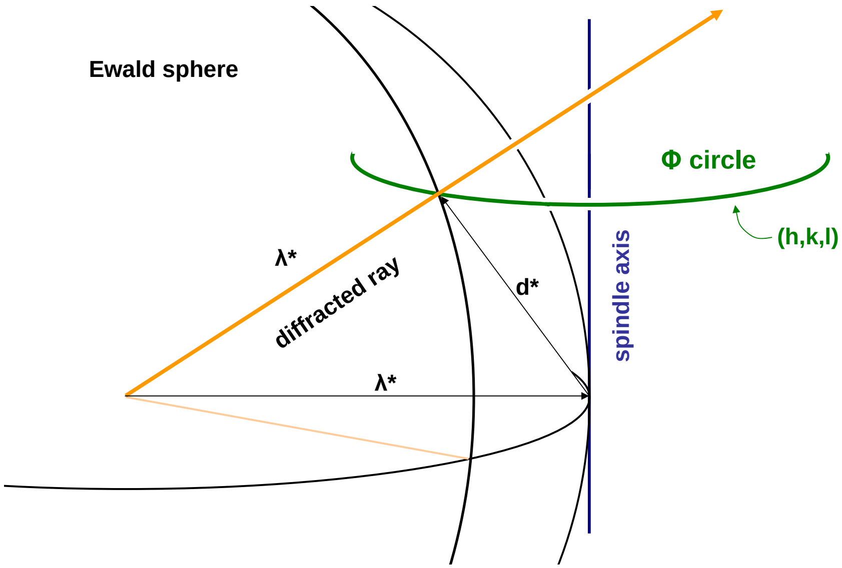
Spot shape



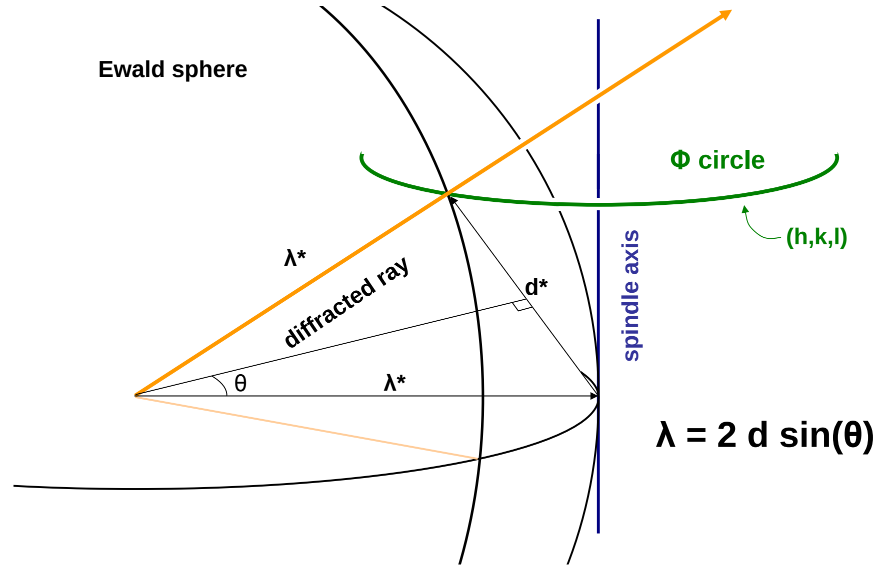
Spot shape



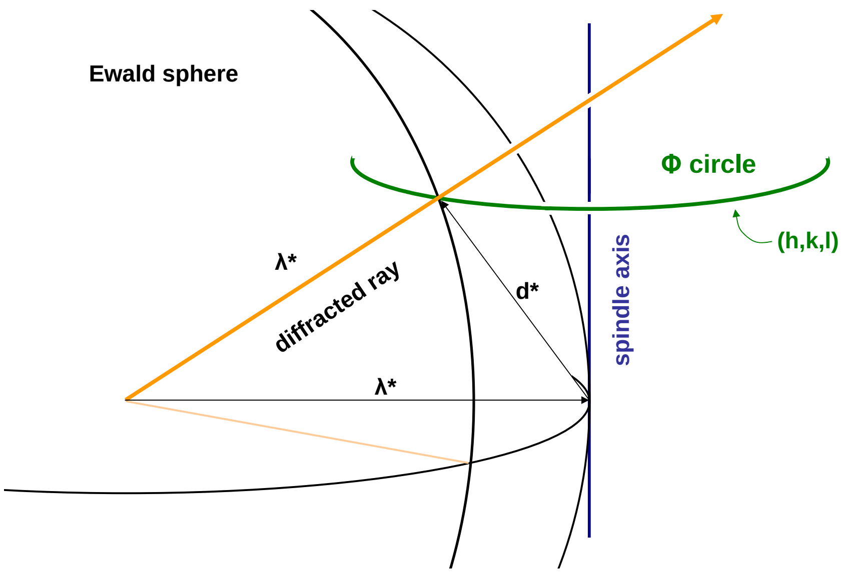
Spot shape



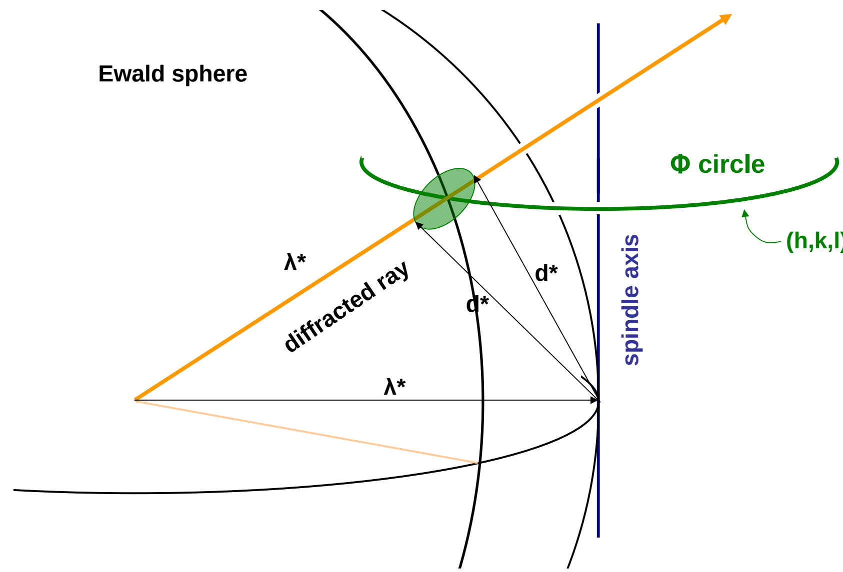
Spot shape



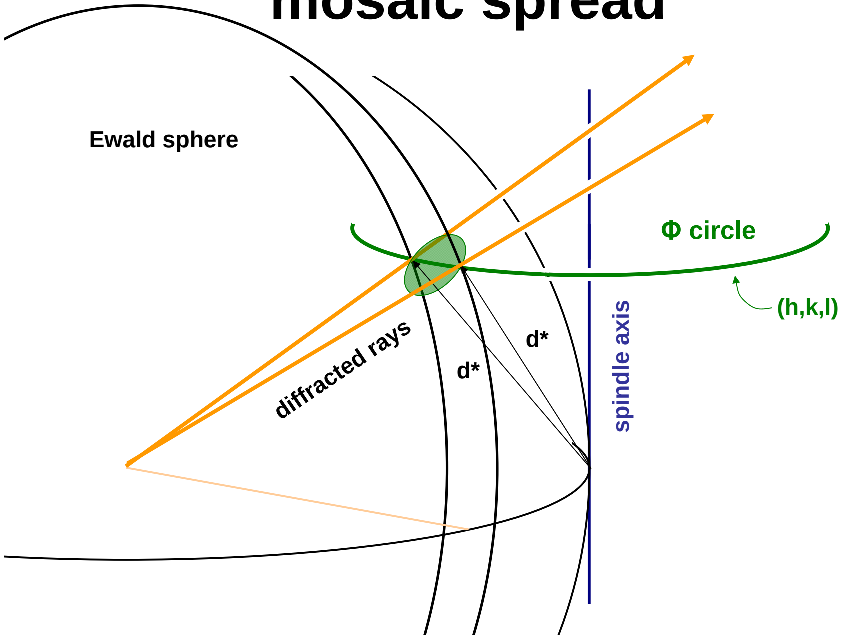
Spot shape



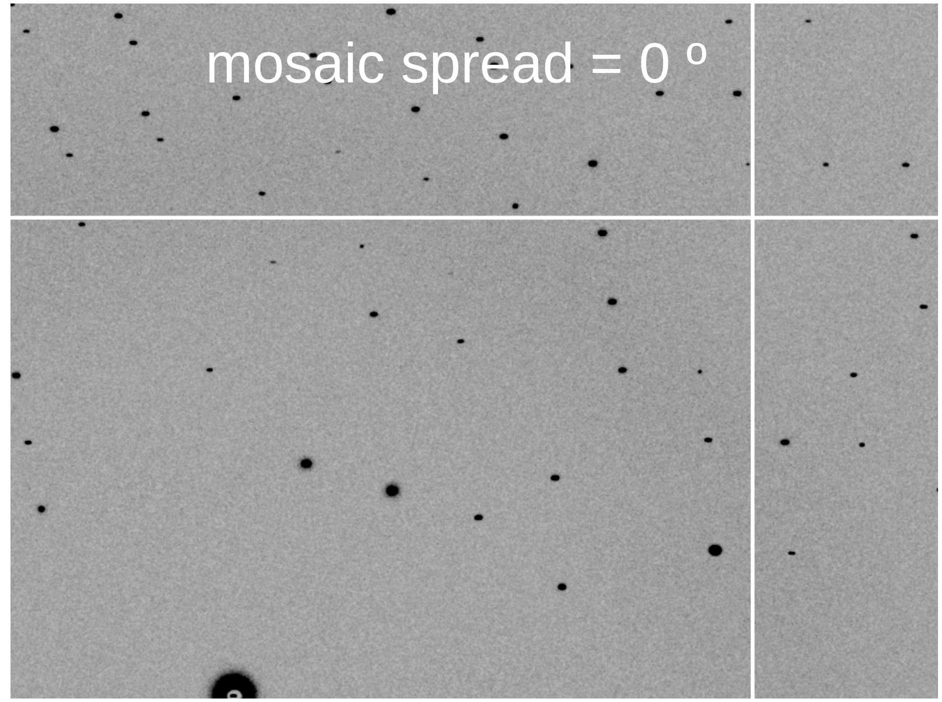
mosaic spread



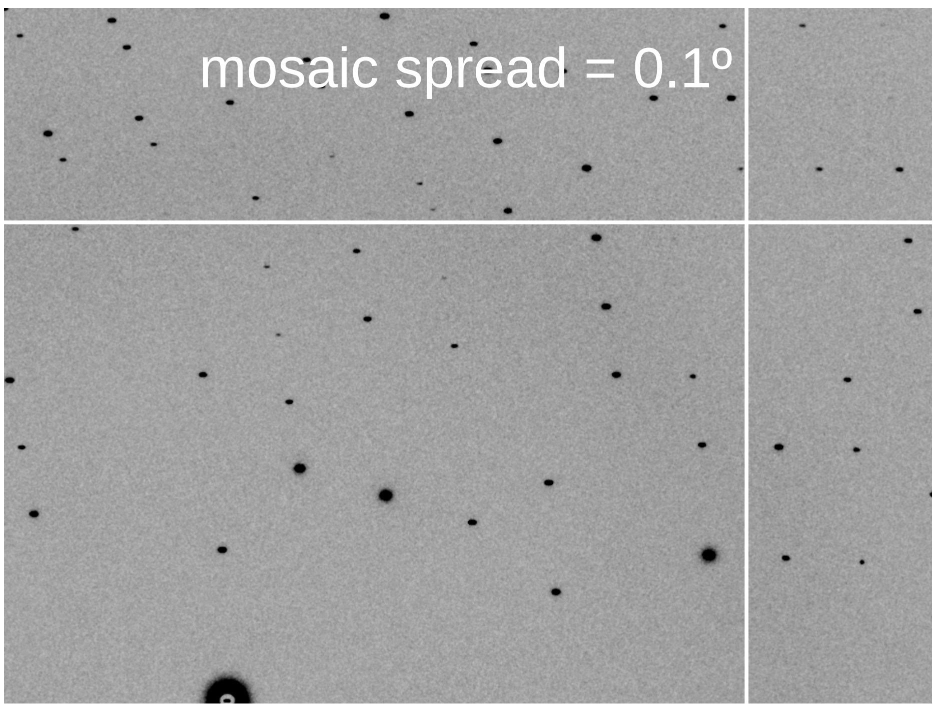
mosaic spread



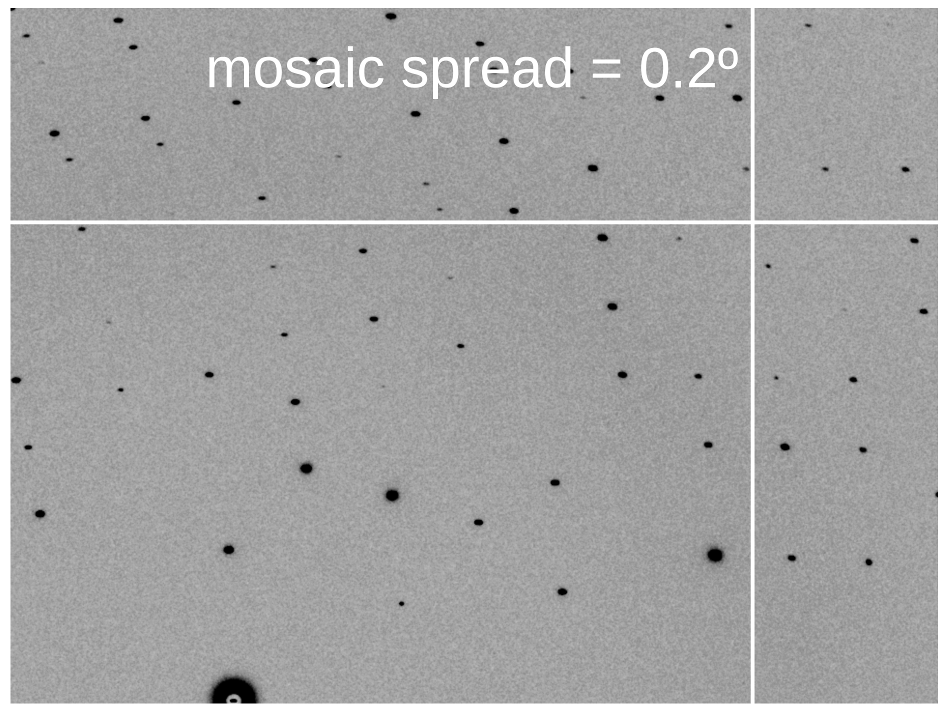
mosaic spread = 0 º

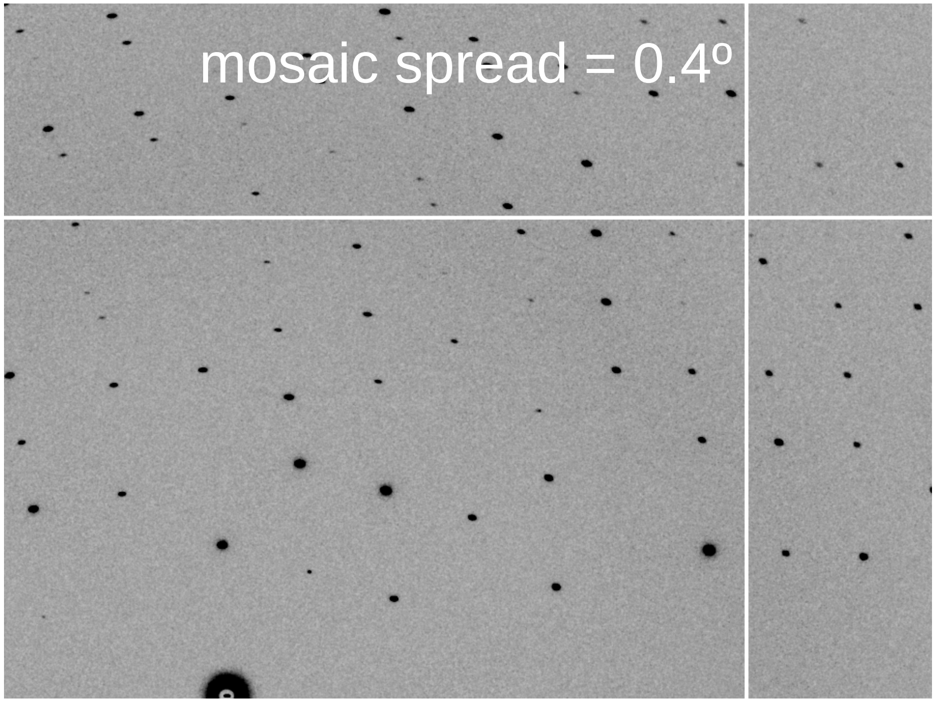


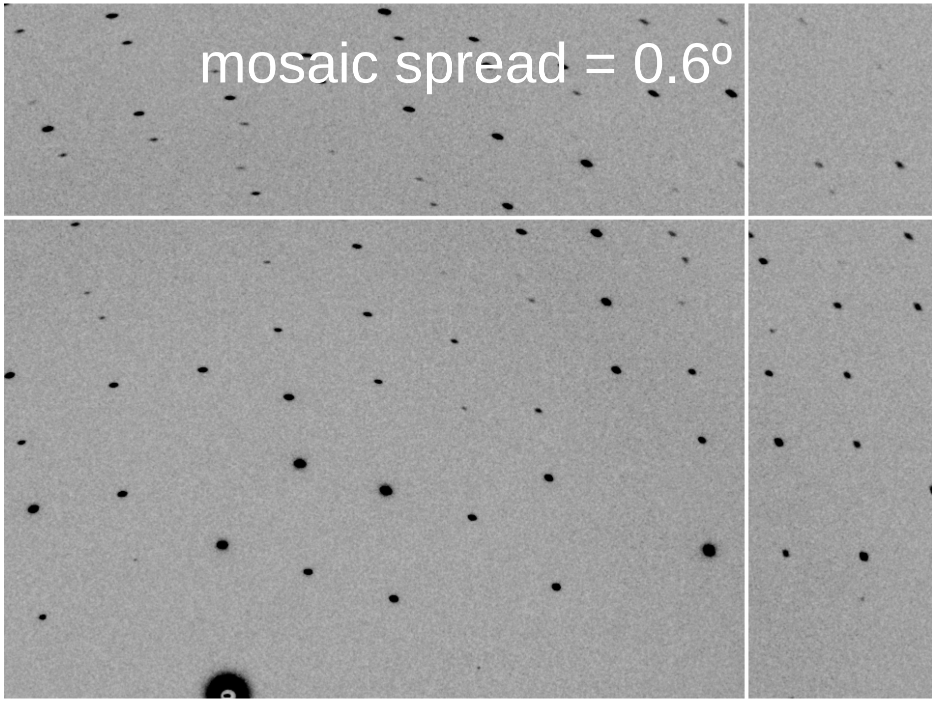
mosaic spread = 0.1º

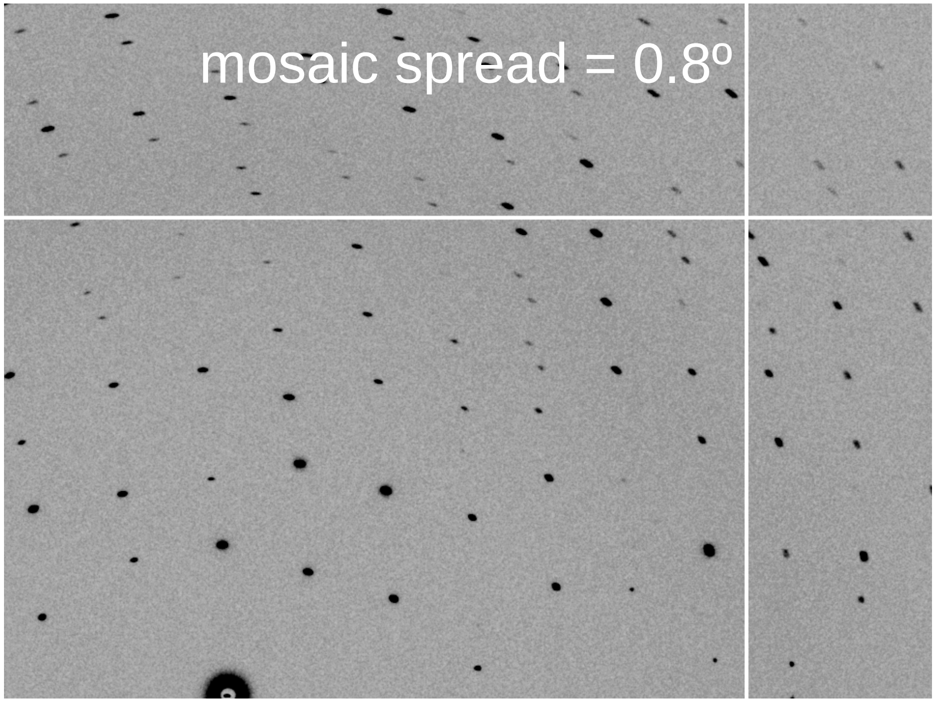


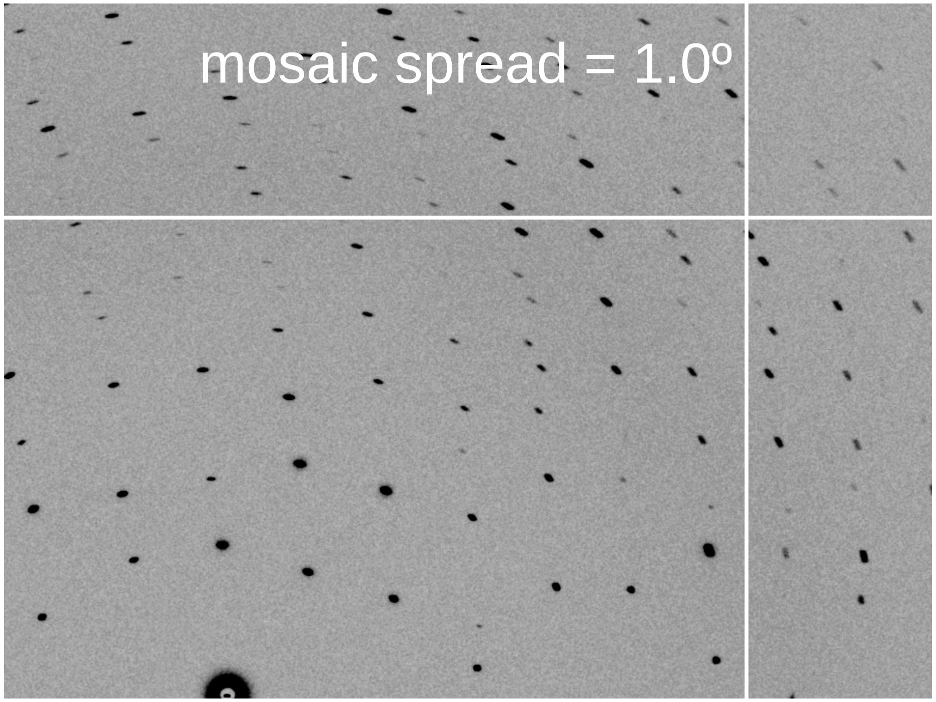
mosaic spread = 0.2º

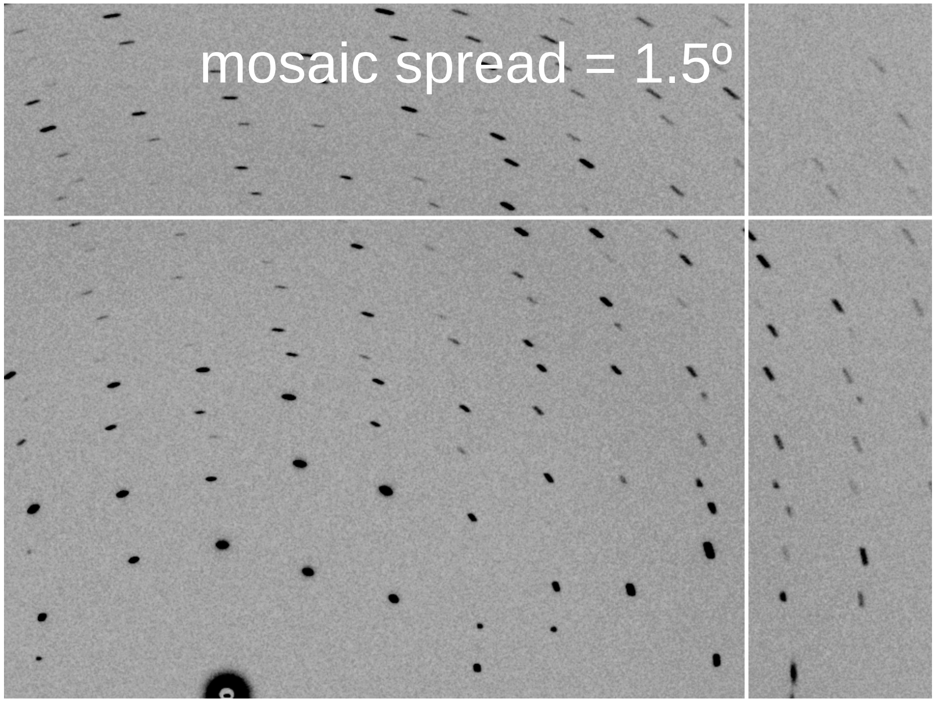


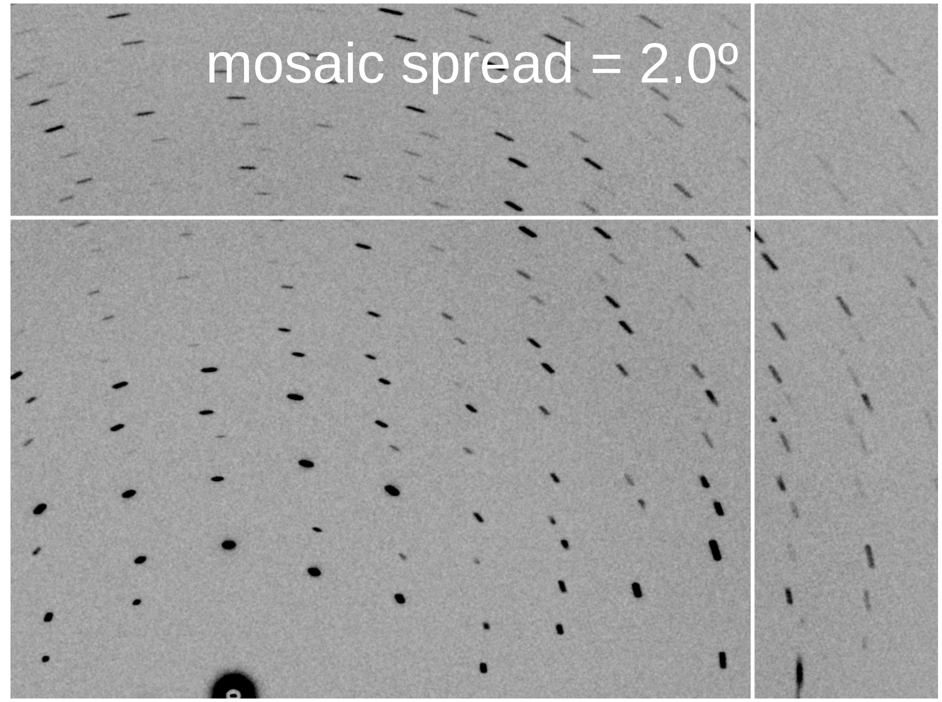

mosaic spread = 0.4º

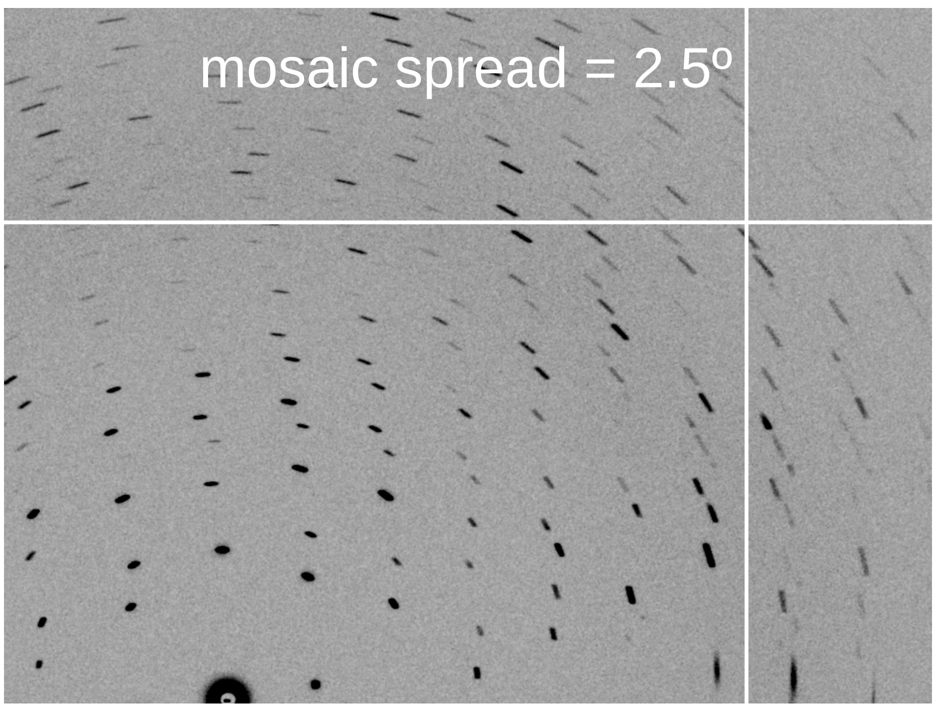

mosaic spread = 0.6º

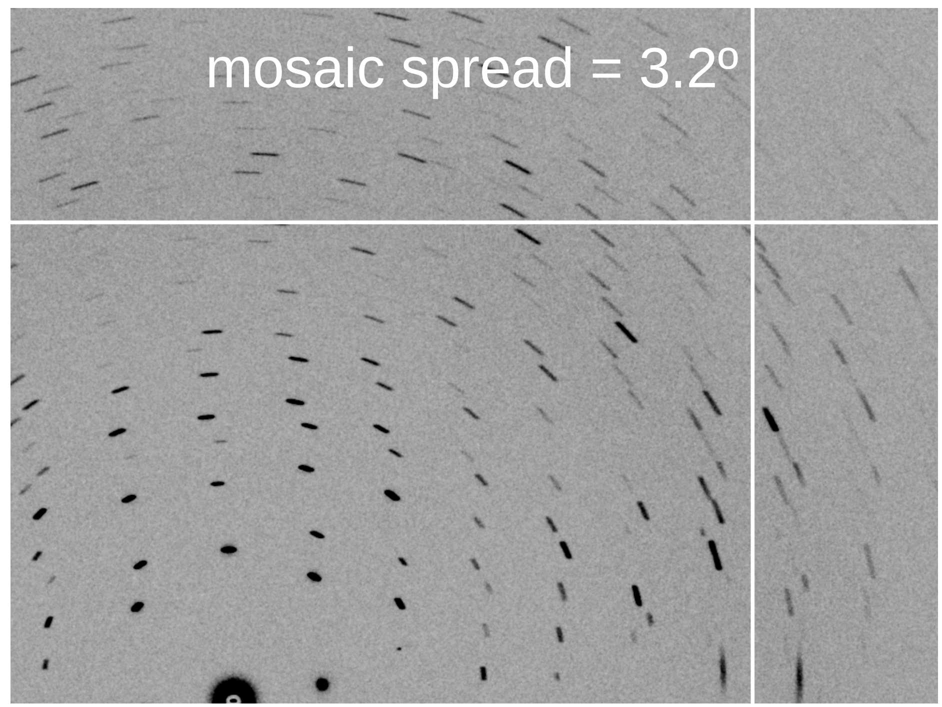

mosaic spread = 0.8º

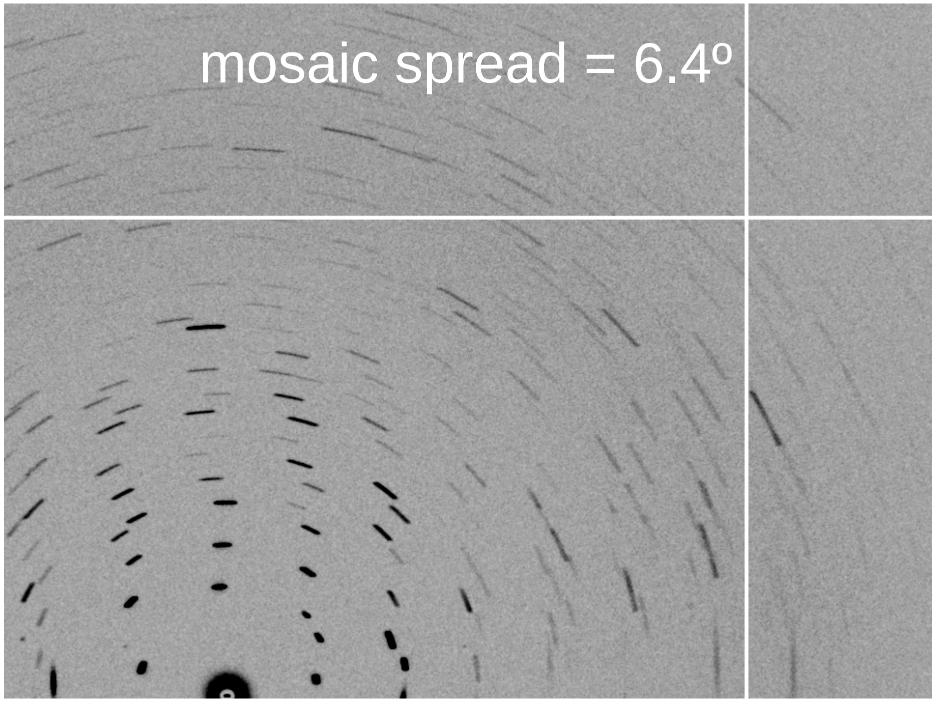

mosaic spread = 1.0º

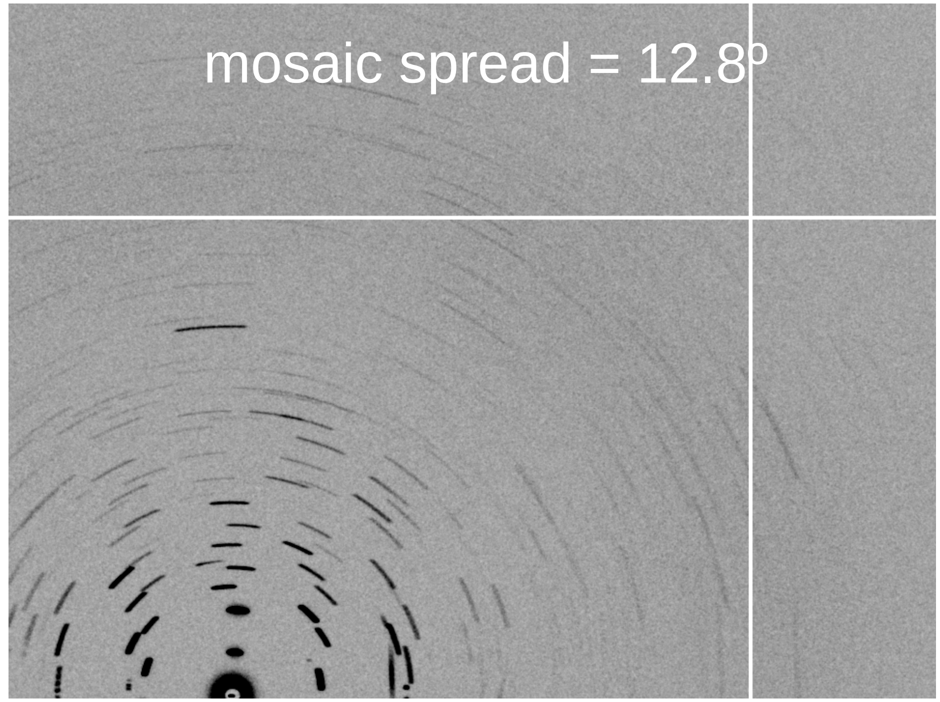

mosaic spread = 1.5º


mosaic spread = 2.0º

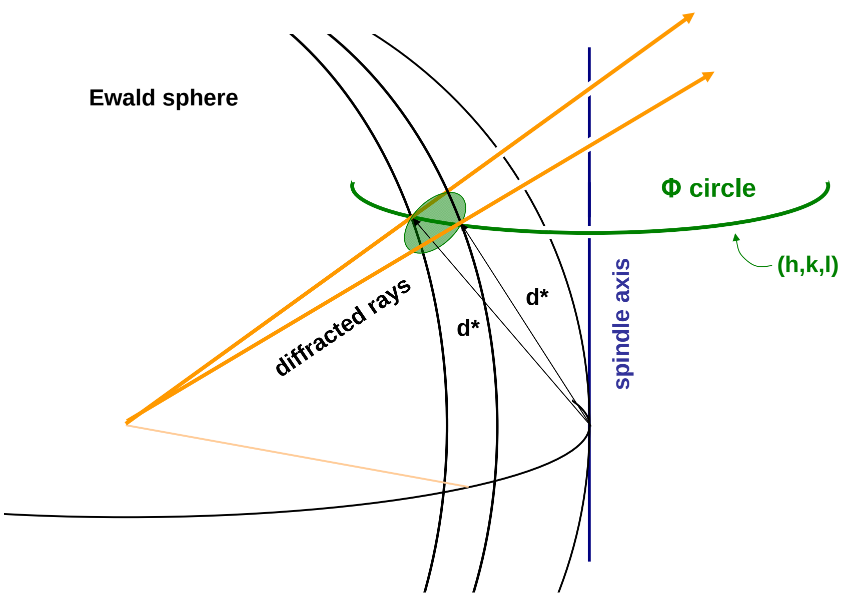

mosaic spread = 2.5º


mosaic spread = 3.2º

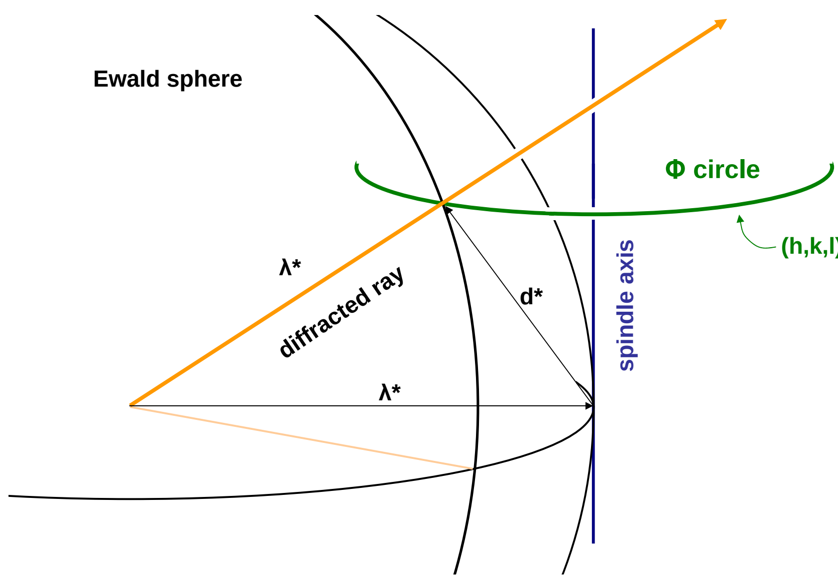




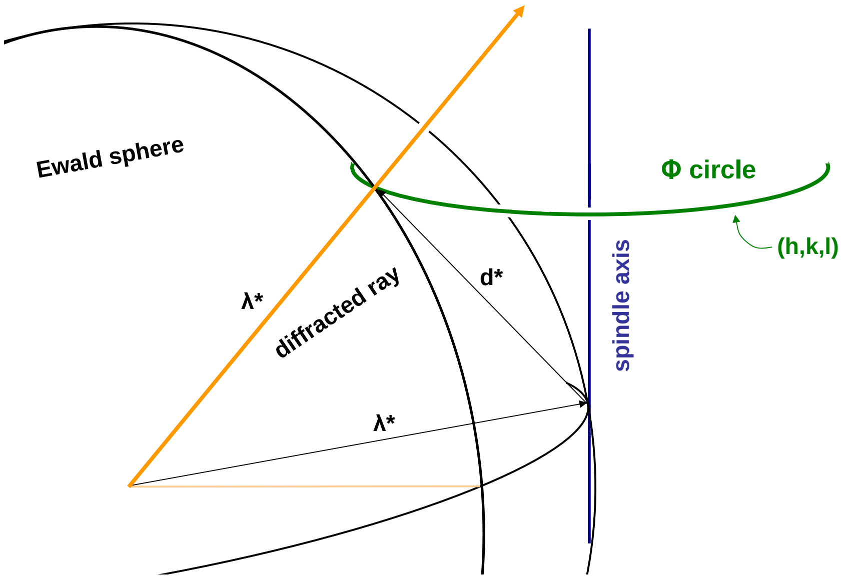
mosaic spread



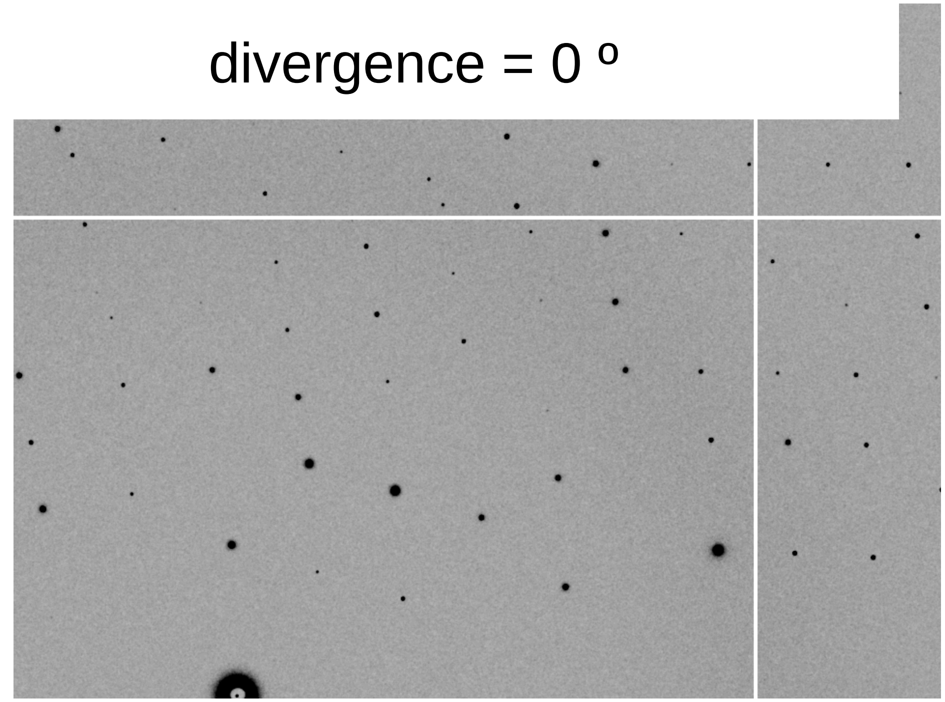
beam divergence



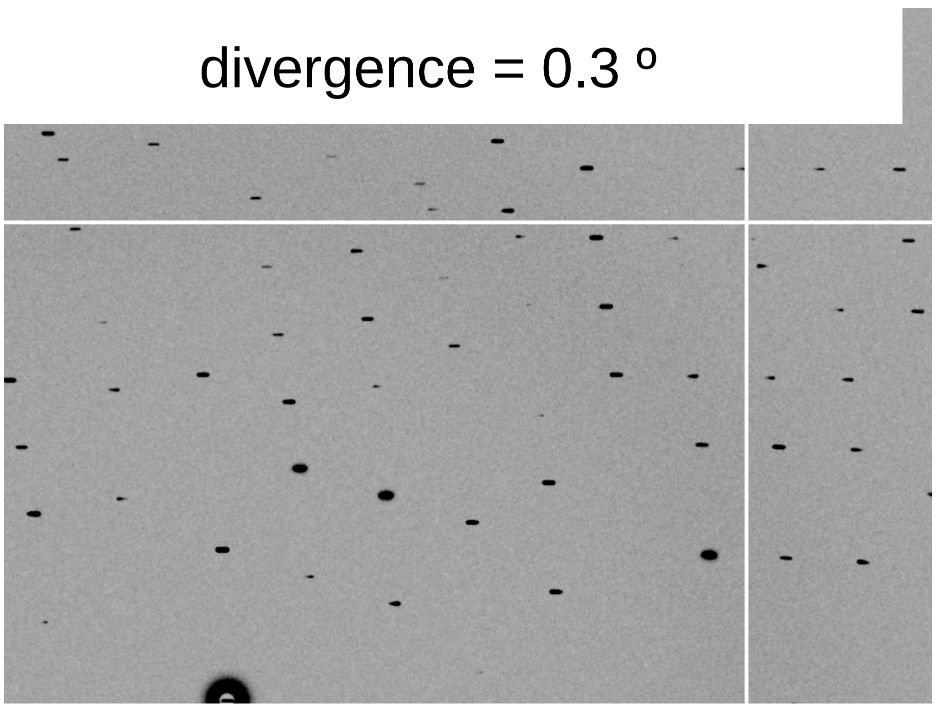
beam divergence



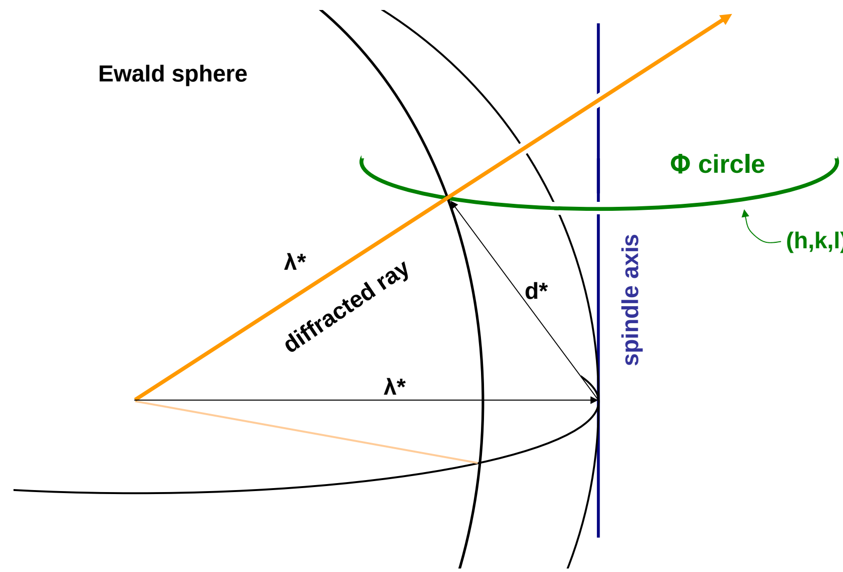
divergence = 0 º



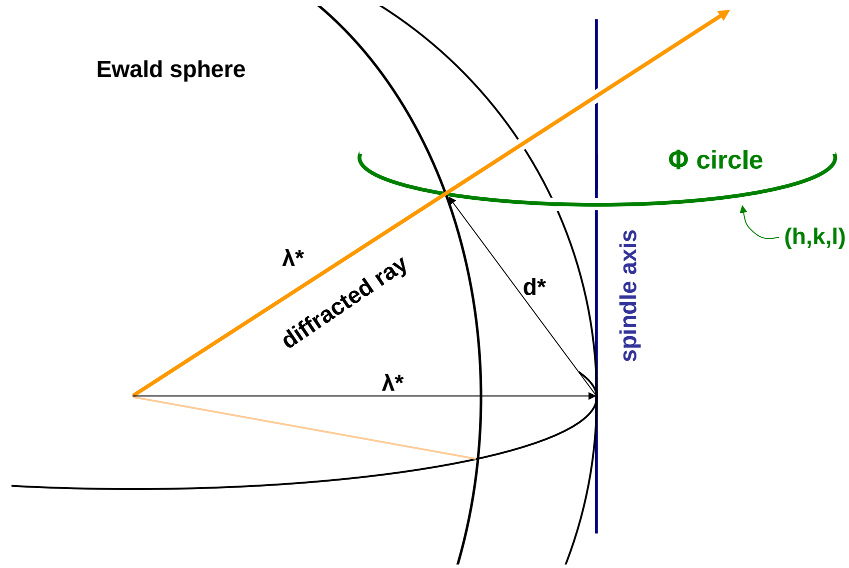
divergence = 0.3 º



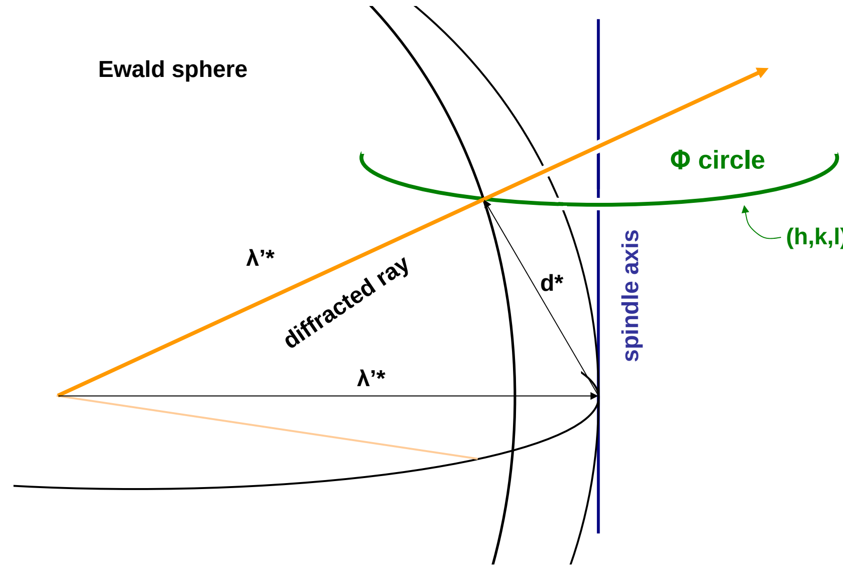
beam divergence



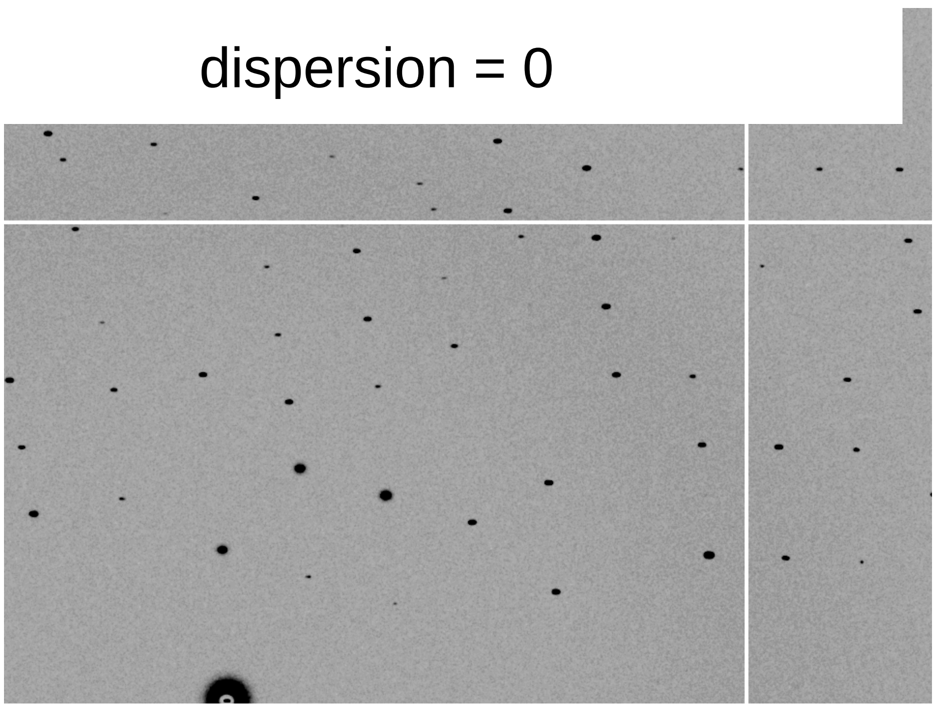
spectral dispersion



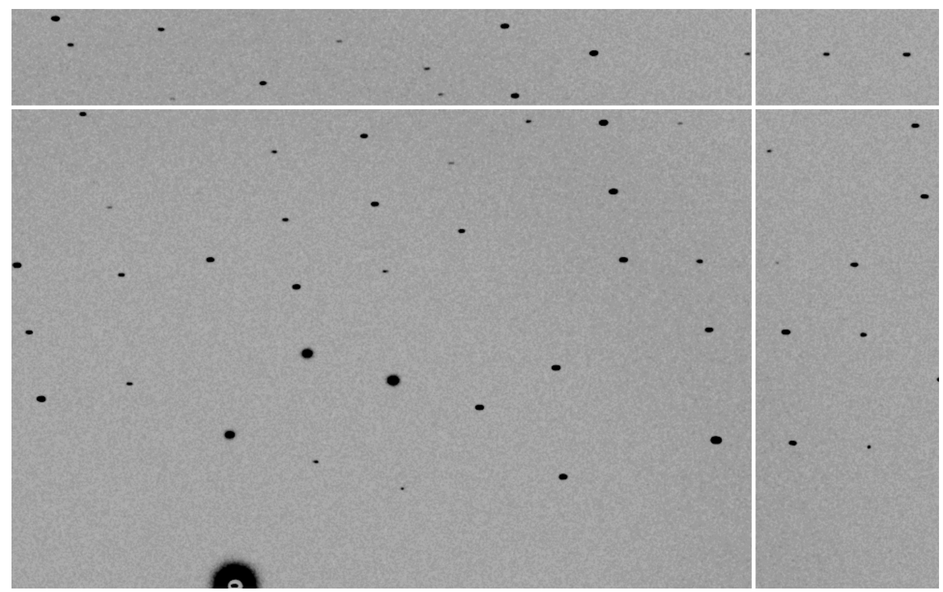
spectral dispersion



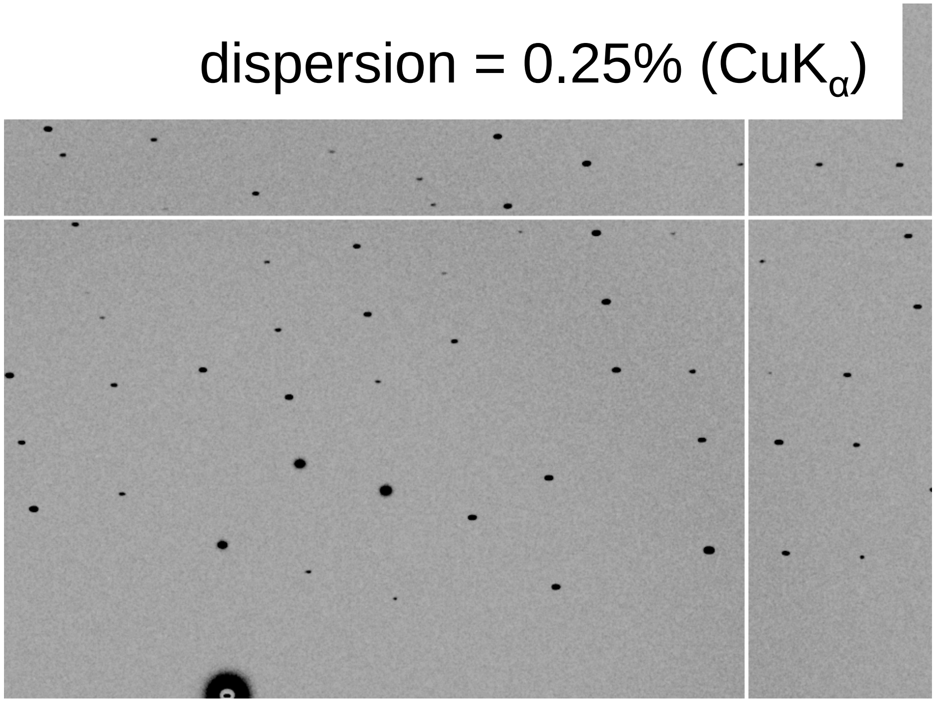
dispersion = 0



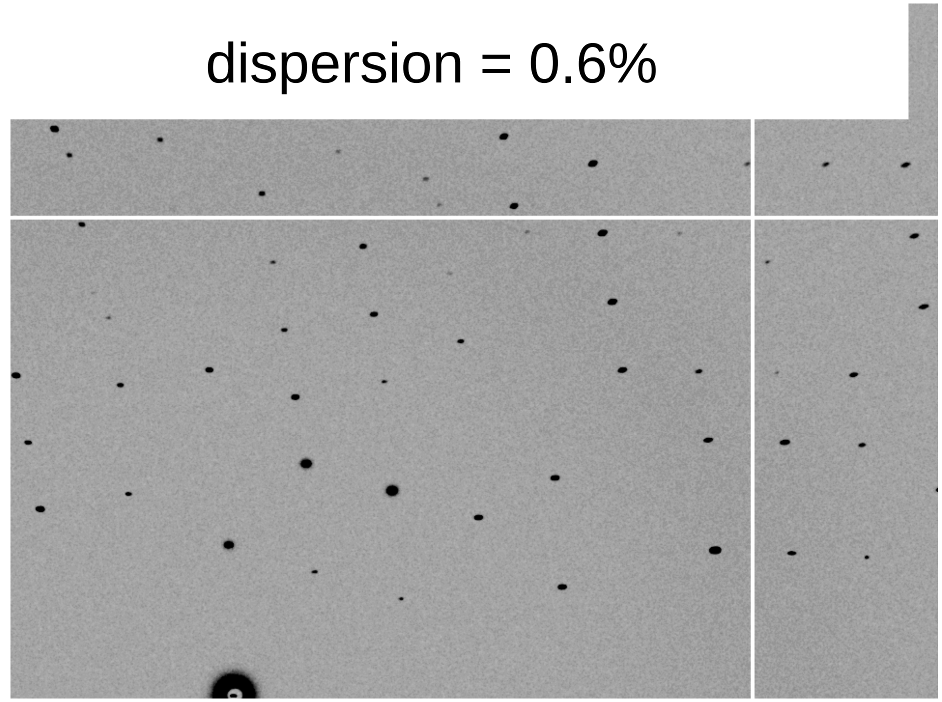
dispersion = 0.014% (Si 111)



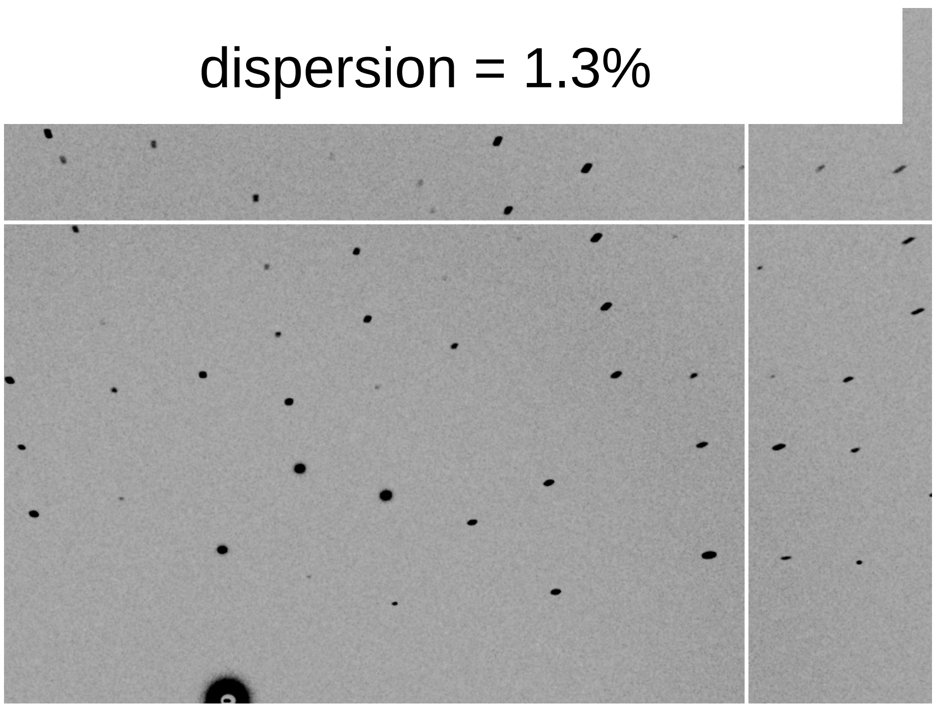
dispersion = 0.25% (CuK_α)



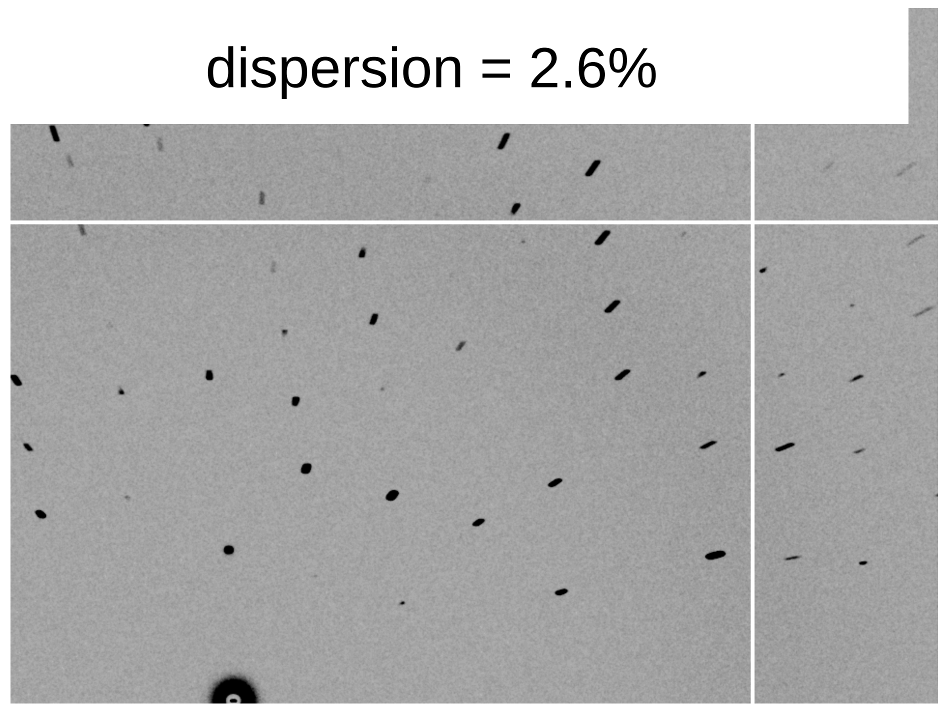
dispersion = 0.6%



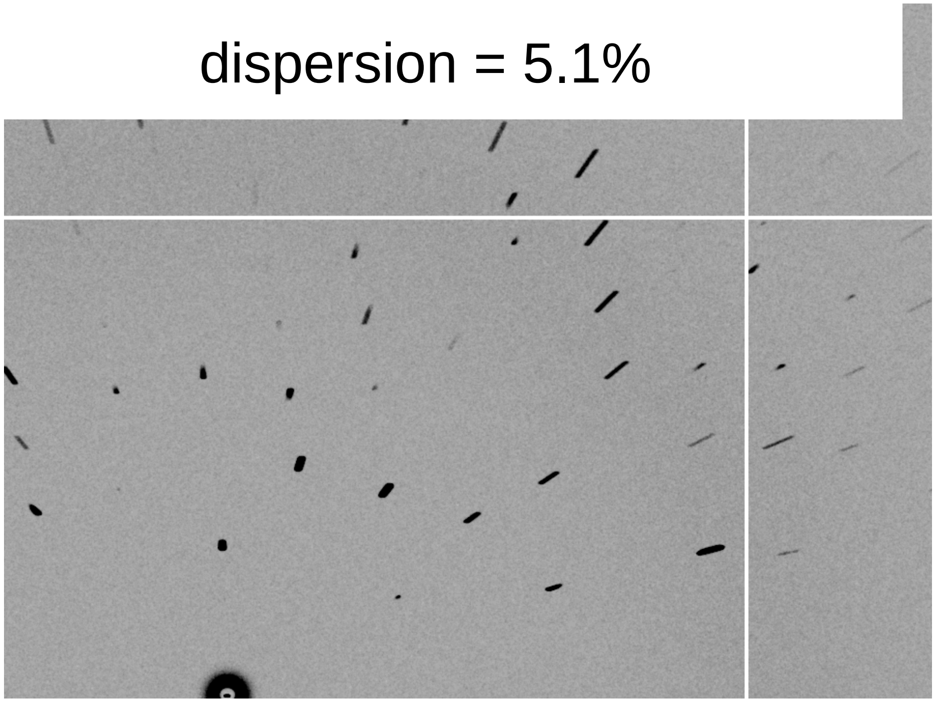
dispersion = 1.3%



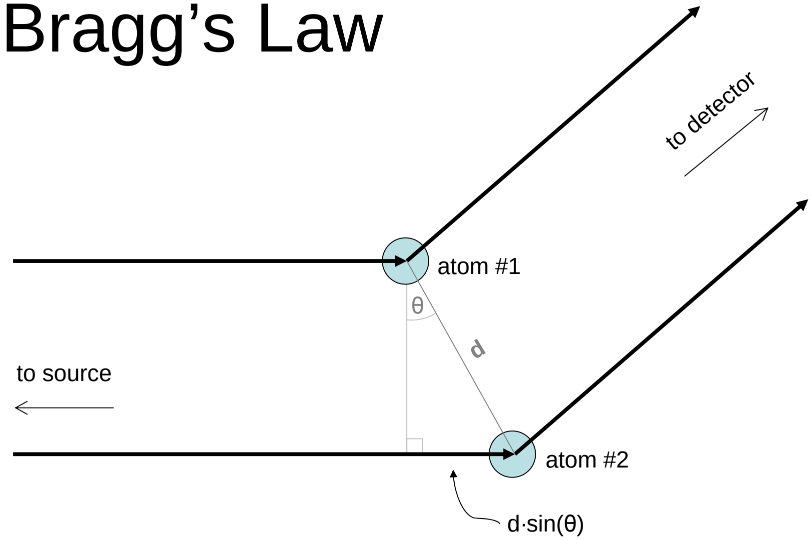
dispersion = 2.6%



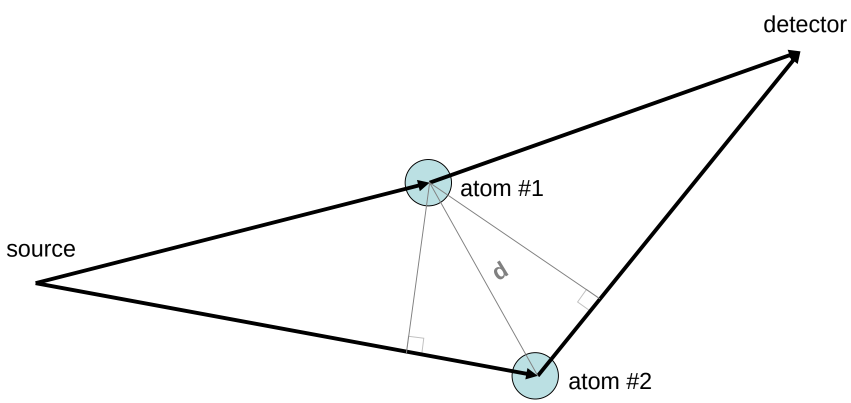
dispersion = 5.1%



Bragg's Law



"near"-ly Bragg's Law



mosaicity vs Wilson B

INTENSITY OF REFLECTION OF X-RAYS BY CRYSTALS 35

(*b*) *The amplitude reflected by a plane sheet of atoms :* We shall first consider the amplitude of the wave reflected by an infinite plane sheet of atoms, each of which scatters the incident X-rays.

Suppose A, fig. 15, is the source of the radiation, and let the amplitude of the reflected wave be required at B. Let the plane APB be normal to the plane of atoms, and let AP, PB make equal angles θ with this plane. Then P is such that the distance APB is the shortest distance from A to B *via* the plane. Let M be a point of the plane such that the distance

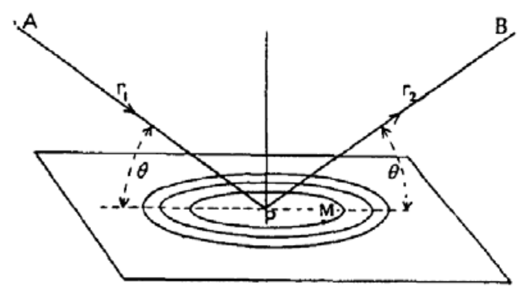
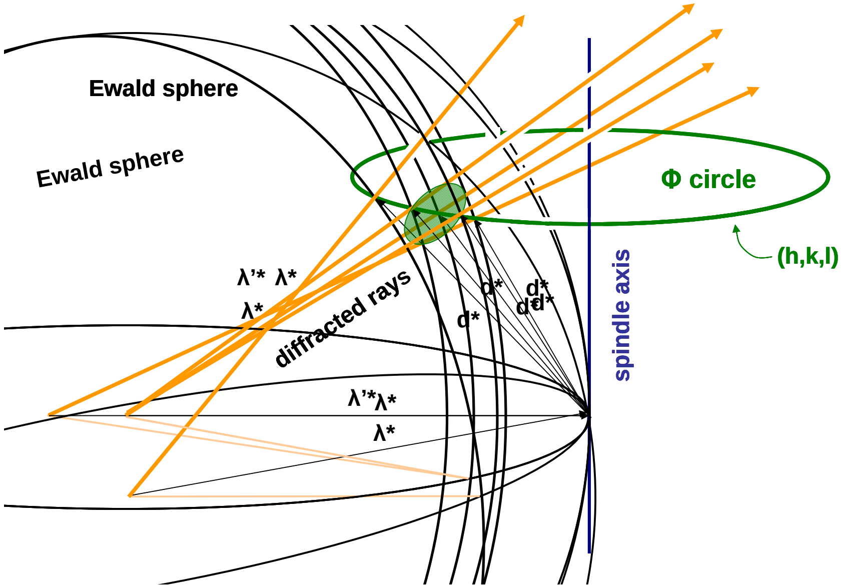
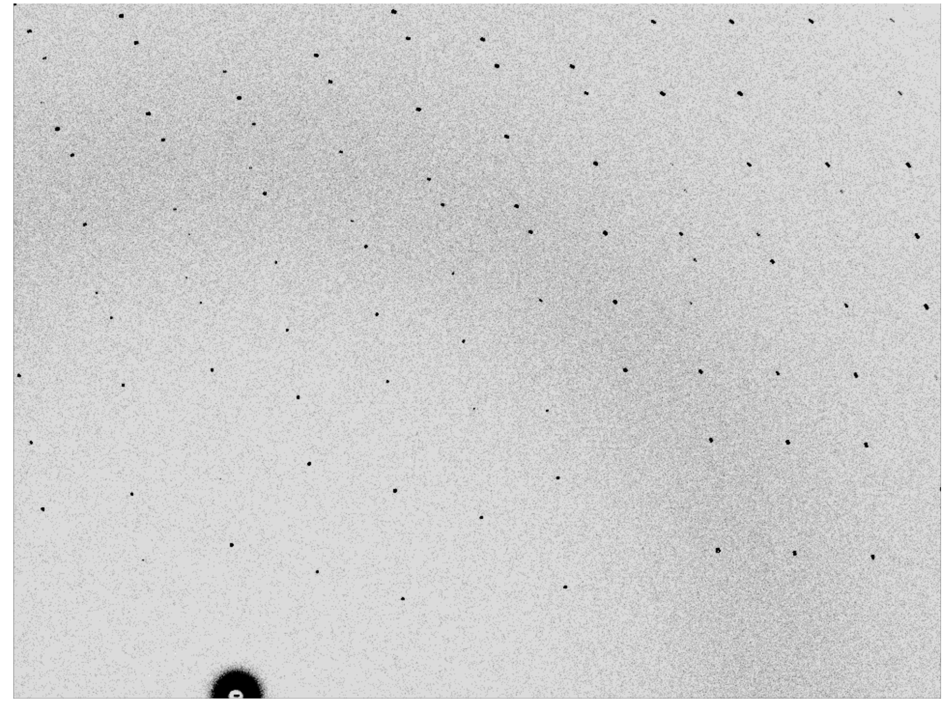


FIG. 15

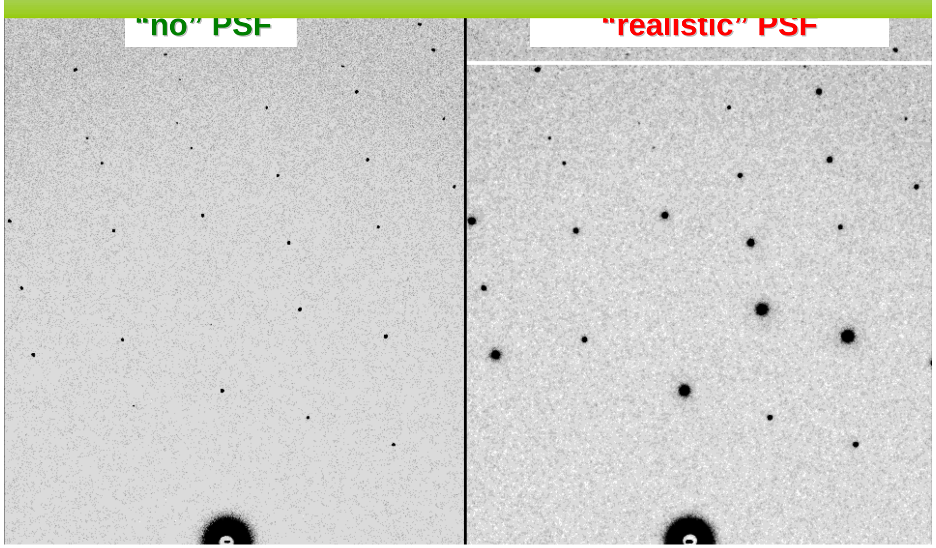
James R. W. (1962) *Optical Principles of the Diffraction of X rays.* Ox Bow press.

spot shape

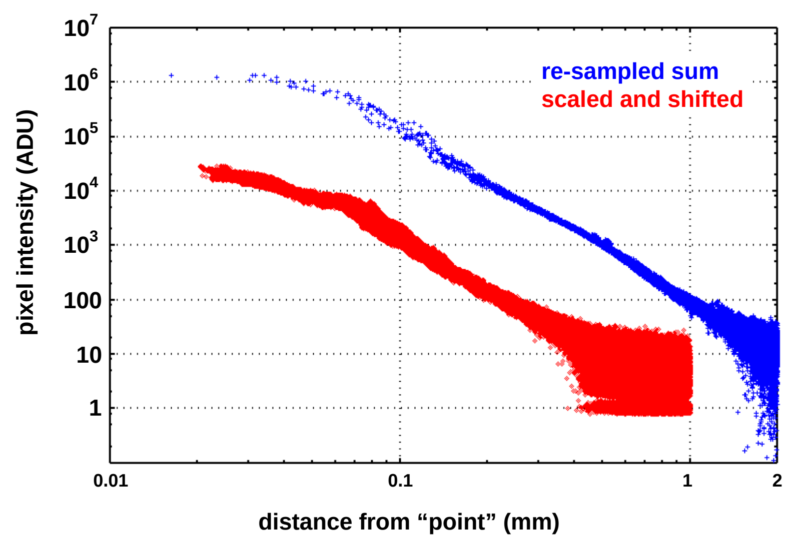




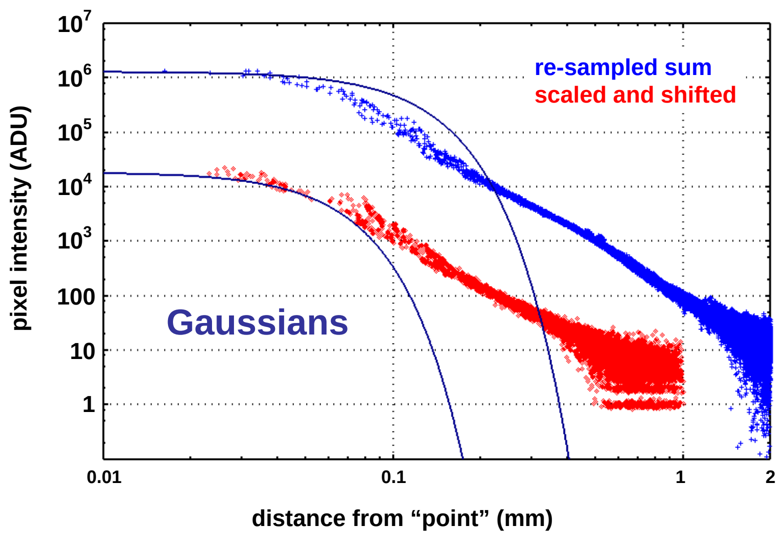
Point Spread Function



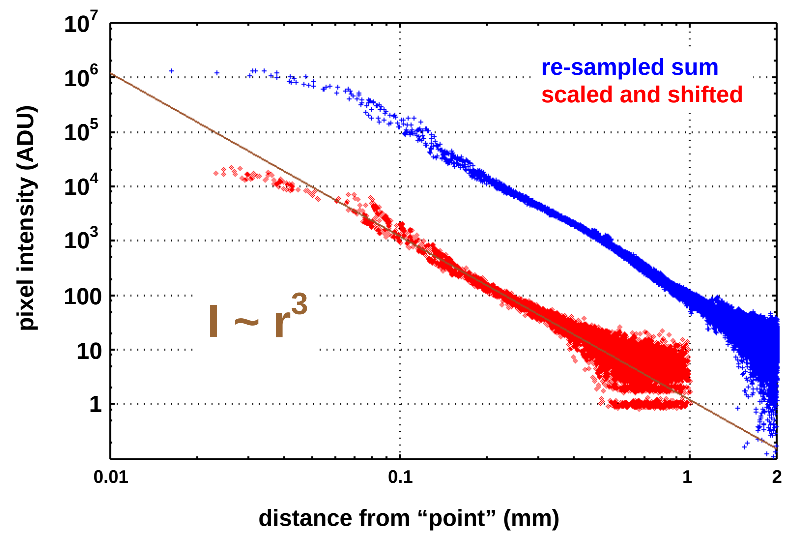
Point Spread Function



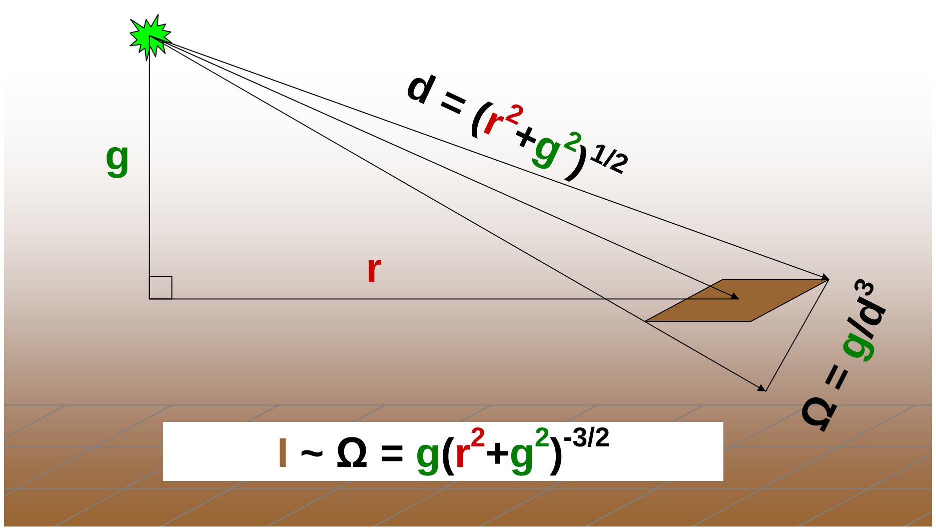
Point Spread Function



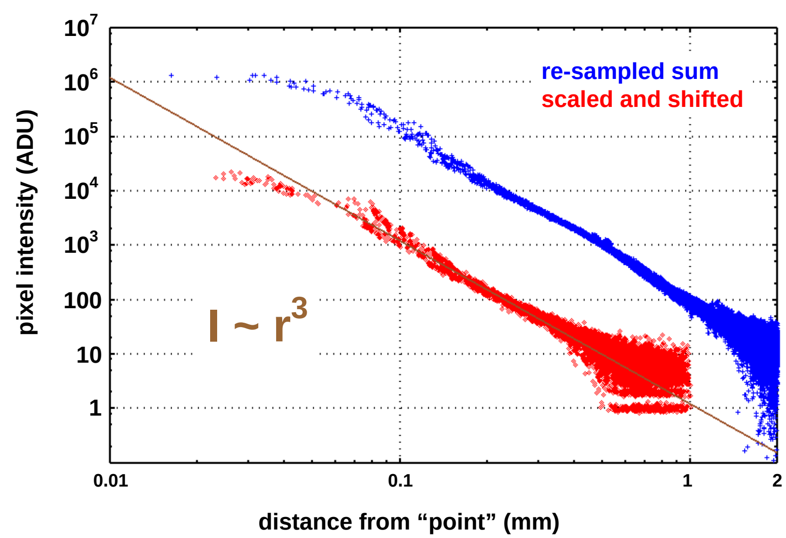
Point Spread Function



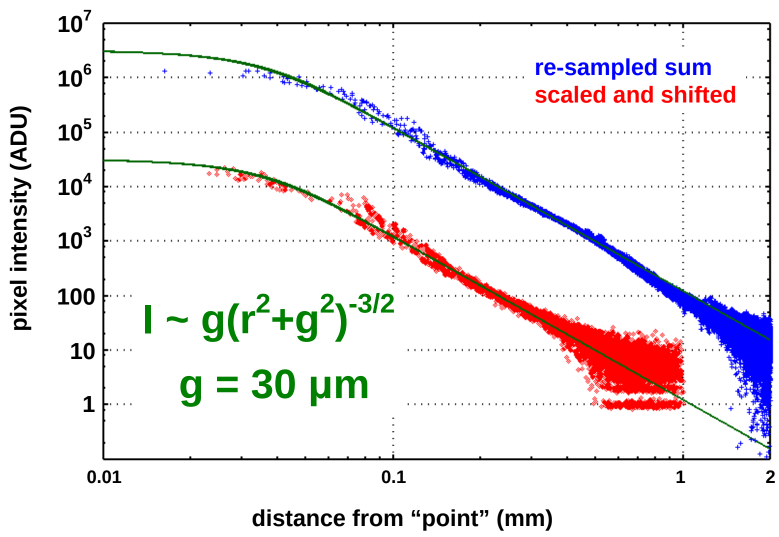
Point Spread Function



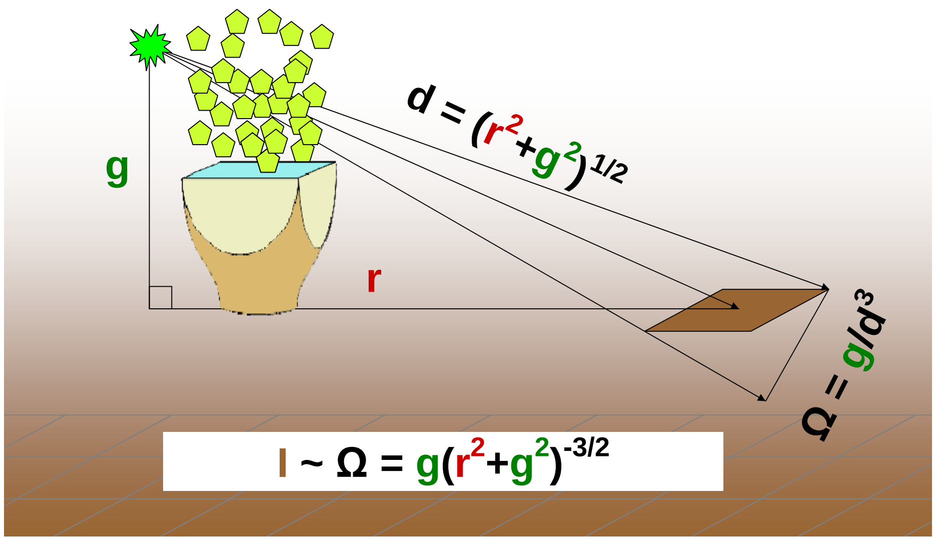
Point Spread Function

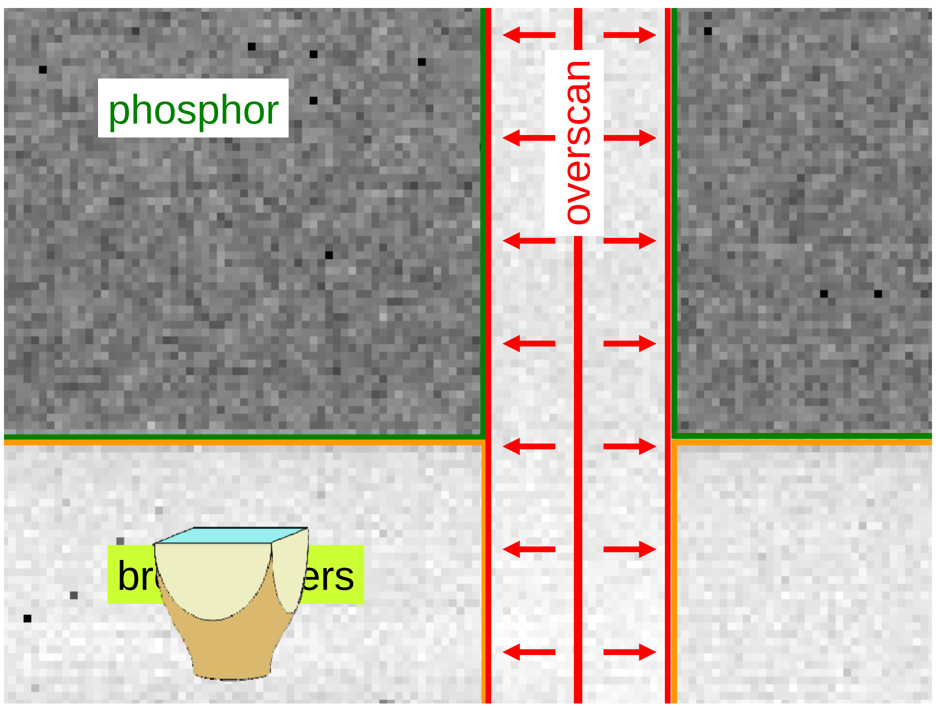


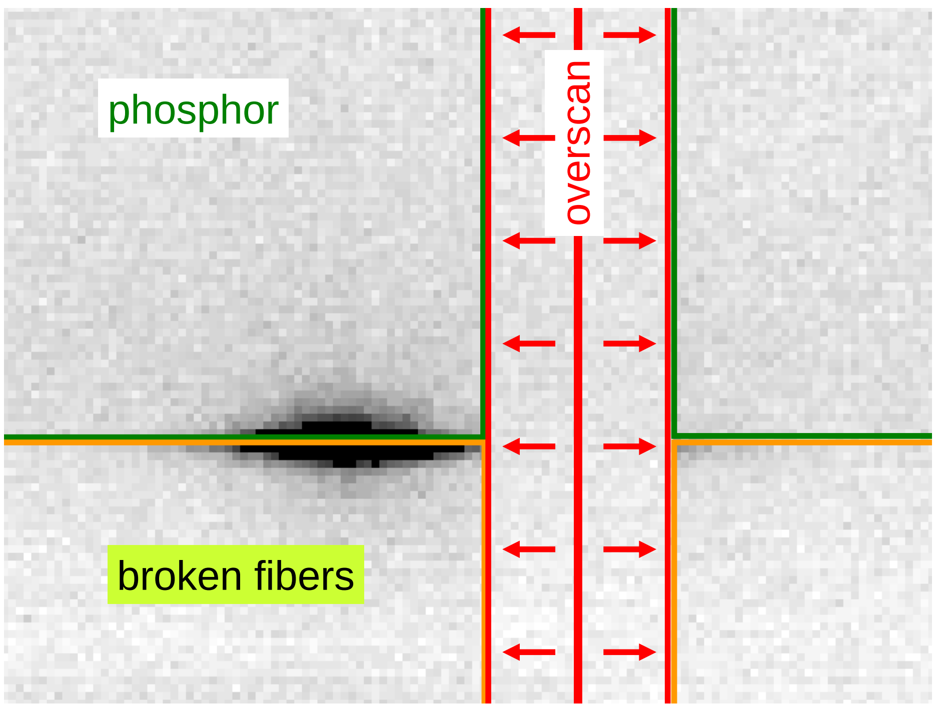
Point Spread Function

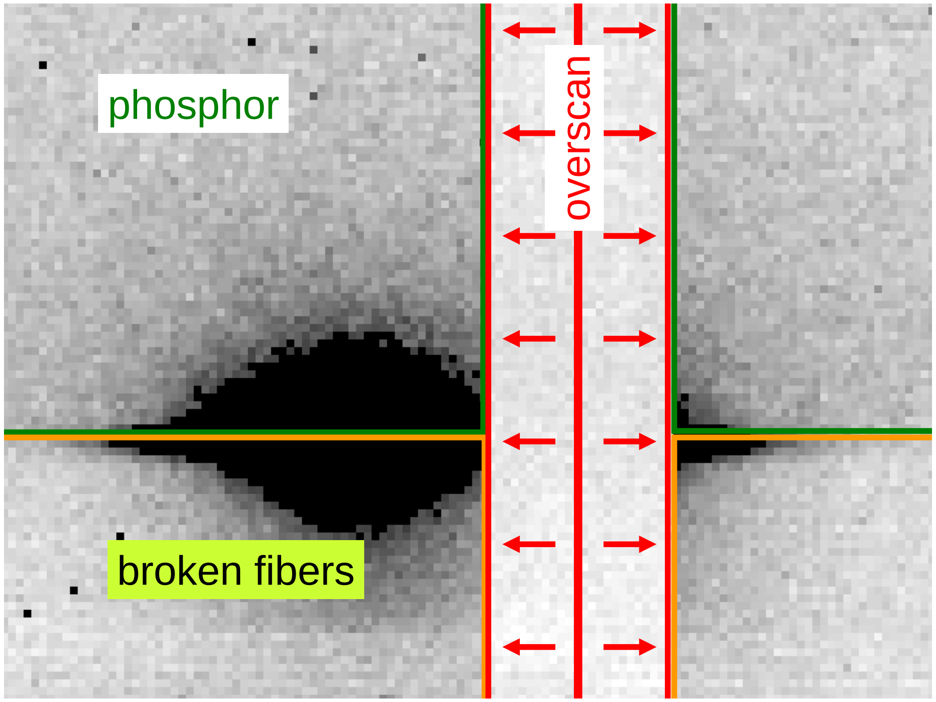


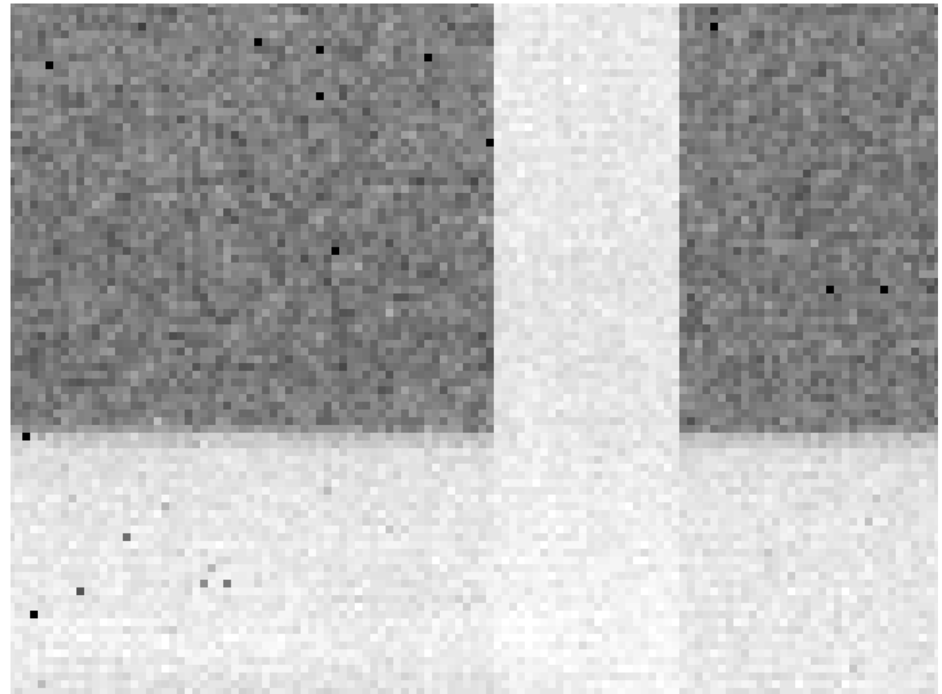
Point Spread Function











Intensity of a Bragg spot

$$I_{hkl} \approx |F(hkl)|^2$$

Darwin's Formula

$$I(hkl) = I_{beam}\, r_e^2 \frac{V_{xtal}}{V_{cell}} \frac{\lambda^3 L}{\omega V_{cell}} P\, A\, |F(hkl)|^2$$

I(hkl)	- photons/spot (fully-recorded)
I_{beam}	- incident (photons/s/m^2)
r_e	- classical electron radius (2.818x10^{-15} m)
V_{xtal}	- volume of crystal (in m^3)
V_{cell}	- volume of unit cell (in m^3)
λ	- x-ray wavelength (in meters!)
ω	- rotation speed (radians/s)
L	- Lorentz factor (speed/speed)
P	- polarization factor $(1+\cos^2(2\theta) - Pfac\cdot\cos(2\Phi)\sin^2(2\theta))/2$
A	- absorption factor $\exp(-\mu_{xtal}\cdot l_{path})$
F(hkl)	- structure amplitude (electrons)

C. G. Darwin (1914)

Darwin's Formula

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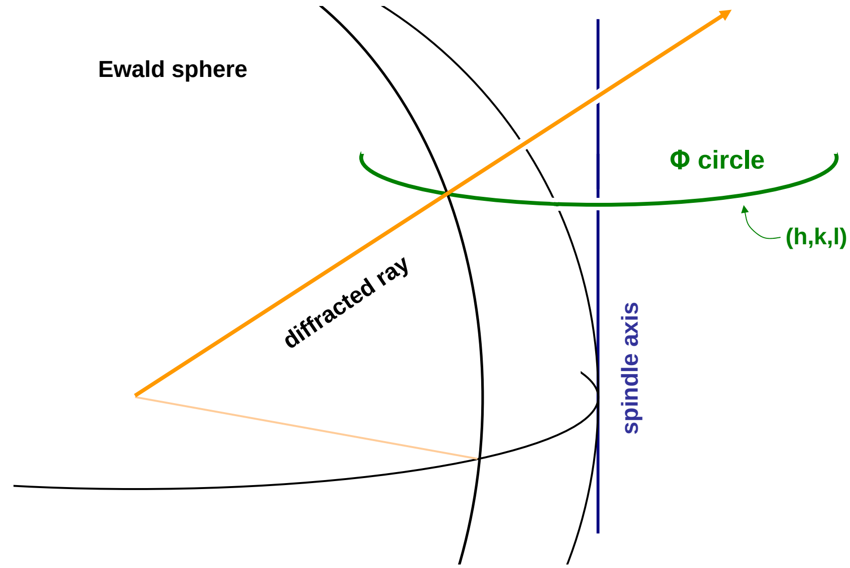
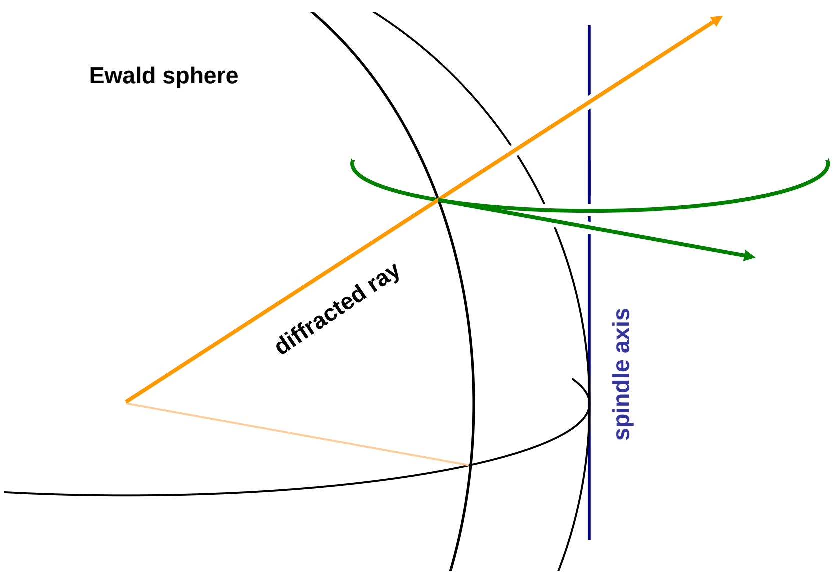
C. G. Darwin (1914)

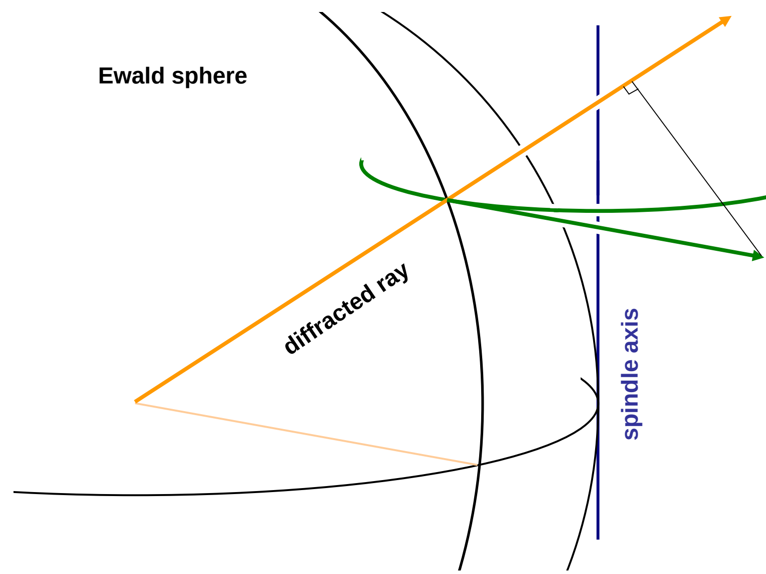
Lorentz Factor



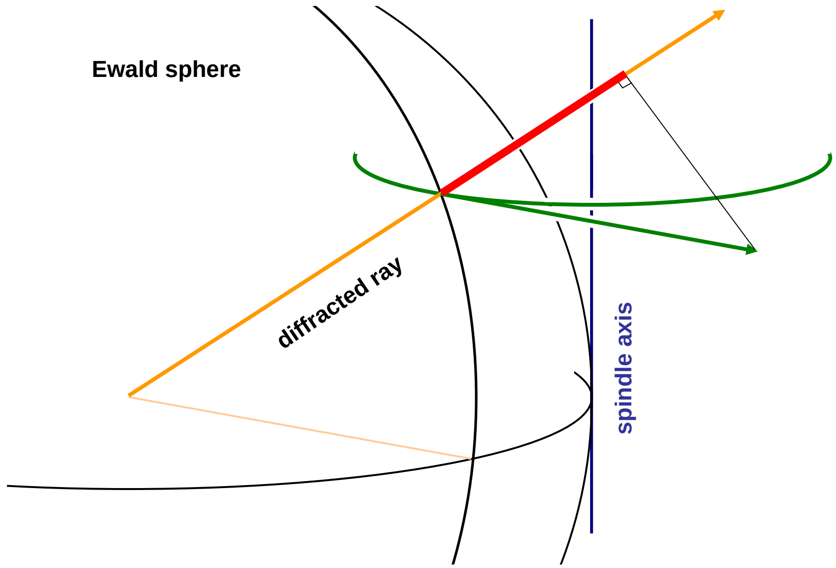
Lorentz Factor



Lorentz Factor



Lorentz Factor



Background scattering

R. W. James (1947)

$$I_{bg} = I_{beam}\ t\ r_e^2\ \frac{N_A \rho V}{Mr}\ P\ A\ |\ f(s)\ |^2$$

- **I_{bg}** - scattered photons/steradian
- **I_{beam}** - incident (photons/s/m^2)
- **t** - exposure time (s)
- **r_e** - classical electron radius (2.818×10^{-15} m)
- **N_A** - Avogadro number (6.02×10^{23})
- **ρ** - density of material (g/m^3)
- **Mr** - molecular weight (g/mol)
- **V** - volume of material (in m3)
- **P** - polarization factor
  $(1+\cos^2(2\theta) - \text{Pfac}\cdot\cos(2\Phi)\sin^2(2\theta))/2$
- **A** - absorption factor
  $\exp(-\mu_{xtal}\cdot l_{path})$
- **f(s)** - molecular structure amplitude (electrons)
- **s** - scattering length ($\sin(\theta)/\lambda$)

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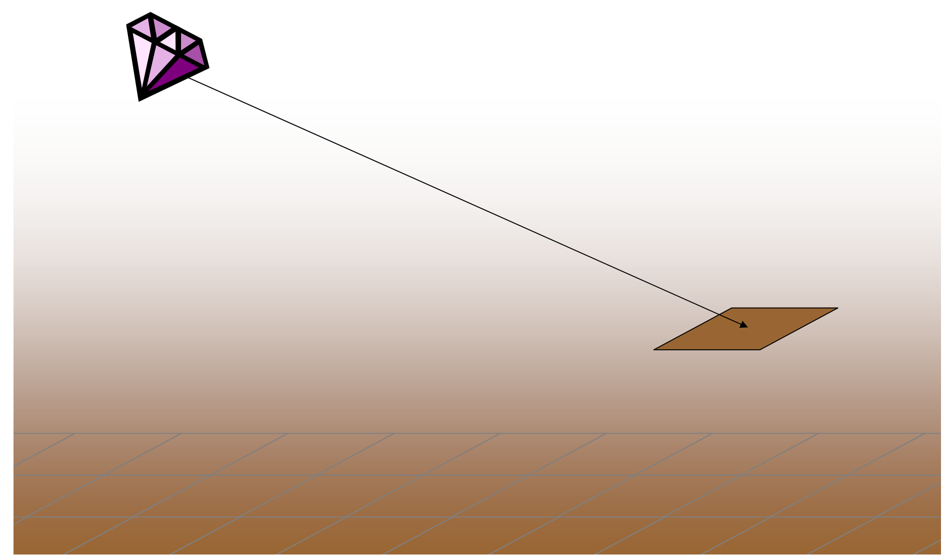
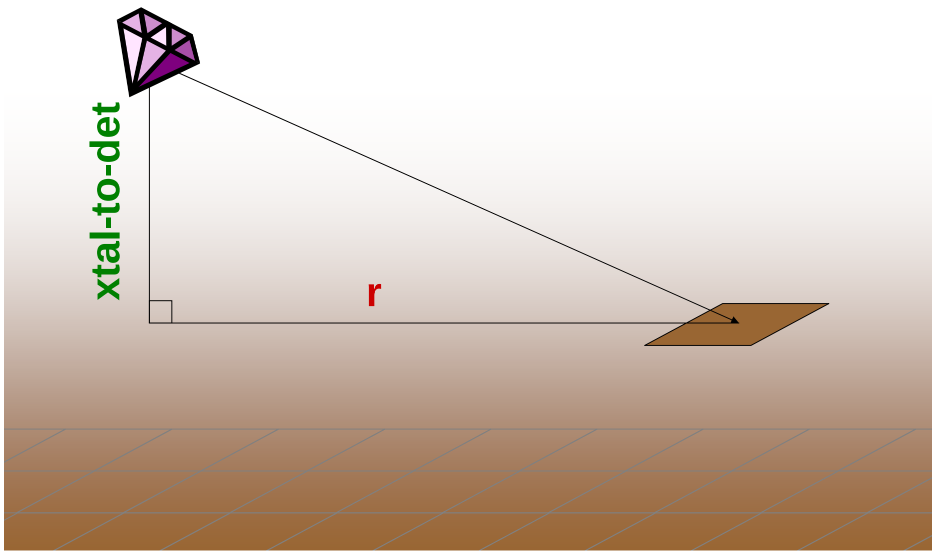
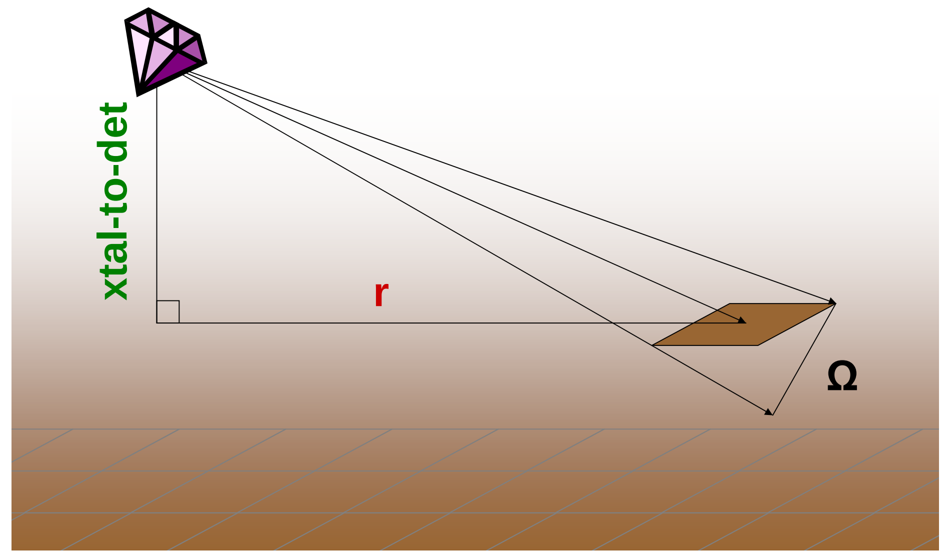
Solid angle of a pixel



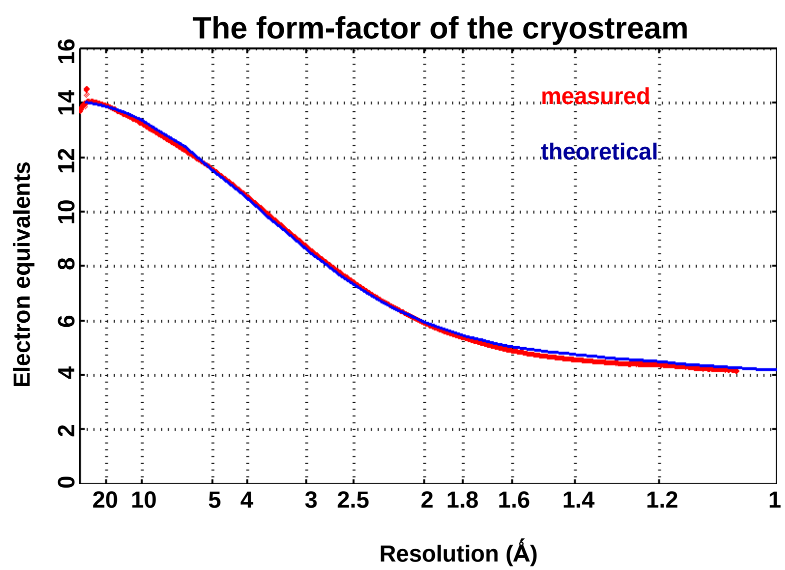
Solid angle of a pixel



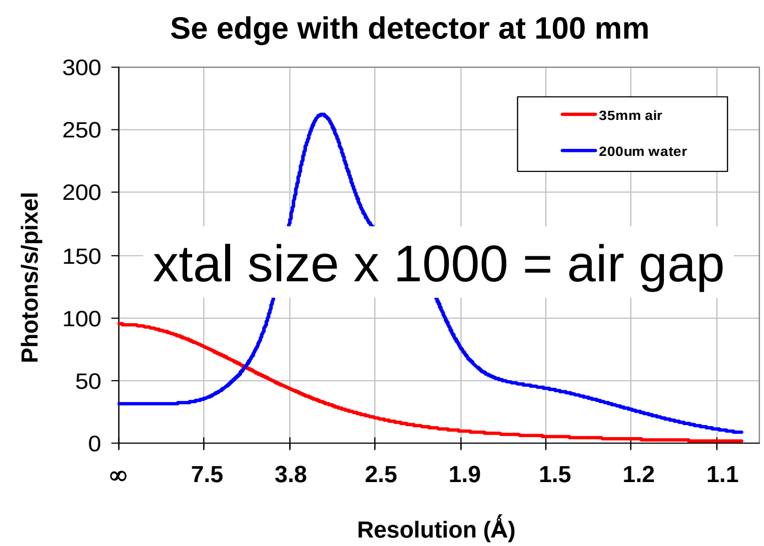
Solid angle of a pixel



Background scattering



Background scattering



Diffuse scattering

R. W. James (1947)

$$I_{ds} = I_{beam}\, t\, r_e^2 \frac{V_{xtal}}{V_{ASU}}\, P\, A \sum_a |f_a(s)|^2 \,(1-\exp(-2B_a \cdot s^2))$$

I_{ds}	- scattered photons/steradian	**P**	- polarization factor
I_{beam}	- incident (photons/s/m^2)	**A**	- absorption factor
t	- exposure time (s)	**a**	- particular atom in the ASU
r_e	- classical electron radius (2.818x10^{-15} m)	$f_a(s)$	- atomic structure amplitude (electrons)
V_{xtal}	- volume of crystal (in m^3)	**s**	- scattering length (sin(θ)/λ)
V_{ASU}	- asymmetric unit (in m^3)	B_a	- atomic B factor

Diffuse scattering

R. W. James (1947)

$$I_{ds} = I_{beam}\, t\, r_e^2 \frac{V_{xtal}}{V_{ASU}}\, P\, A \sum_a |f_a(s)|^2 \,(1-\exp(-2B_a \cdot s^2))$$

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t	- exposure time (s)	**a**	- particular atom in the ASU
r_e	- classical electron radius (2.818x10^{-15} m)	$f_a(s)$	- atomic structure amplitude (electrons)
V_{xtal}	- volume of crystal (in m^3)	**s**	- scattering length (sin(θ)/λ)
V_{ASU}	- asymmetric unit (in m^3)	B_a	- atomic B factor

mosaicity vs Wilson B

INTENSITY OF REFLECTION OF X-RAYS BY CRYSTALS 35

(*b*) *The amplitude reflected by a plane sheet of atoms:* We shall first consider the amplitude of the wave reflected by an infinite plane sheet of atoms, each of which scatters the incident X-rays.

Suppose A, fig. 15, is the source of the radiation, and let the amplitude of the reflected wave be required at B. Let the plane APB be normal to the plane of atoms, and let AP, PB make equal angles θ with this plane. Then P is such that the distance APB is the shortest distance from A to B *via* the plane. Let M be a point of the plane such that the distance

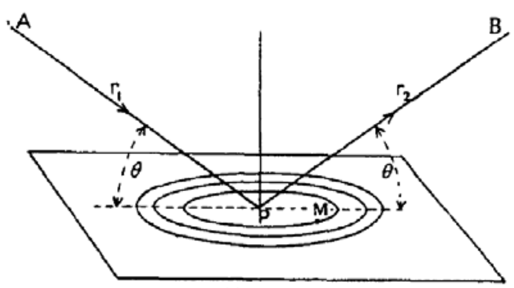

FIG. 15

James R. W. (1962) *Optical Principles of the Diffraction of X rays.* Ox Bow press.

Compton scattering

R. W. James (1947)

$$I_{compton} = I_{beam}\, t\, r_e^2 \frac{V_{xtal}}{V_{ASU}} \frac{P\, A}{1+\kappa\,(1-\cos(\theta))^2} \sum_a Z_a - |f_a(s)|$$

$I_{compton}$	- scattered photons/steradian	**A**	- absorption factor
I_{beam}	- incident (photons/s/m^2)	**a**	- particular atom in the ASU
t	- exposure time (s)	**θ**	- Bragg angle
r_e	- classical electron radius (2.818x10^{-15} m)	**κ**	- photon energy (keV) / 511 keV
		Z_a	- atomic number
V_{xtal}	- volume of crystal (in m^3)	$f_a(s)$	- atomic structure amplitude (electrons)
V_{ASU}	- asymmetric unit (in m^3)		
P	- polarization factor	**s**	- scattering length (sin(θ)/λ)

Compton scattering

R. W. James (1947)

$$I_{compton} = I_{beam}\, t\, r_e^2 \frac{V_{xtal}}{V_{ASU}} \frac{P\,A}{1+\kappa\,(1-\cos(\theta))^2} \sum_a Z_a - |f_a(s)|$$

$I_{compton}$	- scattered photons/steradian	**A**	- absorption factor
I_{beam}	- incident (photons/s/m^2)	**a**	- particular atom in the ASU
t	- exposure time (s)	**θ**	- Bragg angle
r_e	- classical electron radius (2.818x10^{-15} m)	**κ**	- photon energy (keV) / 511 keV
V_{xtal}	- volume of crystal (in m^3)	Z_a	- atomic number
V_{ASU}	- asymmetric unit (in m^3)	$f_a(s)$	- atomic structure amplitude (electrons)
P	- polarization factor	**s**	- scattering length (sin(θ)/λ)

Radiation Damage Model

$$dose = I_{beam}\, t\, E\, (1-\exp(-\mu_{xtal} T_{xtal}))\ /\ \rho$$

dose	- absorbed dose (Gy)
I_{beam}	- incident (photons/s/m^2)
E	- photon energy (J/photon)
t	- exposure time (s)
μ_{xtal}	- absorption coefficient (in 1/m)
T_{xtal}	- thickness of crystal (in m)
ρ	- crystal density (kg/m^3)

Radiation Damage Model

$$dose = I_{beam}\, t\, k_{dose}$$

dose	- absorbed dose (MGy)
I_{beam}	- incident (~20 M photons/s/m^2)
t	- exposure time (s)
k_{dose}	- 2000 (photon/μm^2/Gy)

Holton J. M. (2009) *J. Synchrotron Rad.* **16** 133-42

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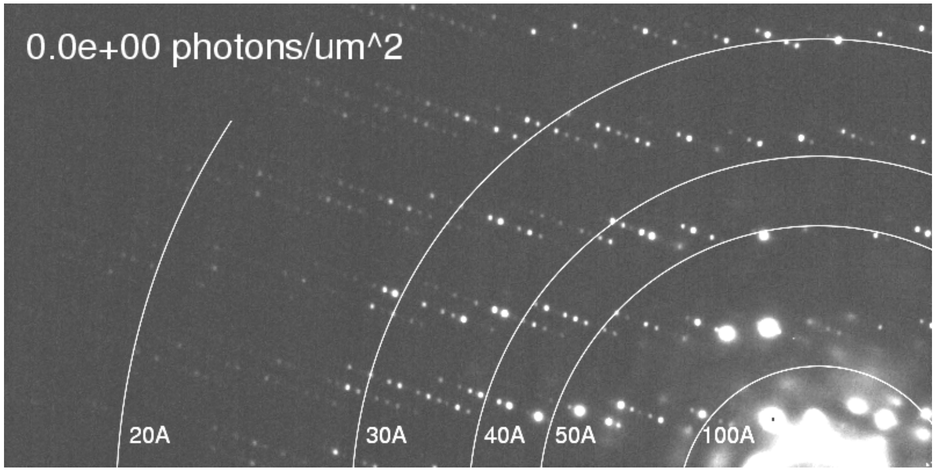
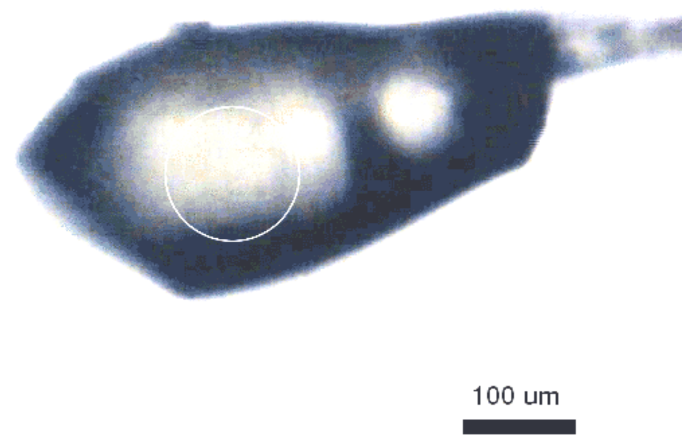
Holton J. M. (2009) *J. Synchrotron Rad.* **16** 133-42

Radiation damage



Macroscopic damage

0.0e+00 photons/um^2



crystal expansion

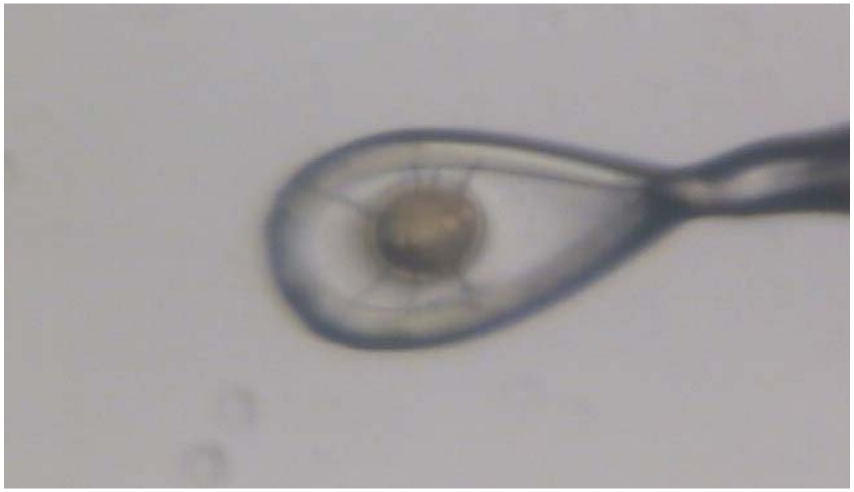
Protein crystal in sucrose, NaWO4 and oil

crystal expansion

Protein crystal in sucrose, NaWO4 and oil

crystal expansion

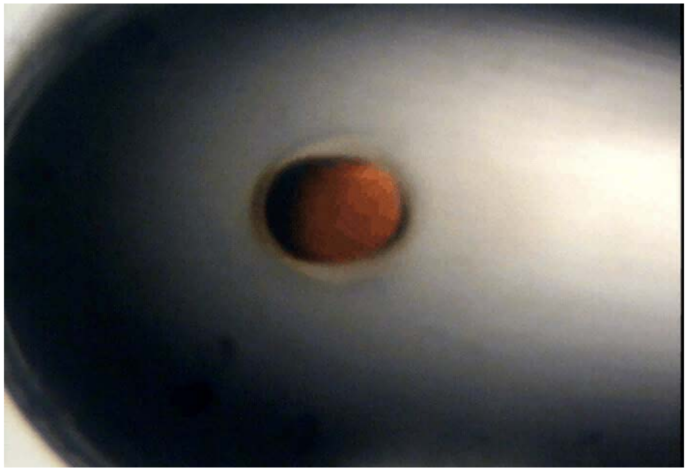
Protein crystal in sucrose, NaWO4 and oil



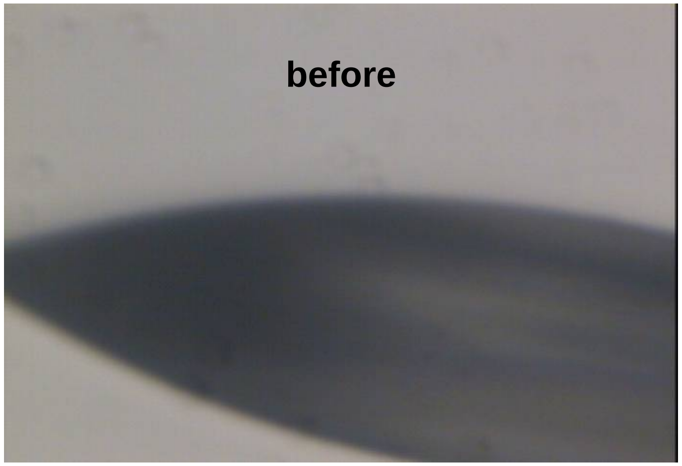
crystal expansion

Protein crystal in sucrose, NaWO4 and oil

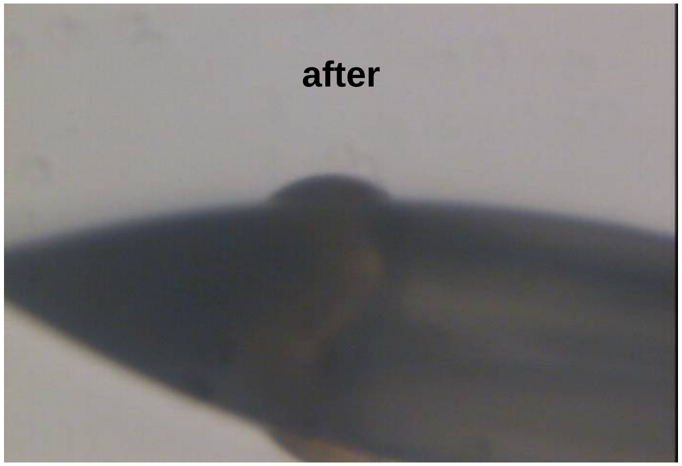
Distention of cryo with dose



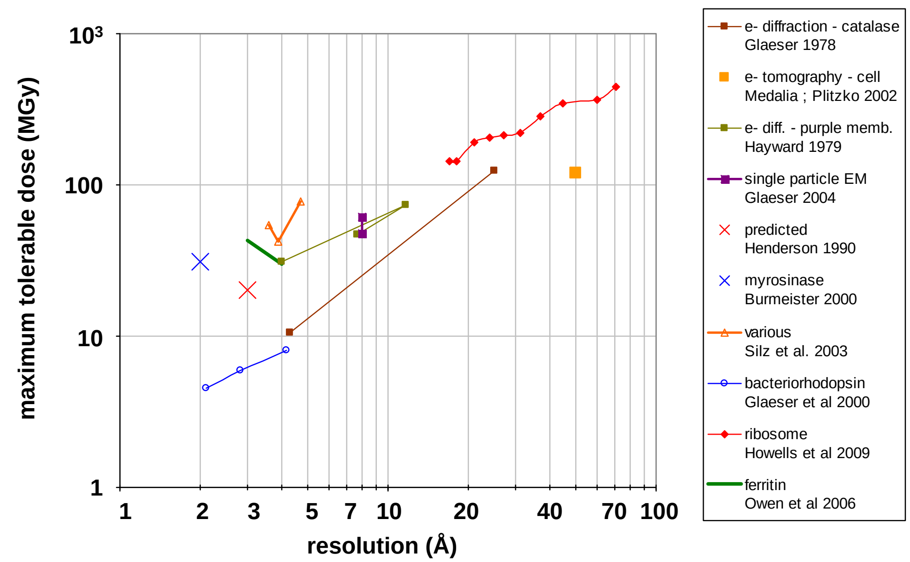
Distention of cryo with dose



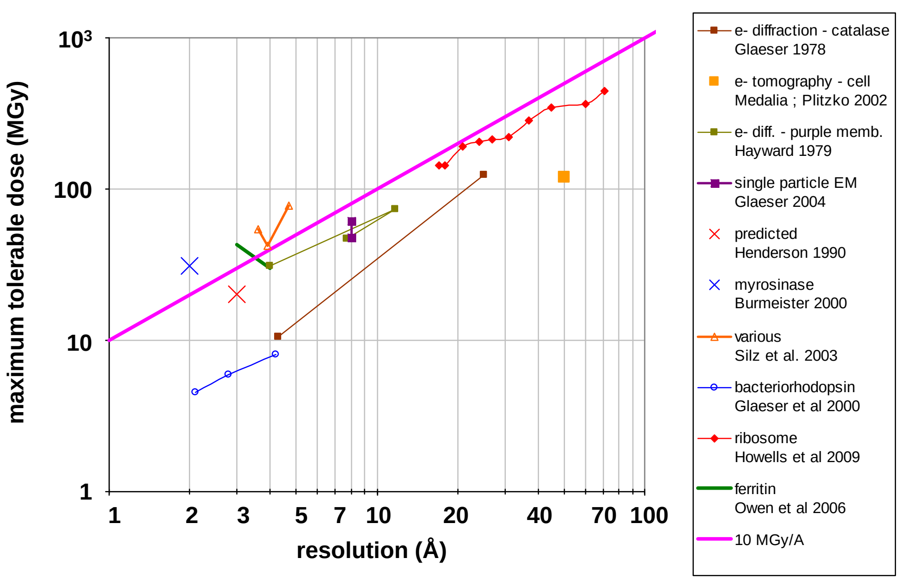
Distention of cryo with dose



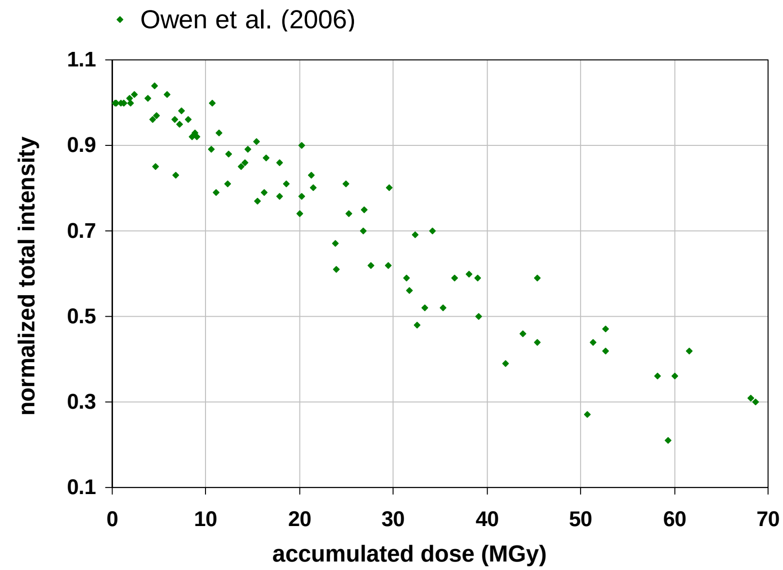
Howells *et al.* (2009)
J. Electron. Spectrosc. Relat. Phenom. **170** 4-12



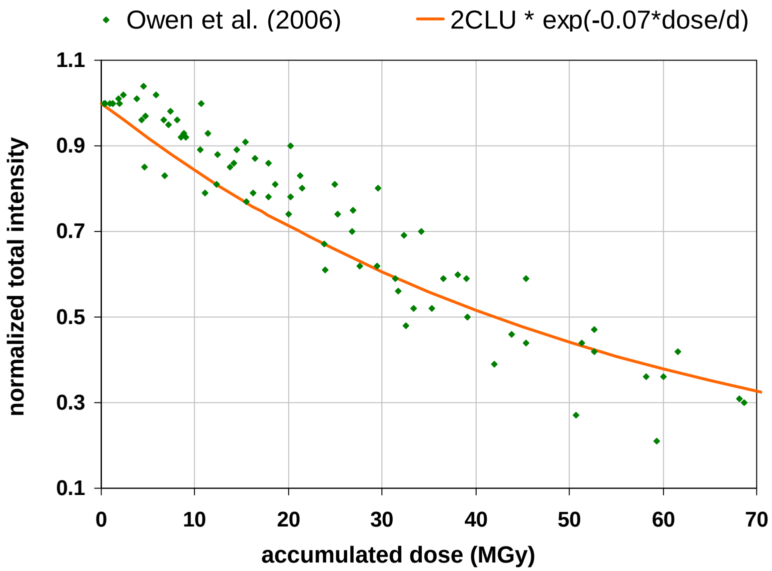
Howells *et al.* (2009)
J. Electron. Spectrosc. Relat. Phenom. **170** 4-12



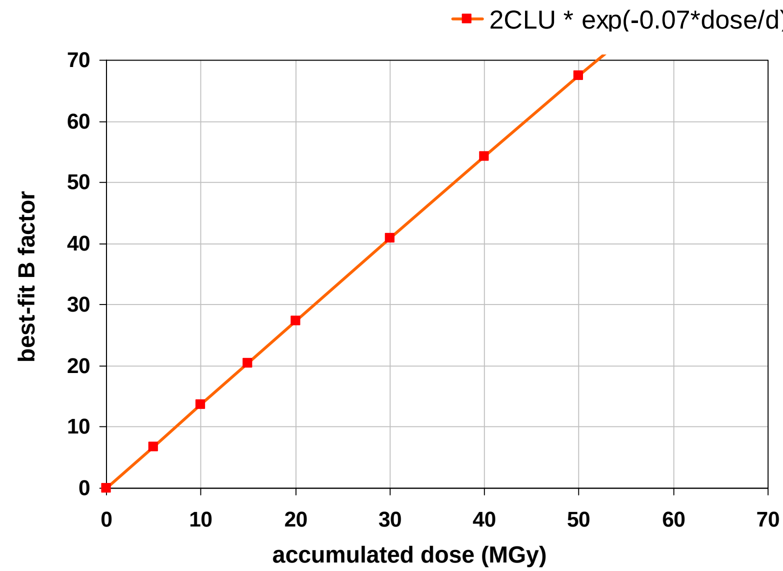
Radiation Damage Model



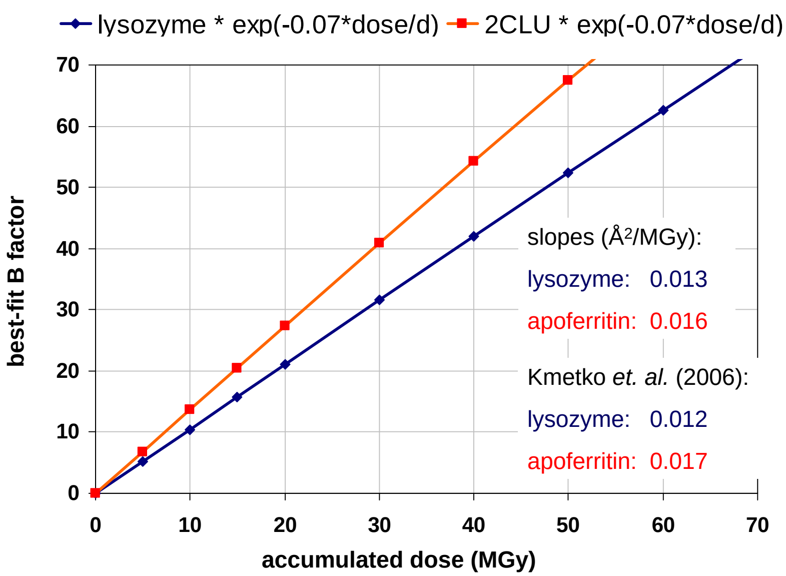
Radiation Damage Model



Radiation Damage Model



Radiation Damage Model

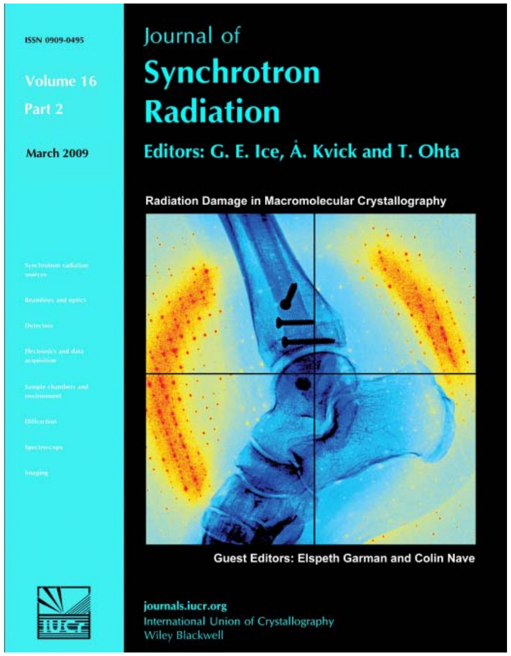


10 MGy/Å

what the is a MGy?

http://bl831.als.lbl.gov/

damage_rates.pdf



Holton J. M. (2009) *J. Synchrotron Rad.* **16** 133-42

Radiation Damage Model

global (lattice) damage

$$|F_{used}| = |F_{undam}| \exp(-\ln(2) \frac{dose}{d \cdot H})$$

F_{used}	- structure factor used for spot
F_{undam}	- structure factor of undamaged crystal
dose	- absorbed dose (MGy)
H	- 10 MGy/Å
d	- resolution of spot (Å)

Radiation Damage Model

global (lattice) damage

$$F = F_0 \exp(- A \cdot s)$$

F	- structure factor used for spot
F_0 crystal	- structure factor of undamaged
A	- something Debye said was zero
s	- 0.5/**d**
d	- resolution of spot (Å)

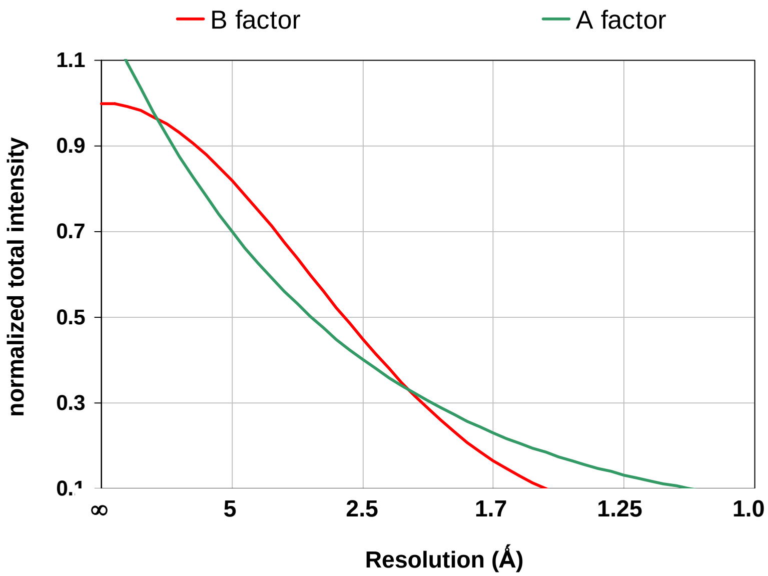
Radiation Damage Model

global (lattice) damage

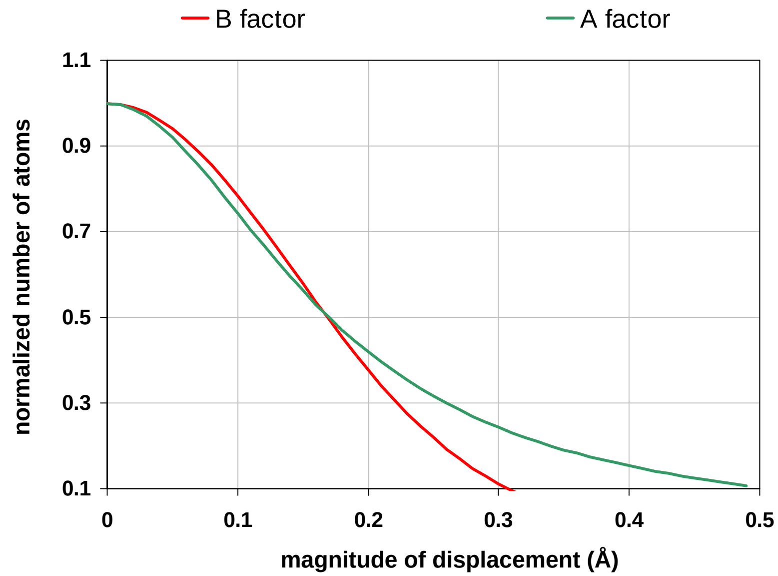
$$F = F_0 \exp(- A \cdot s - B \cdot s^2 - C \cdot s^3 - \dots)$$

A	- something Debye said was zero
B	- canonical Debye-Waller factor
C	- something else Debye said was zero
s	- 0.5/**d**
d	- resolution of spot (Å)

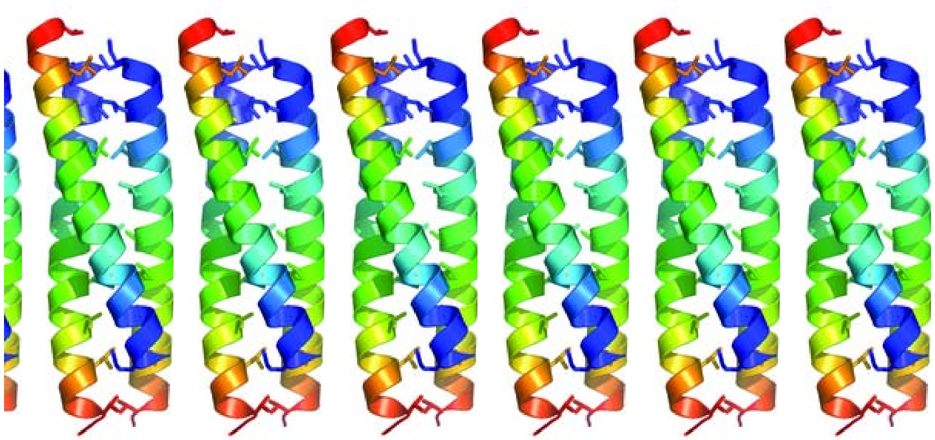
Radiation Damage Model



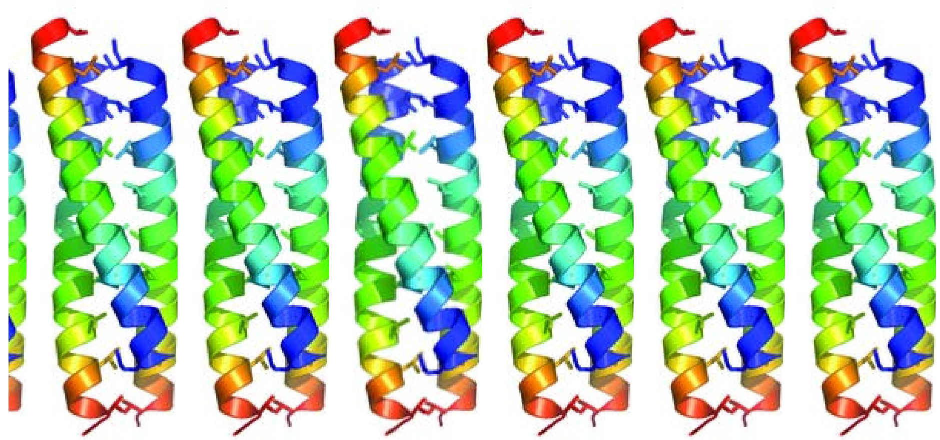
Radiation Damage Model



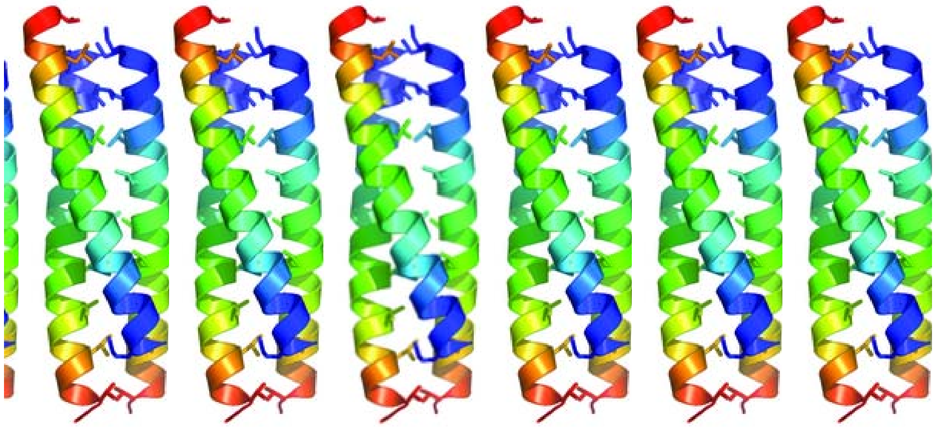
Radiation Damage Model



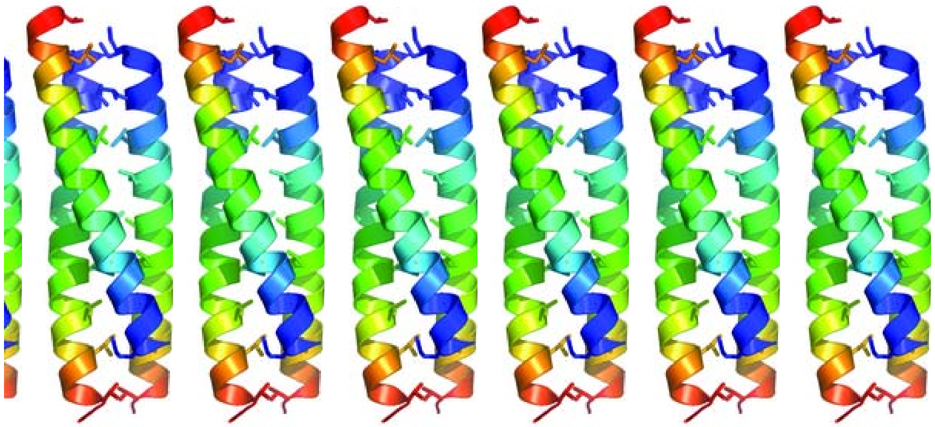
Radiation Damage Model



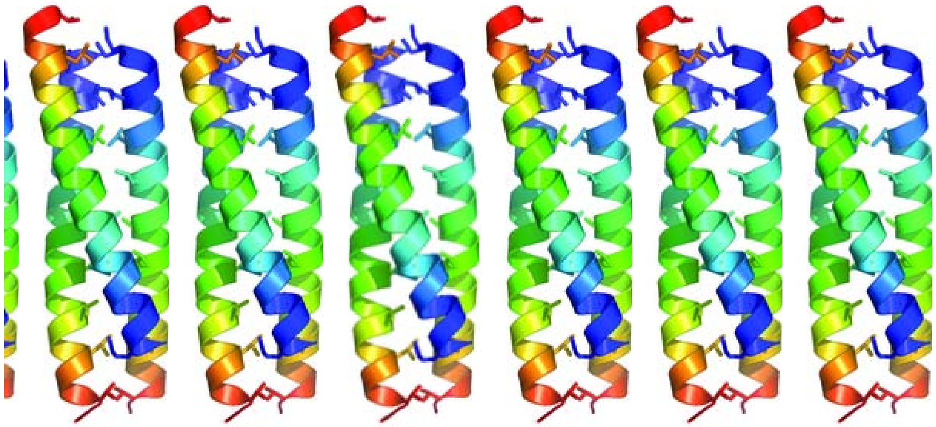
Radiation Damage Model



Radiation Damage Model

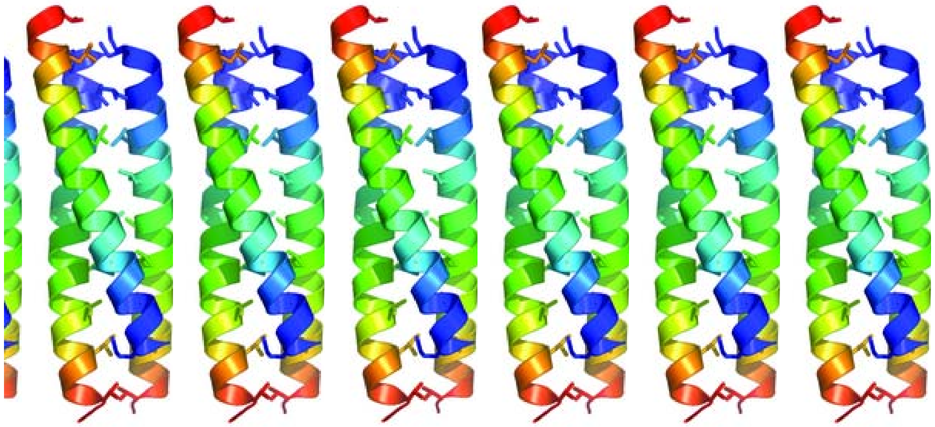


Radiation Damage Model



Kanzaki 1957

Radiation Damage Model



Kanzaki 1957

Radiation Damage Model

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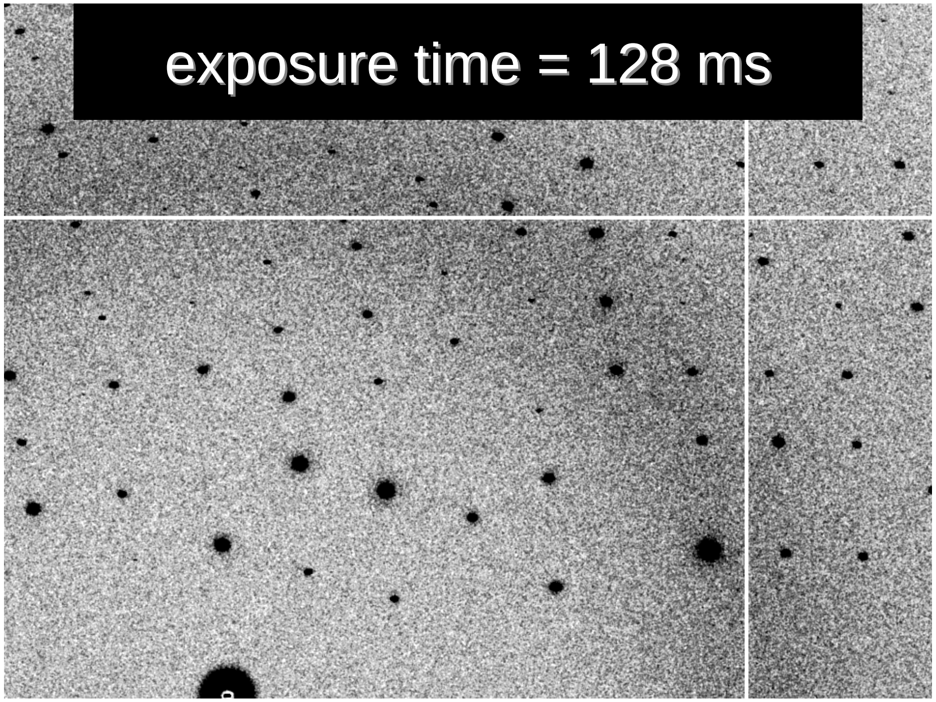
dose	- absorbed dose (MGy)
H	- 10 MGy/Å
d	- resolution of spot (Å)

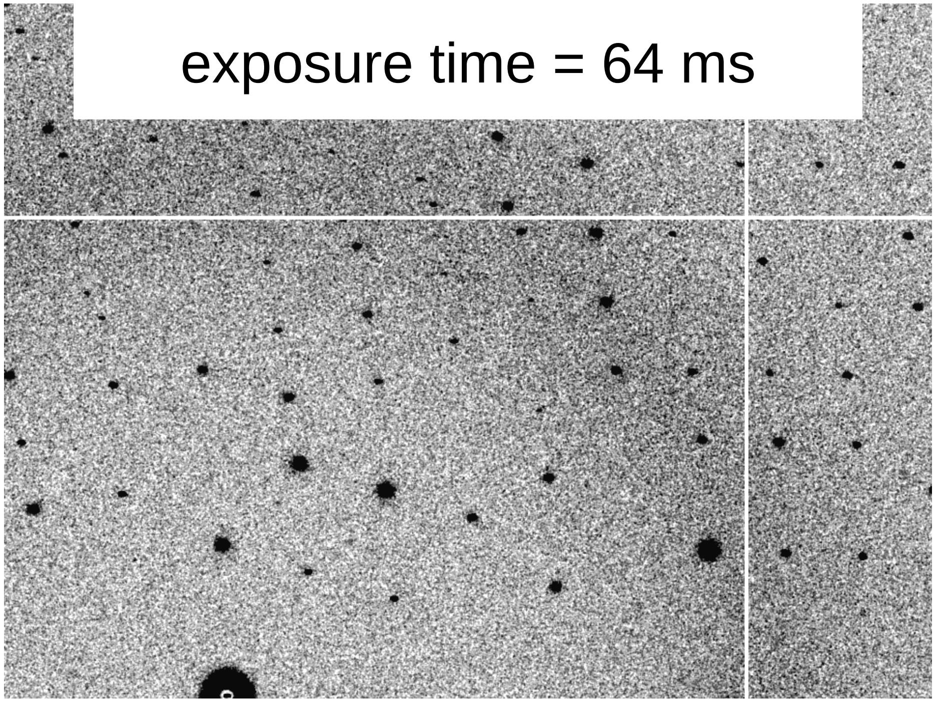
Development Snapshot

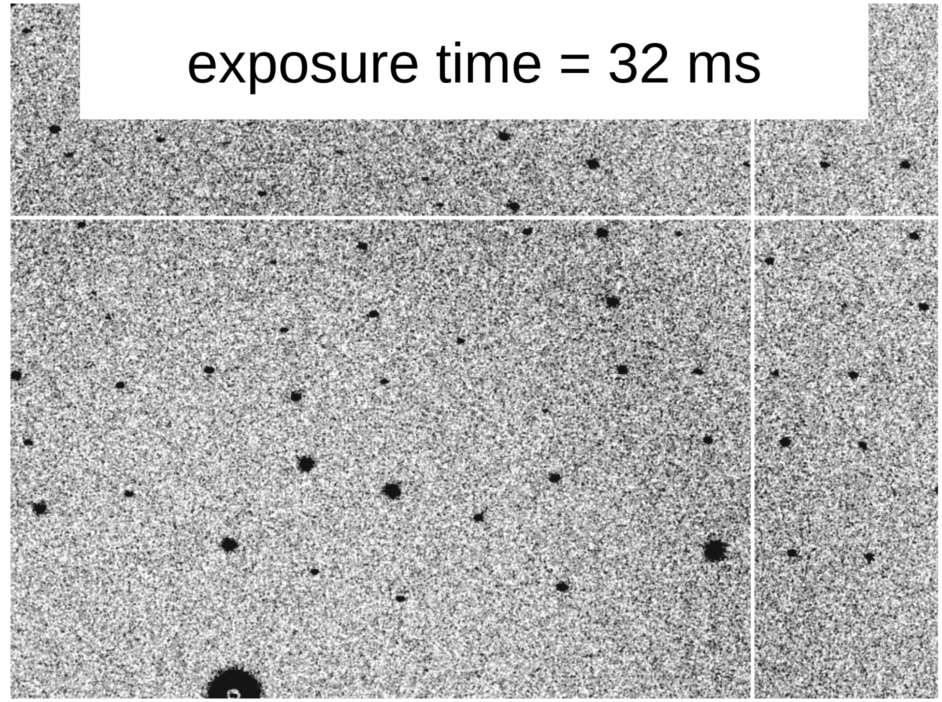
http://bl831.als.lbl.gov/~jamesh/mlfsom/development_snapshot.tar.gz

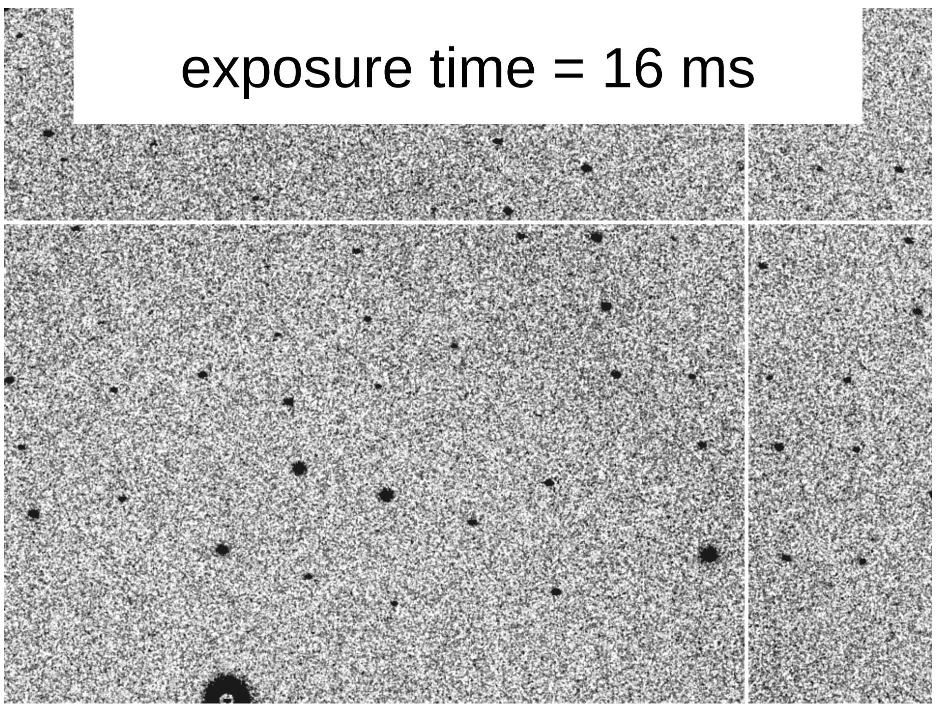
http://bl831.als.lbl.gov/~jamesh/powerpoint/ACA_2009.ppt

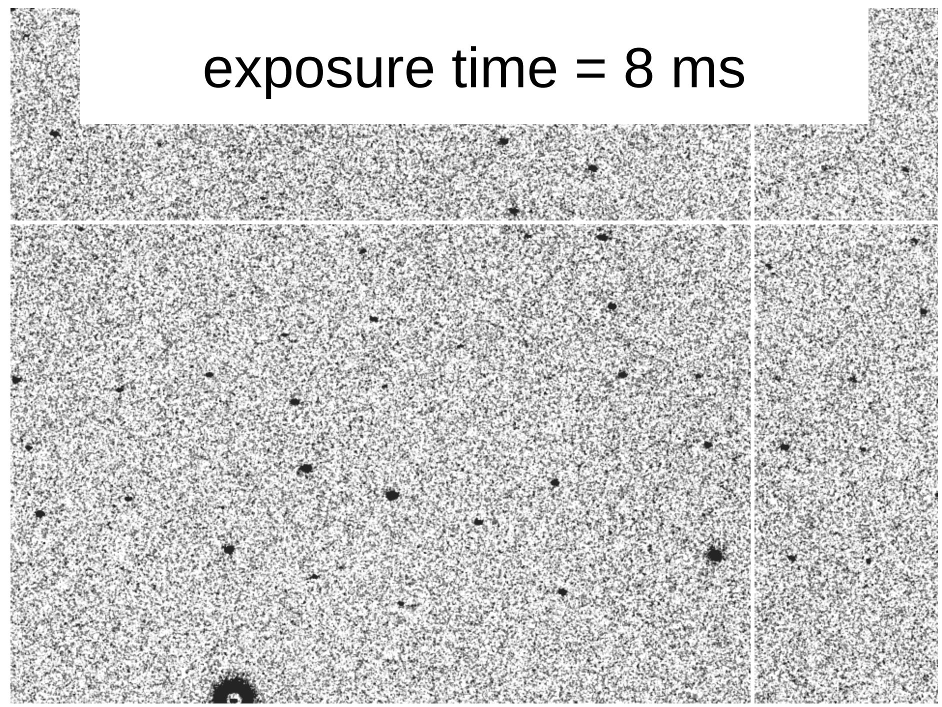
What is the best exposure time?

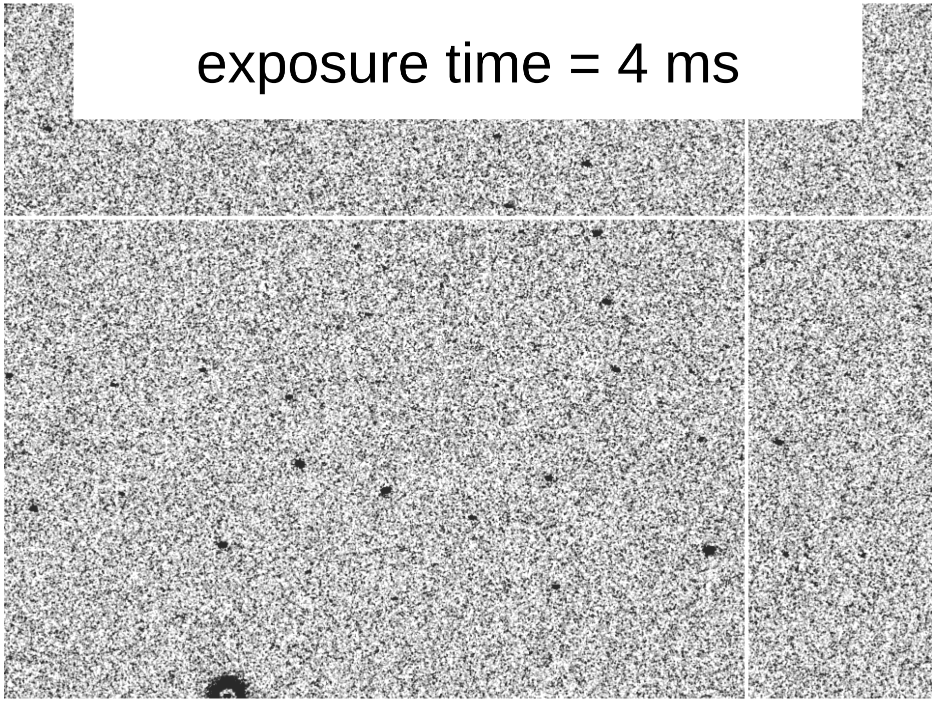


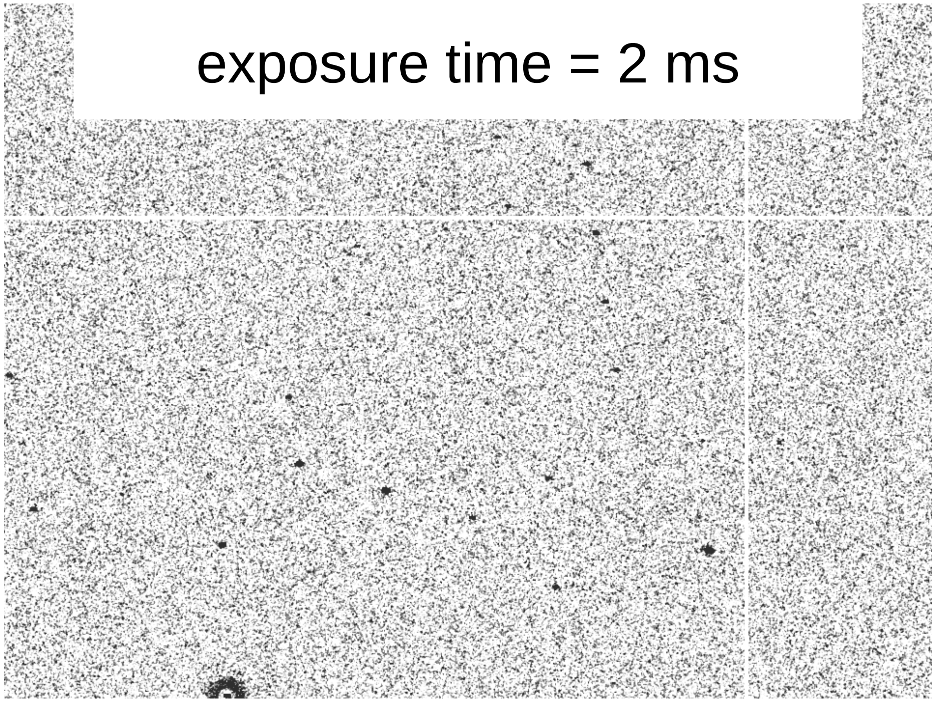

exposure time = 64 ms

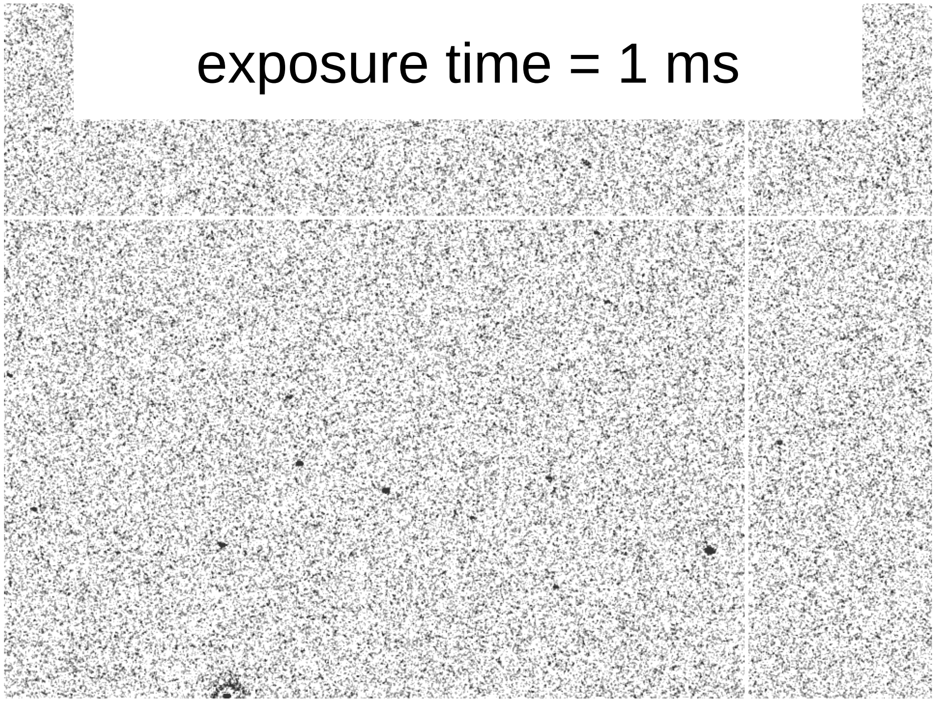

exposure time = 32 ms

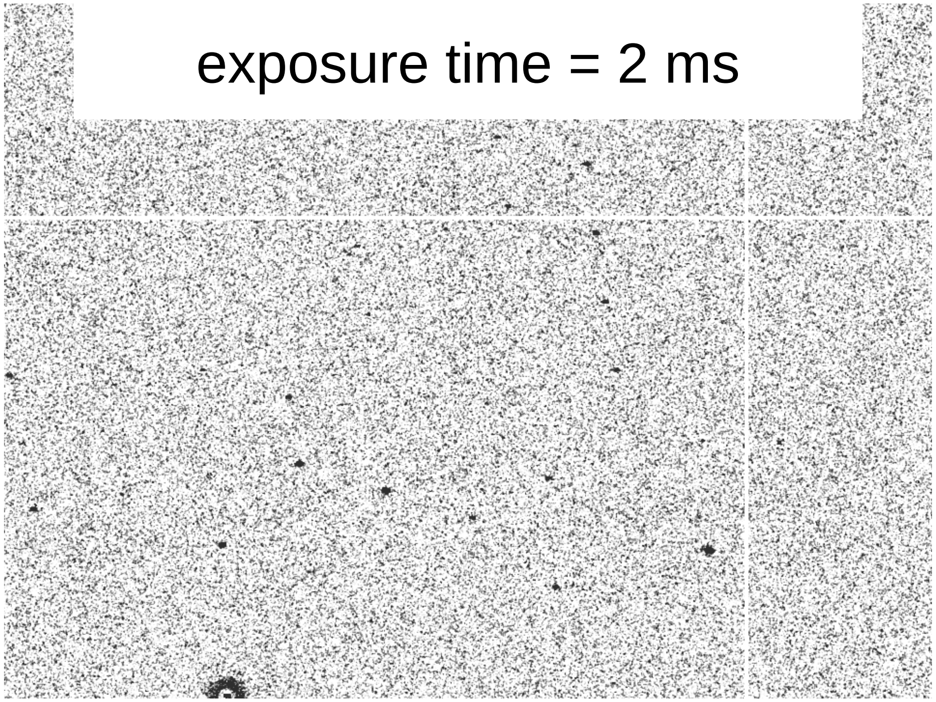

exposure time = 16 ms

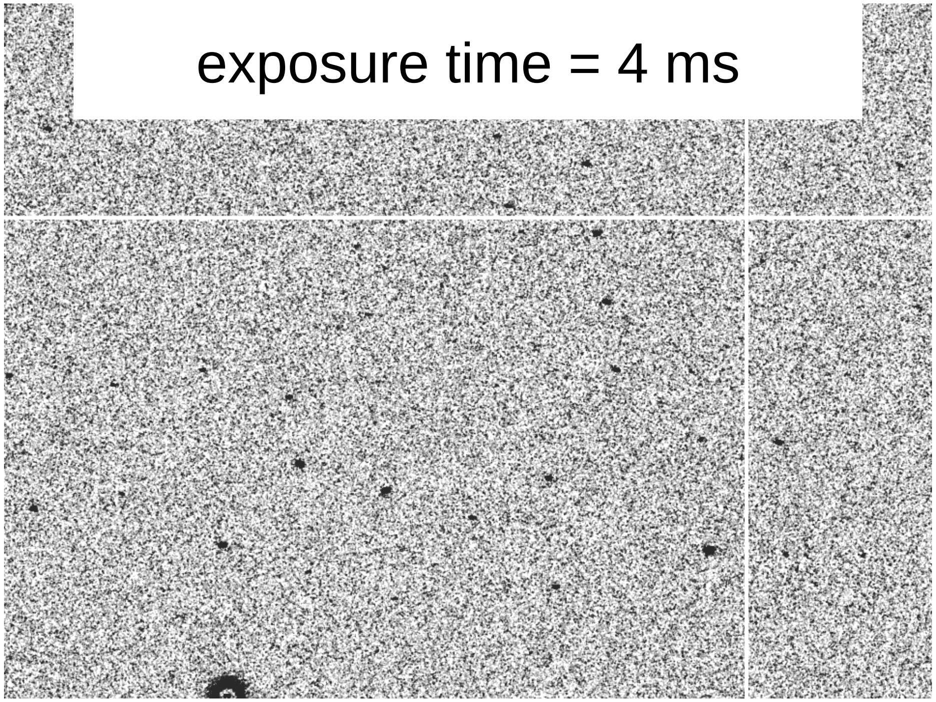

exposure time = 8 ms

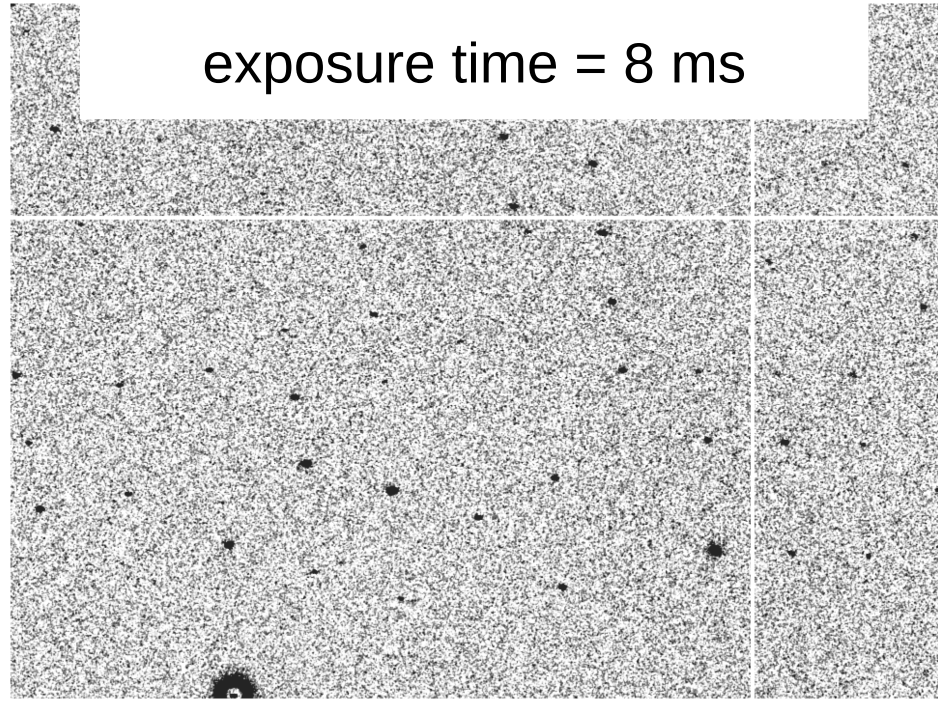

exposure time = 4 ms

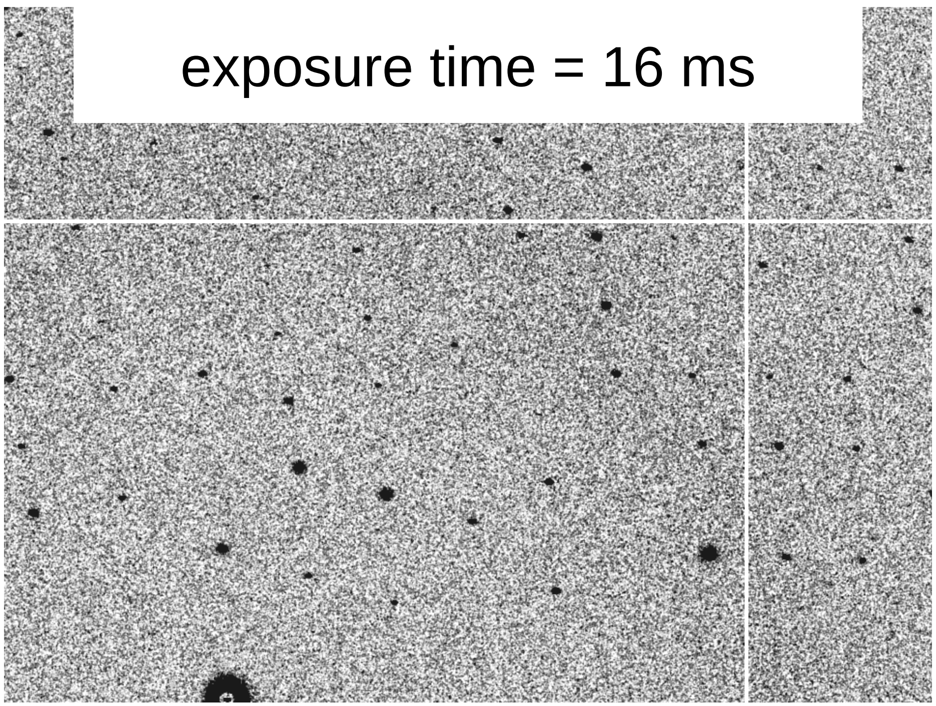

exposure time = 2 ms

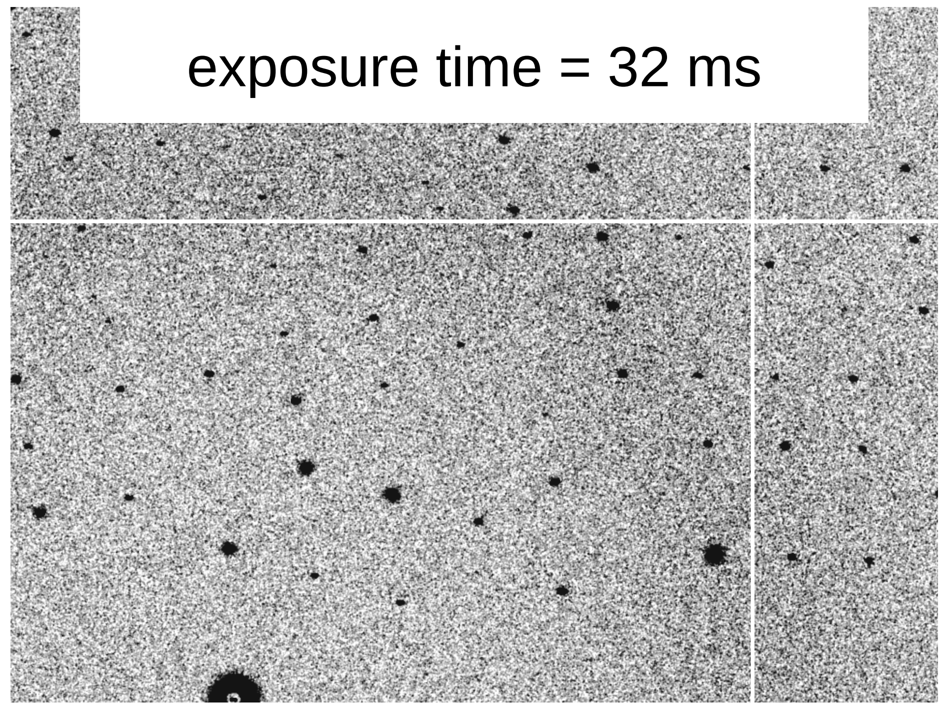

exposure time = 1 ms

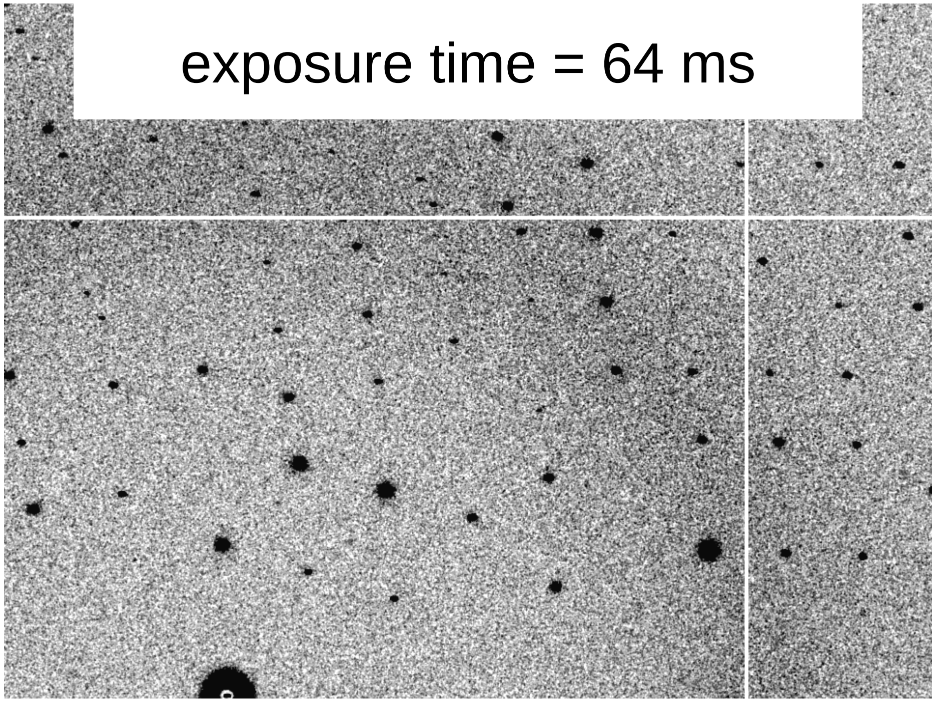
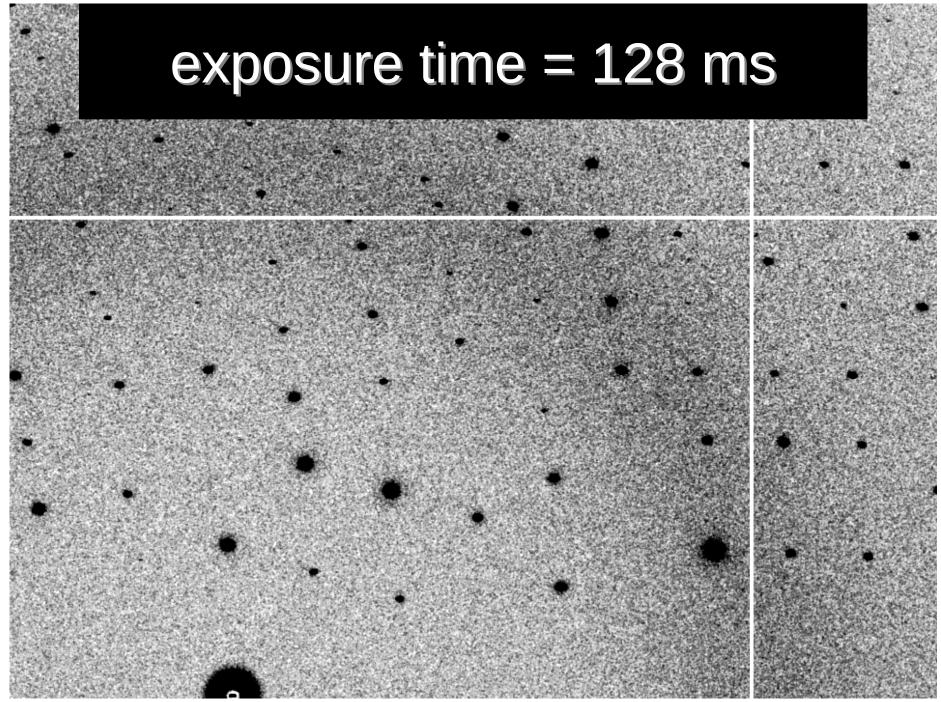
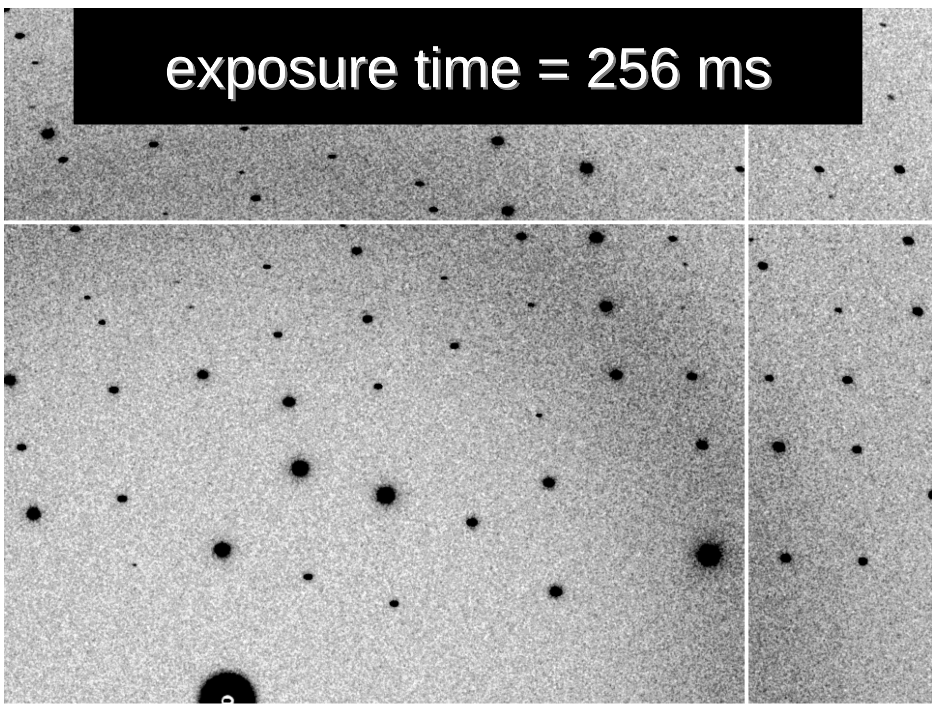
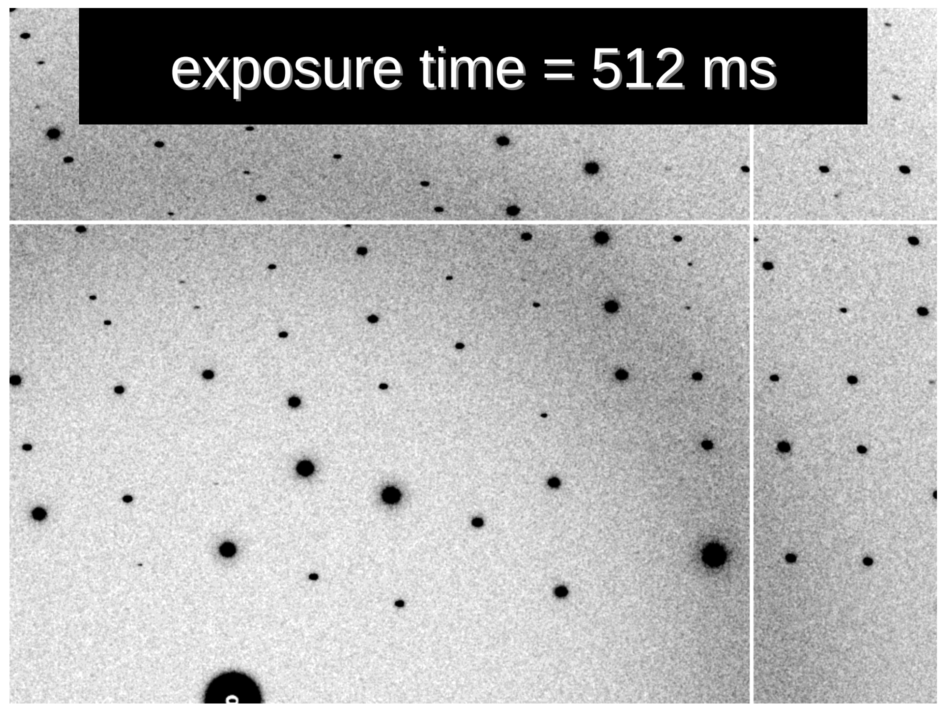

exposure time = 2 ms

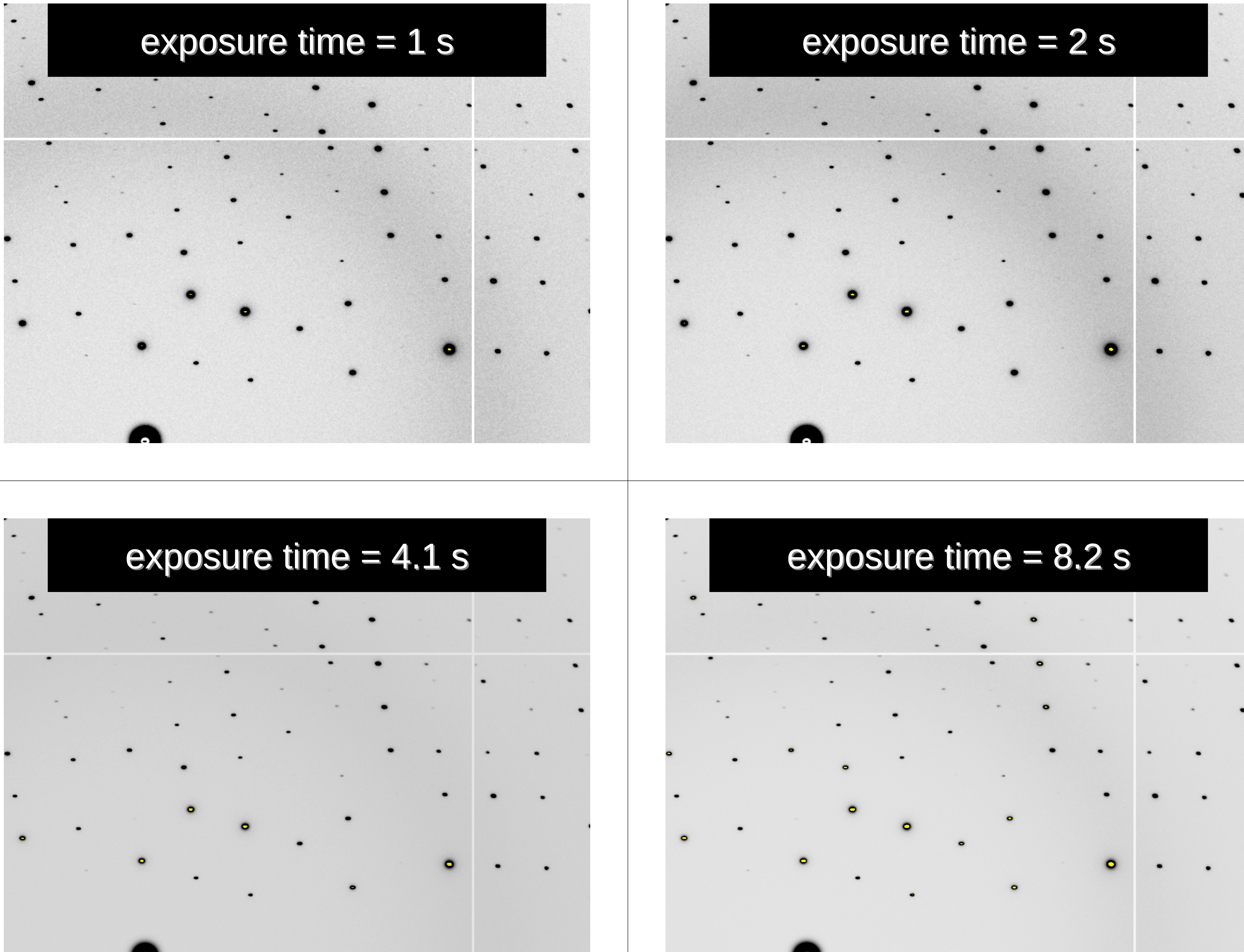

exposure time = 4 ms

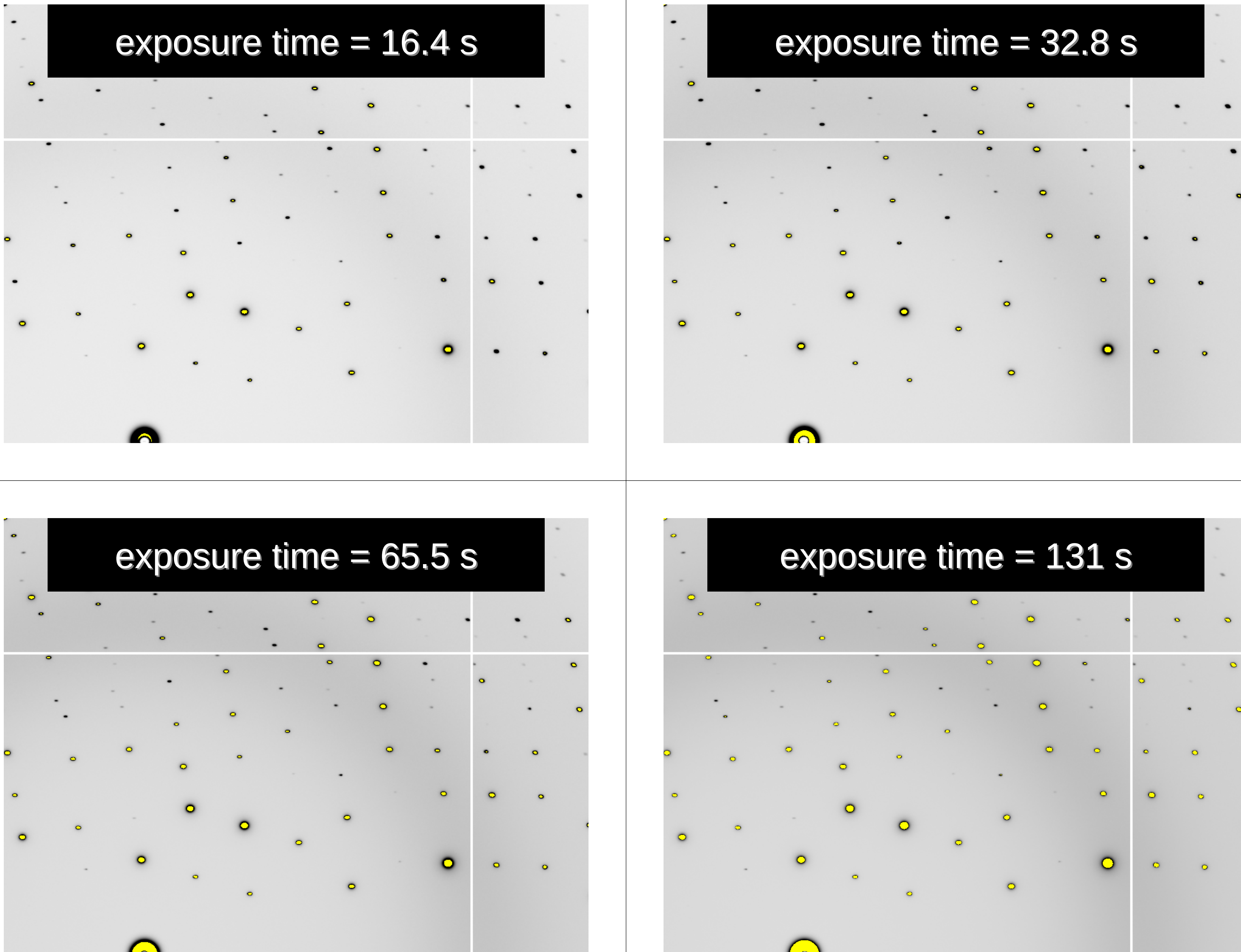

exposure time = 8 ms

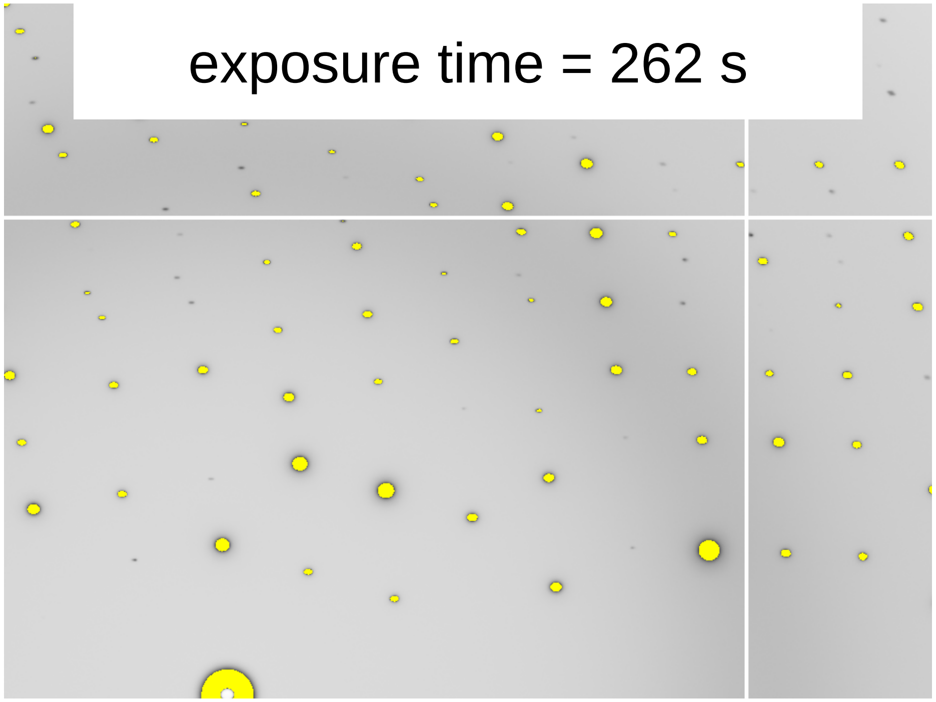

exposure time = 16 ms


exposure time = 32 ms

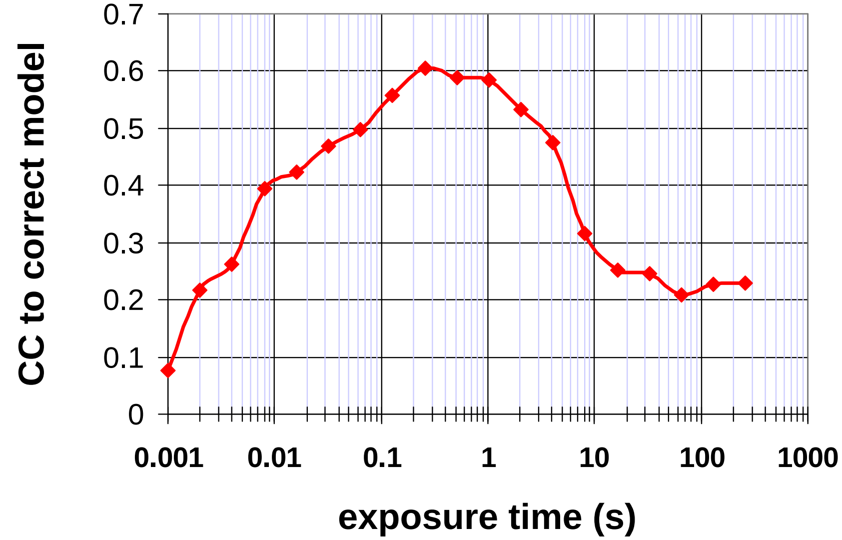

exposure time = 64 ms

exposure time = 128 ms

exposure time = 256 ms

exposure time = 512 ms


exposure time = 1 s
exposure time = 2 s
exposure time = 4.1 s
exposure time = 8.2 s

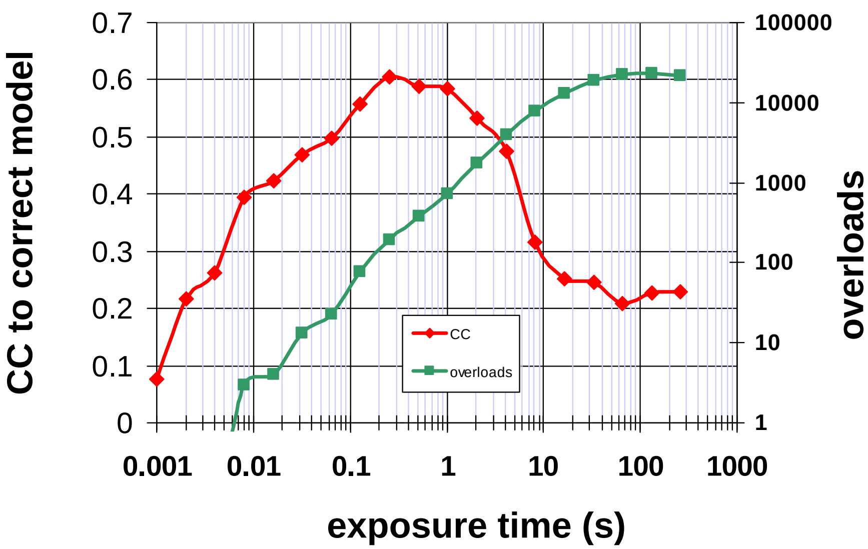

exposure time = 16.4 s
exposure time = 32.8 s
exposure time = 65.5 s
exposure time = 131 s



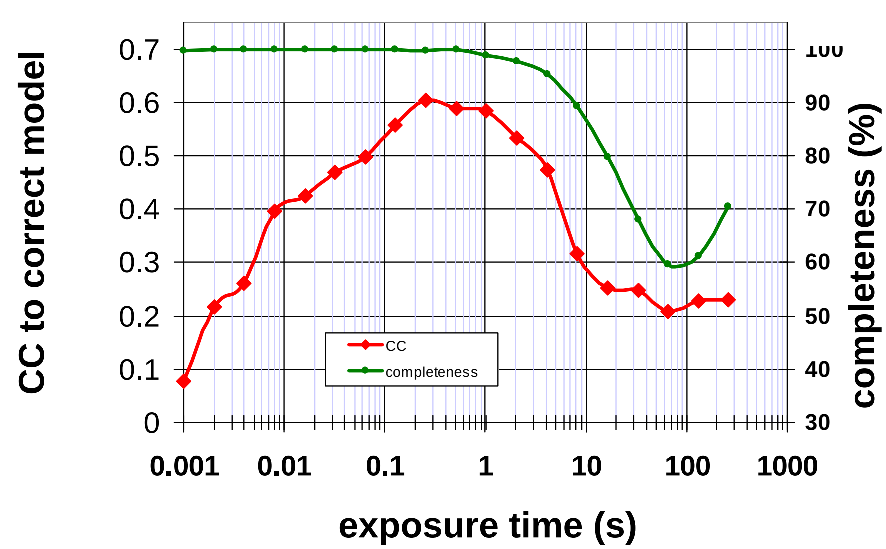
Exposure time



Exposure time



Exposure time



Darwin's Formula

$$I(hkl) = I_{beam}\, r_e^2 \frac{V_{xtal}}{V_{cell}} \frac{\lambda^3 L}{\omega V_{cell}} P\, A\, |\, F(hkl)\, |^2$$

I(hkl) - photons/spot (fully-recorded)
I_{beam} - incident (photons/s/m^2)
r_e - classical electron radius (2.818×10^{-15} m)
V_{xtal} - volume of crystal (in m^3)
V_{cell} - volume of unit cell (in m^3)
λ - x-ray wavelength (in meters!)
ω - rotation speed (radians/s)
L - Lorentz factor (speed/speed)
P - polarization factor
$(1+\cos^2(2\theta) - Pfac \cdot \cos(2\Phi)\sin^2(2\theta))/2$
A - absorption factor
$\exp(-\mu_{xtal} \cdot l_{path})$
F(hkl) - structure amplitude (electrons)

C. G. Darwin (1914)

Darwin's Formula

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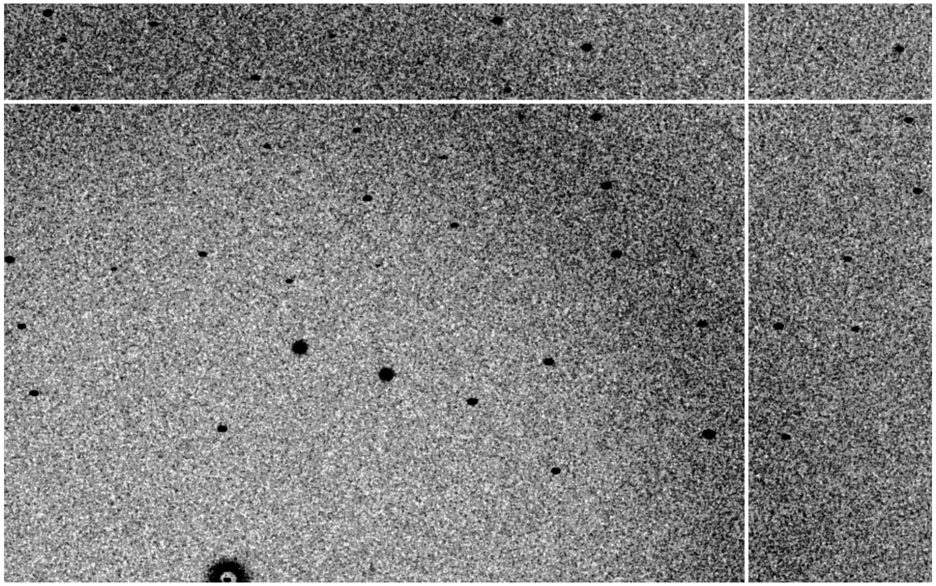
A - absorption factor
$\exp(-\mu_{xtal} \cdot l_{path})$
F(hkl) - structure amplitude (electrons)

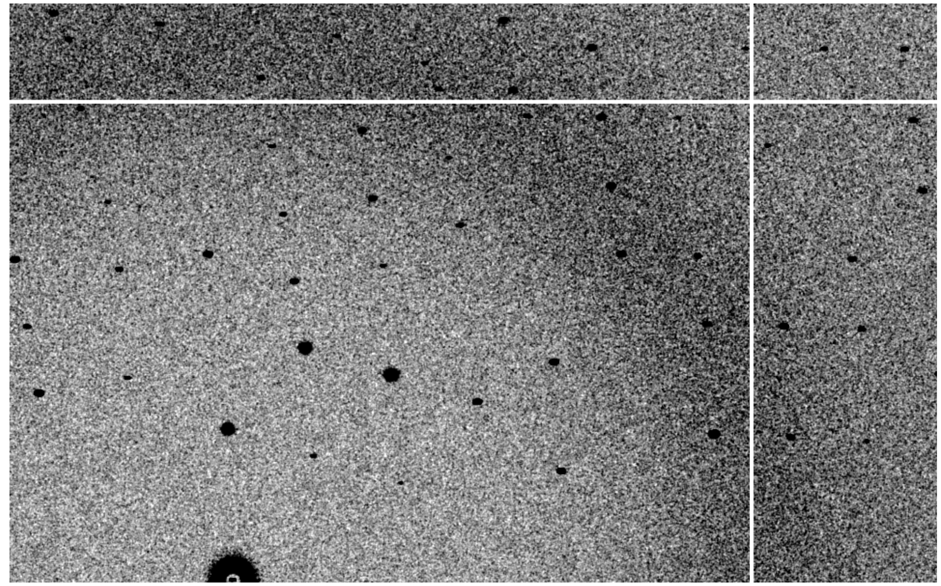
C. G. Darwin (1914)

How small can the crystal be?

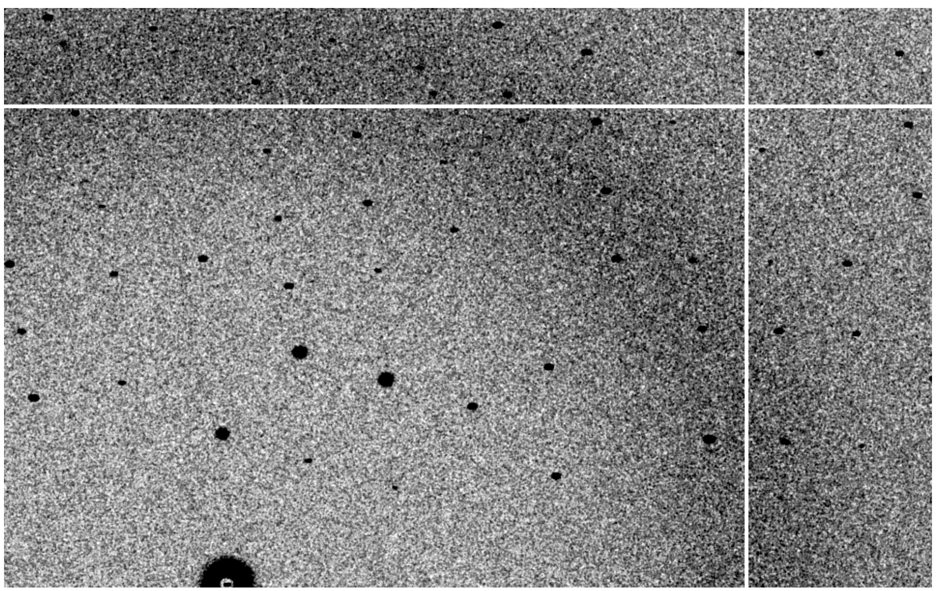
crystal size = 1 mm



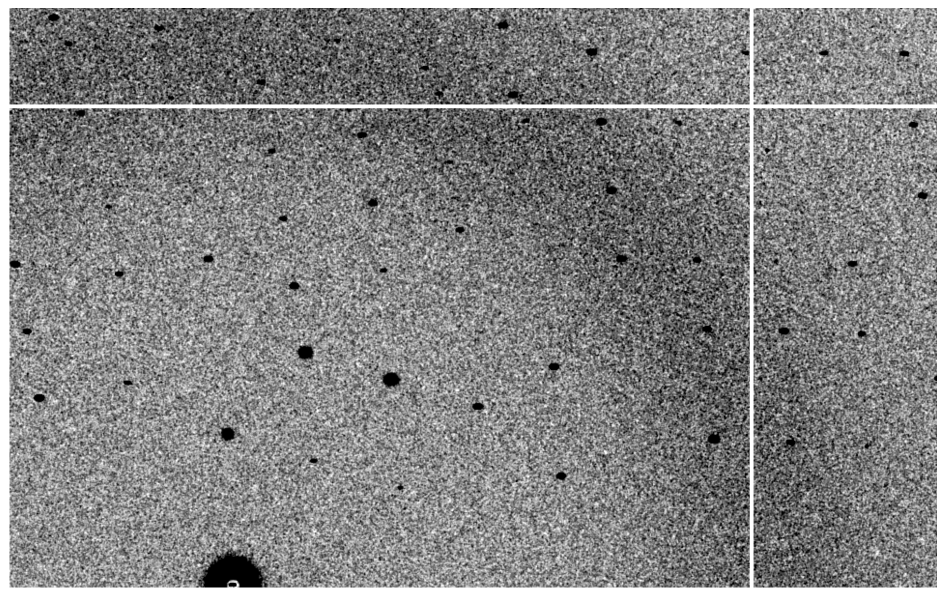
crystal size = 512 μm



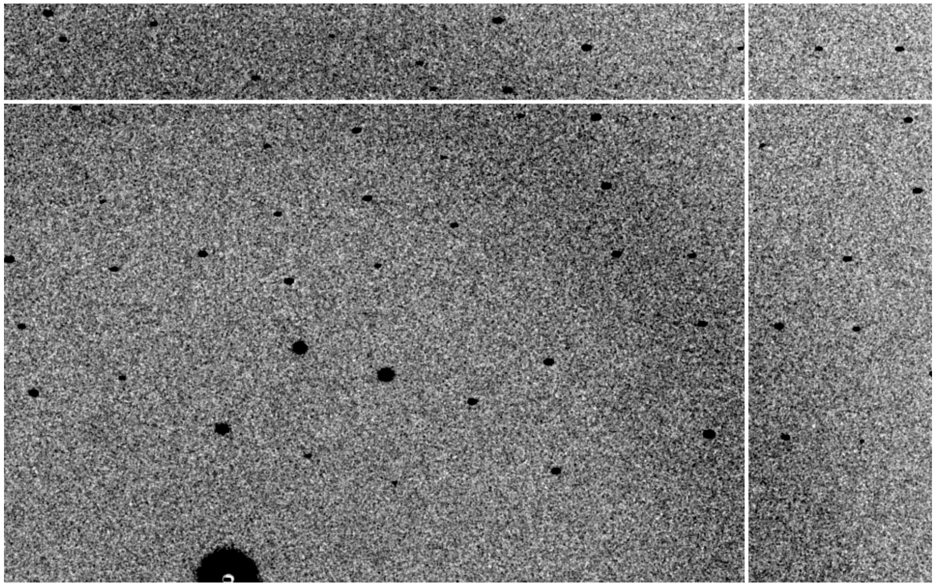
crystal size = 256 μm



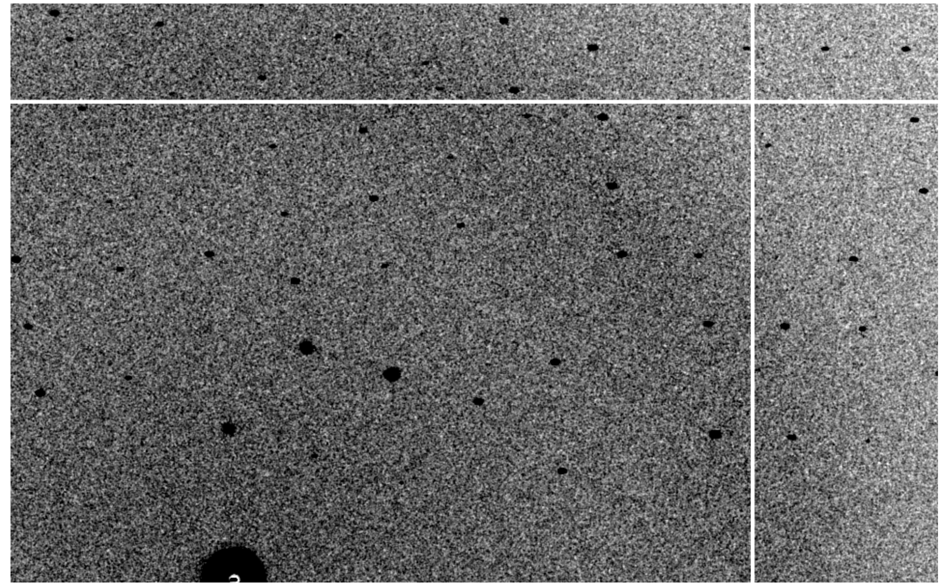
crystal size = 128 μm



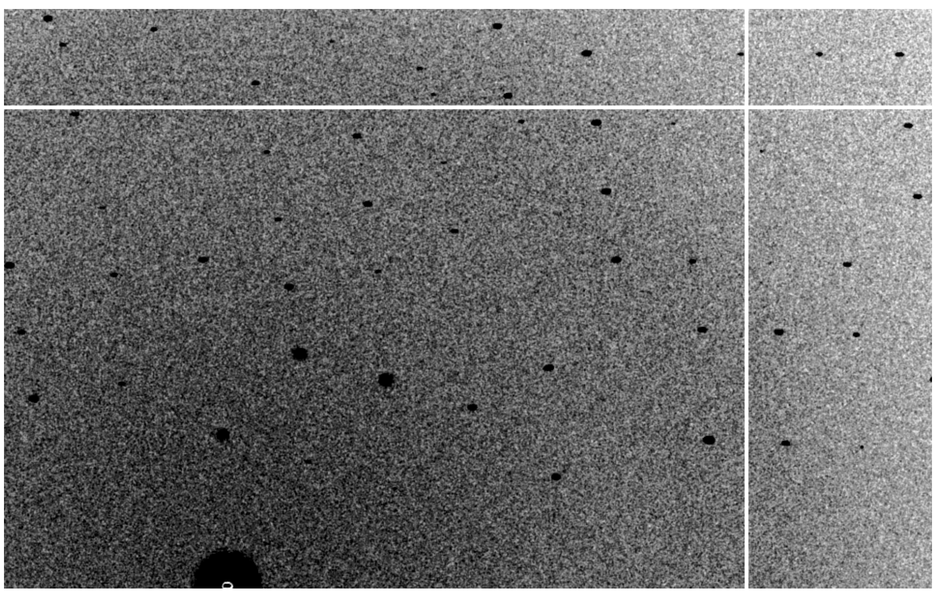
crystal size = 64 μm



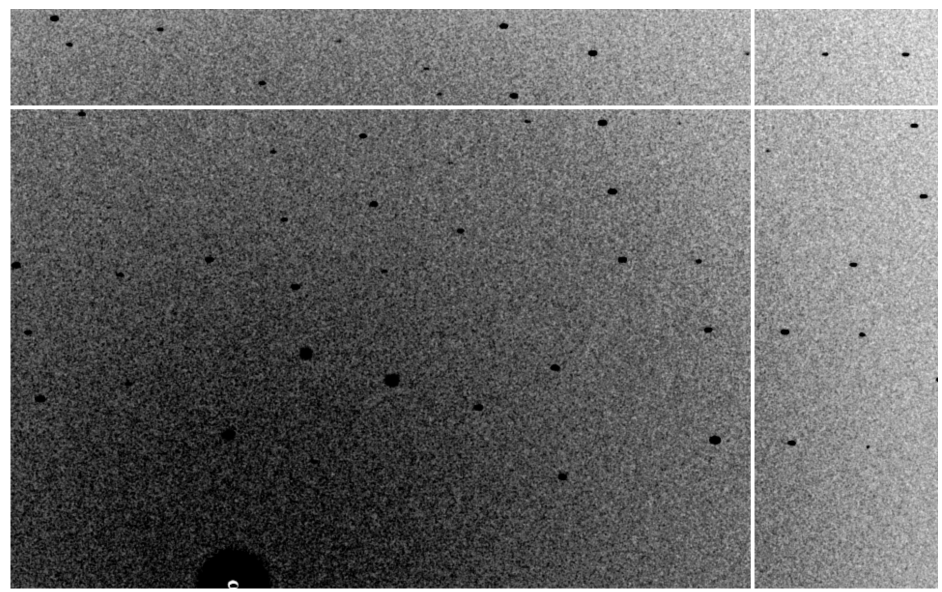
crystal size = 32 μm



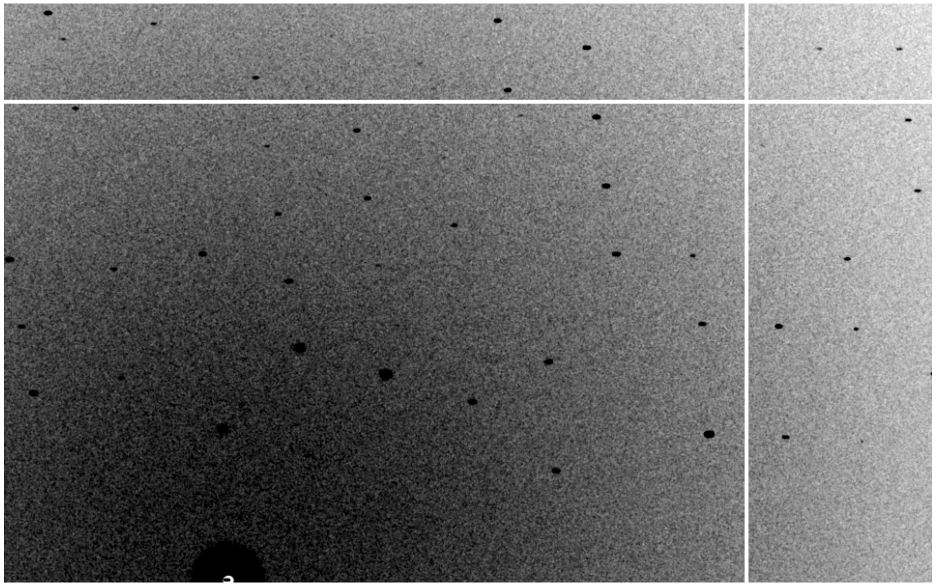
crystal size = 16 μm



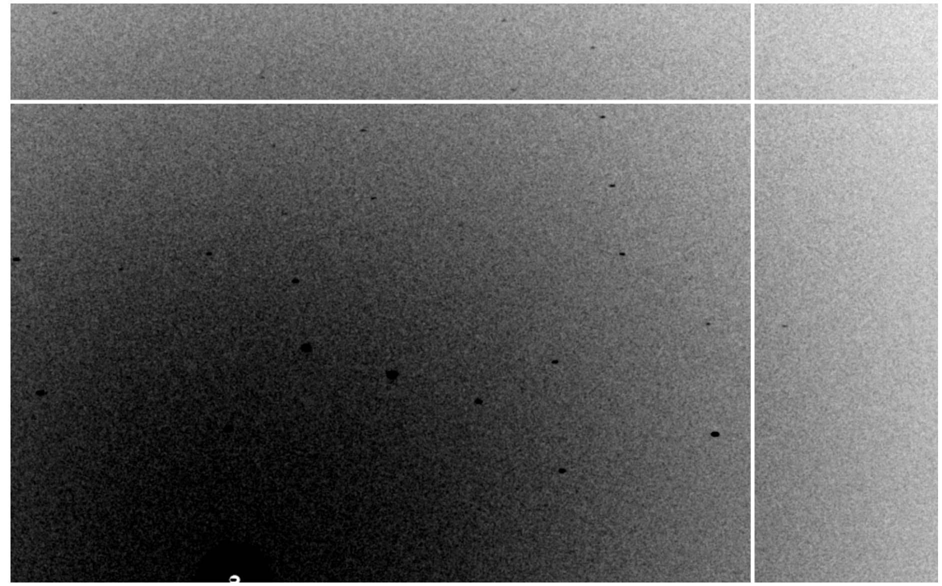
crystal size = 8 μm



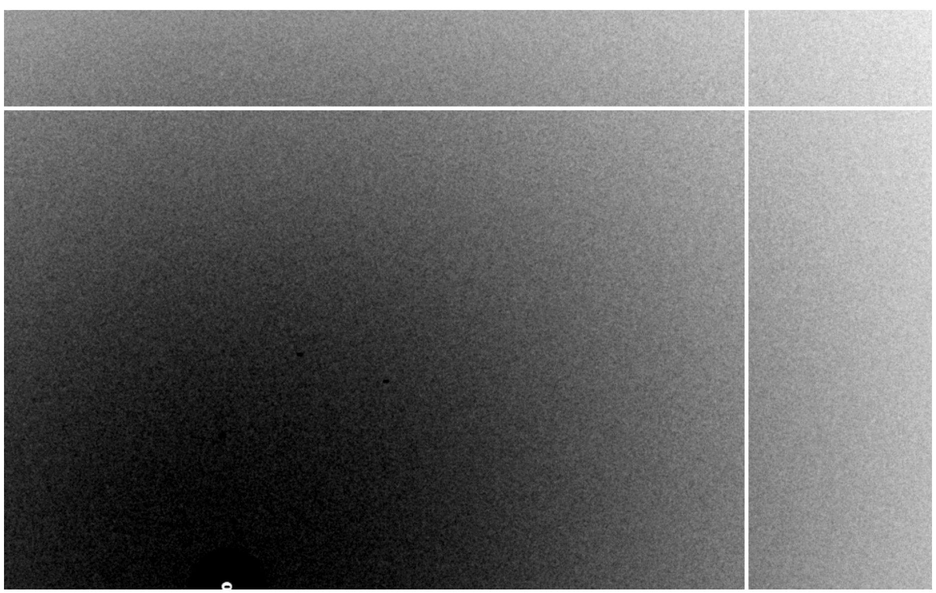
crystal size = 4 μm



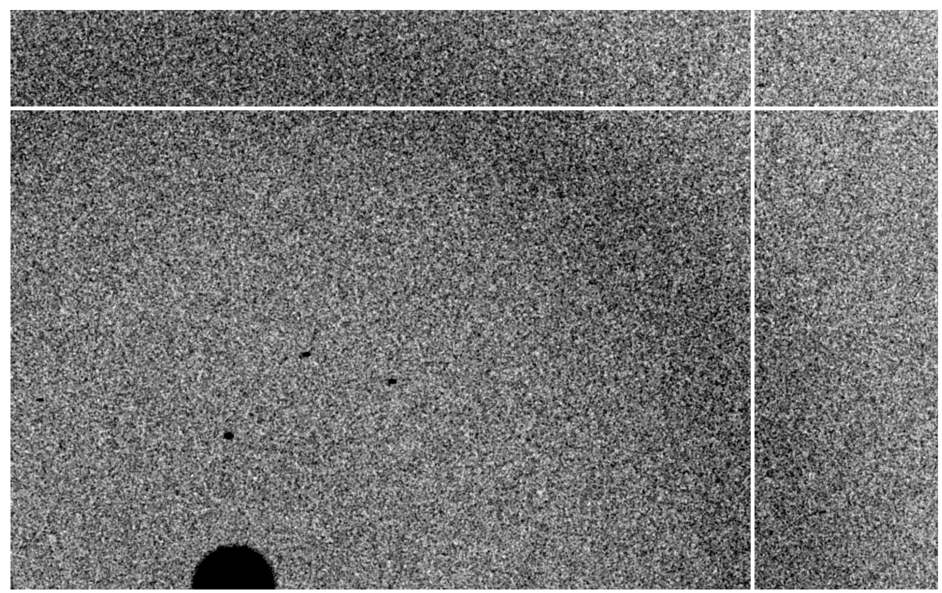
crystal size = 2 μm



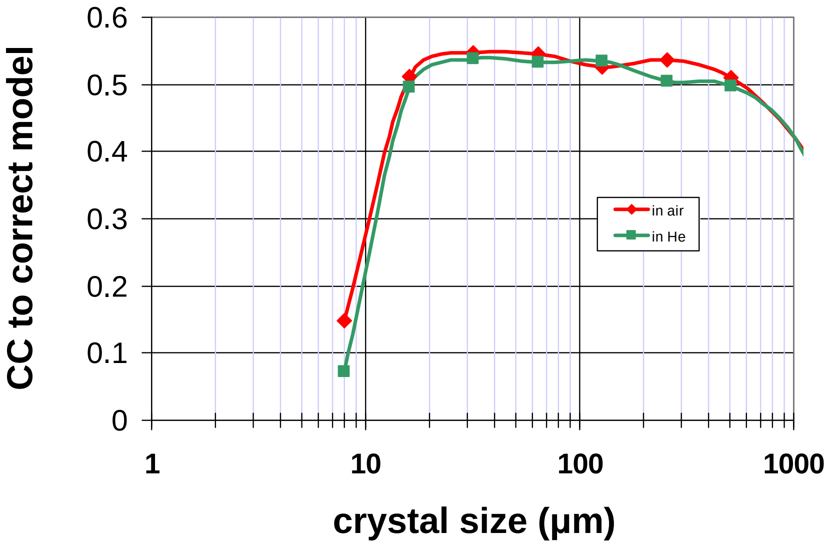
crystal size = 1 μm



crystal size = 1 μm (in He)



Crystal Size



Darwin's Formula

$$I(hkl) = I_{beam}\, r_e^2 \frac{V_{xtal}}{V_{cell}} \frac{\lambda^3 L}{\omega V_{cell}} P\ A\ | F(hkl) |^2$$

I(hkl) - photons/spot (fully-recorded)

I_{beam} - incident (photons/s/m^2)

r_e - classical electron radius (2.818×10^{-15} m)

V_{xtal} - volume of crystal (in m^3)

V_{cell} - volume of unit cell (in m^3)

λ - x-ray wavelength (in meters!)

ω - rotation speed (radians/s)

L - Lorentz factor (speed/speed)

P - polarization factor

$(1+\cos^2(2\theta) - Pfac \cdot \cos(2\Phi)\sin^2(2\theta))/2$

A - absorption factor

$\exp(-\mu_{xtal} \cdot l_{path})$

F(hkl) - structure amplitude (electrons)

C. G. Darwin (1914)

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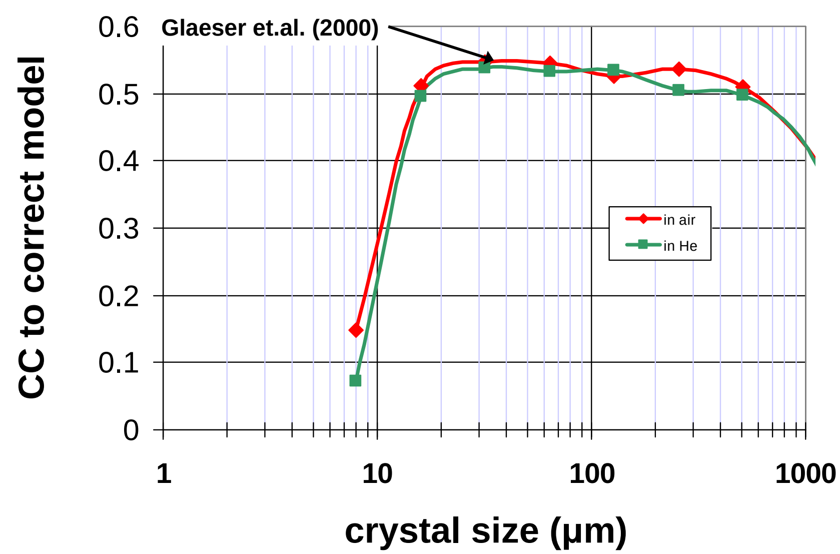
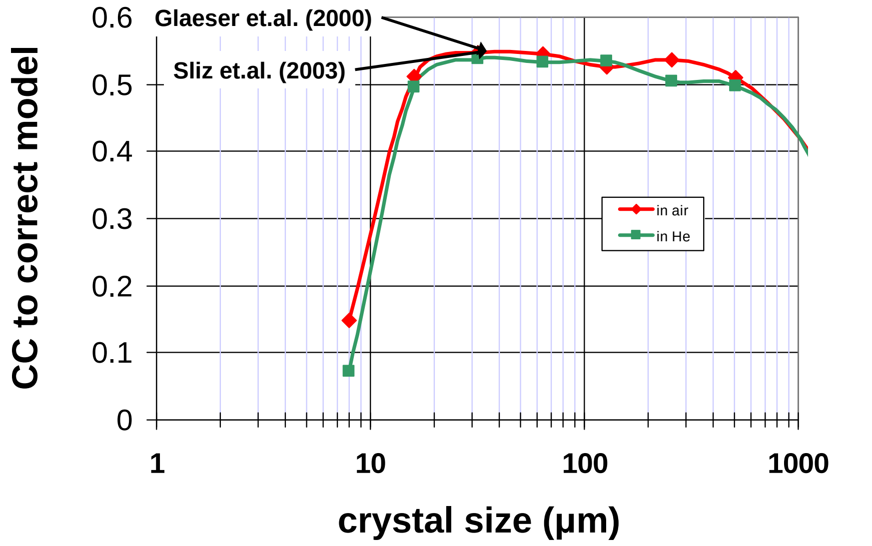
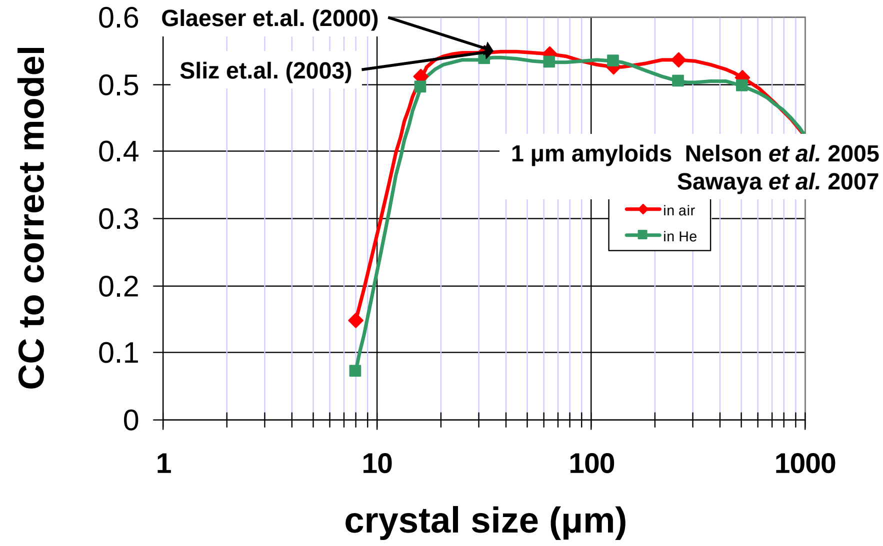
Crystal Size



Crystal Size



Crystal Size



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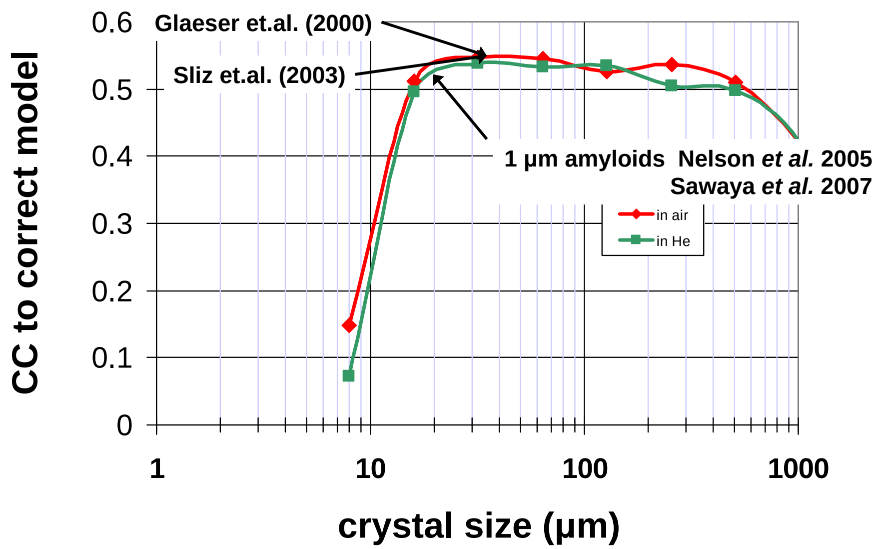

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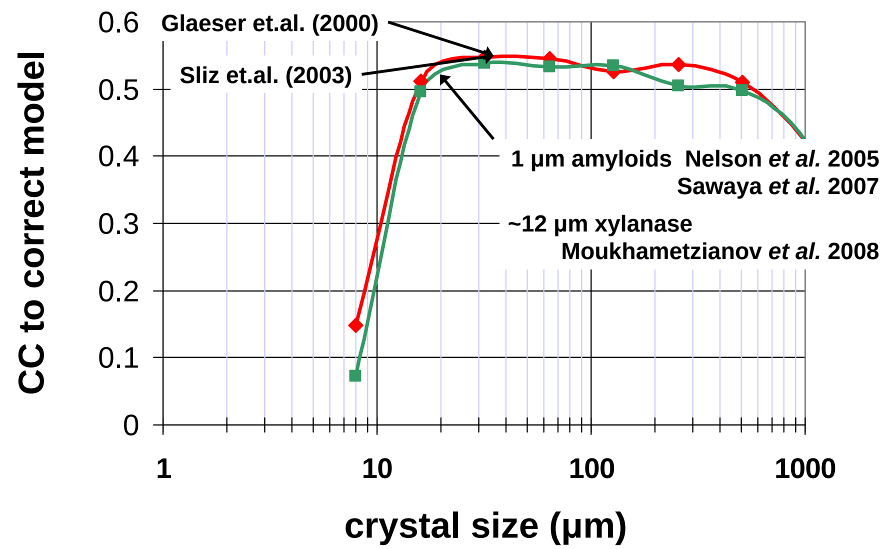
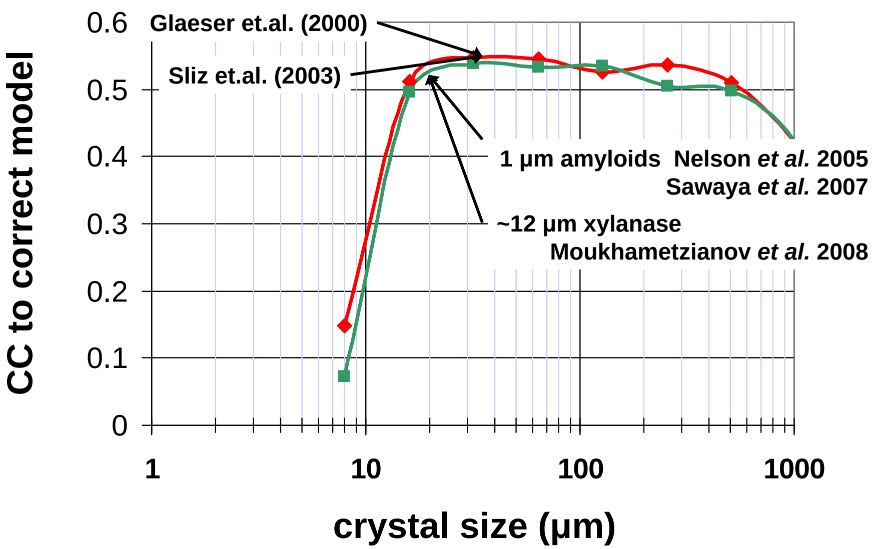


Crystal Size



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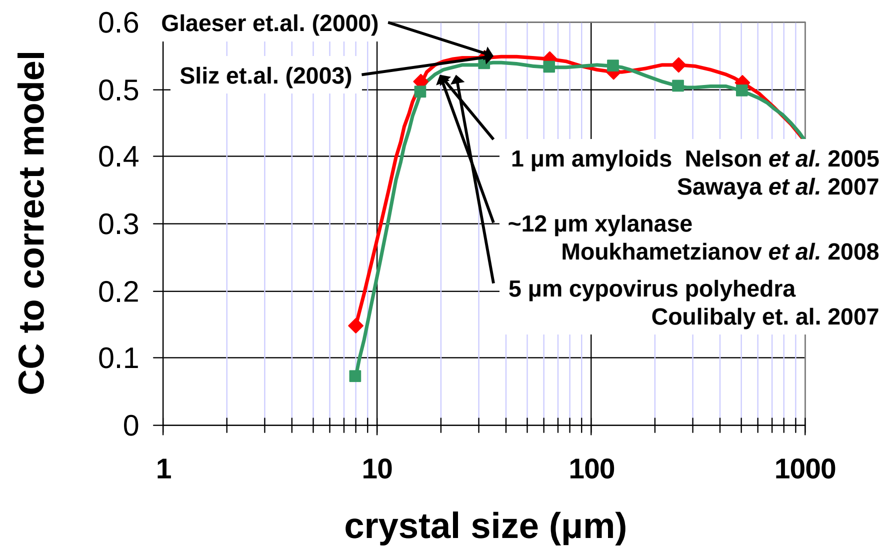
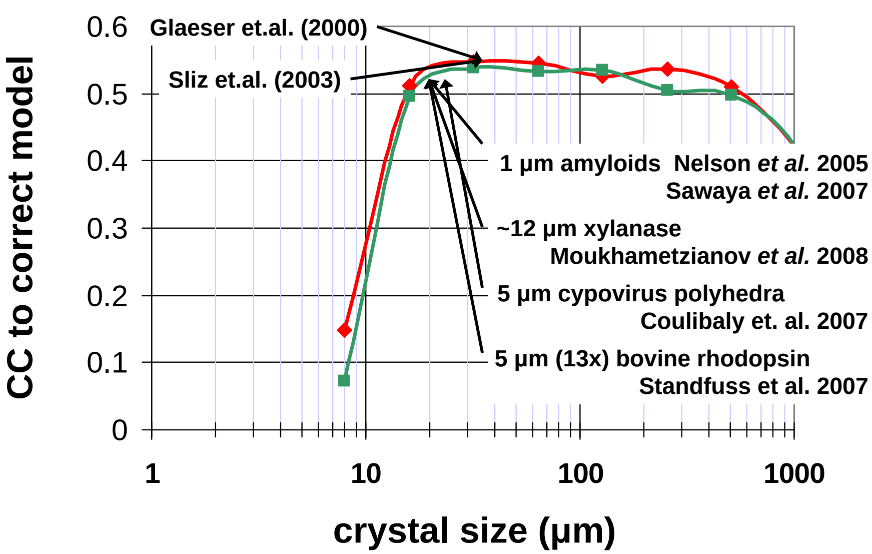


Crystal Size



Minimum Crystal Size

$$n_{xtal} = n_0 \frac{MW \;\; V_M^{\;2}}{\ell_x \ell_y \ell_z \,(d^3 - 1.53)\, \exp(-0.5\, B/d^2)}$$

n_{xtal} - number of crystals needed

n_0 - empirical constant (~ 3)

MW - molecular weight (kDa)

V_M - Matthews number (~2.5 Å³/Da)

ℓ - crystal size (microns)

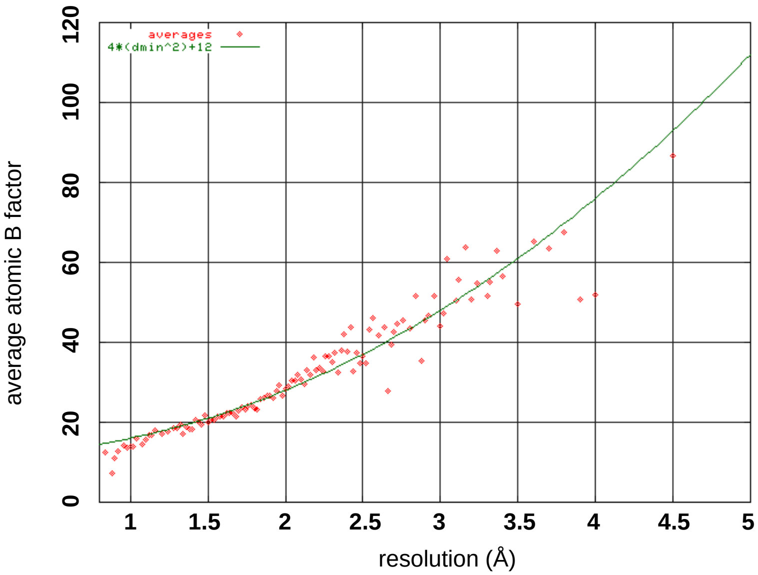
d - d-spacing of interest (Å)

B - Wilson B factor (Å²)

$B \approx 4\, d^2 + 12$

Holton J. M. (2009) *J. Synchrotron Rad.* **16** 133-42

$B \approx 4 d^2 + 12$



Minimum Crystal Size

http://bl831.als.lbl.gov/~jamesh/xtalsize.html

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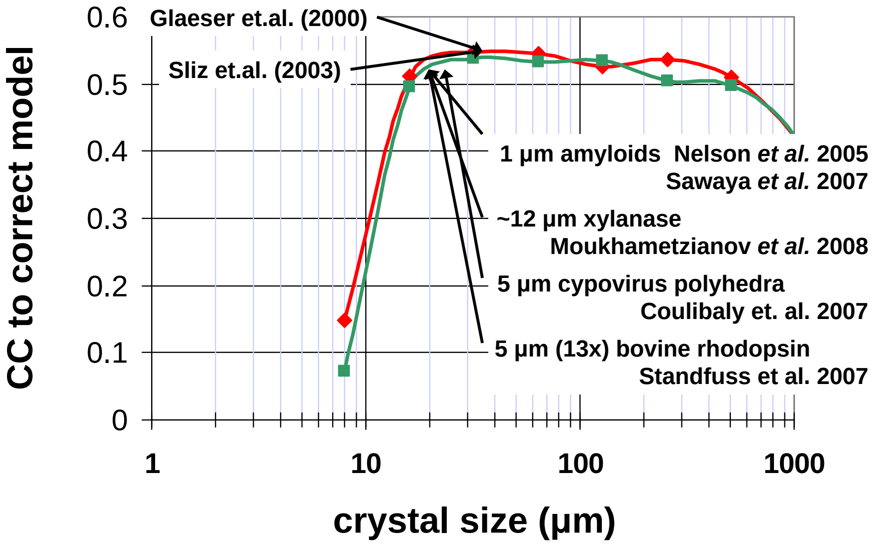

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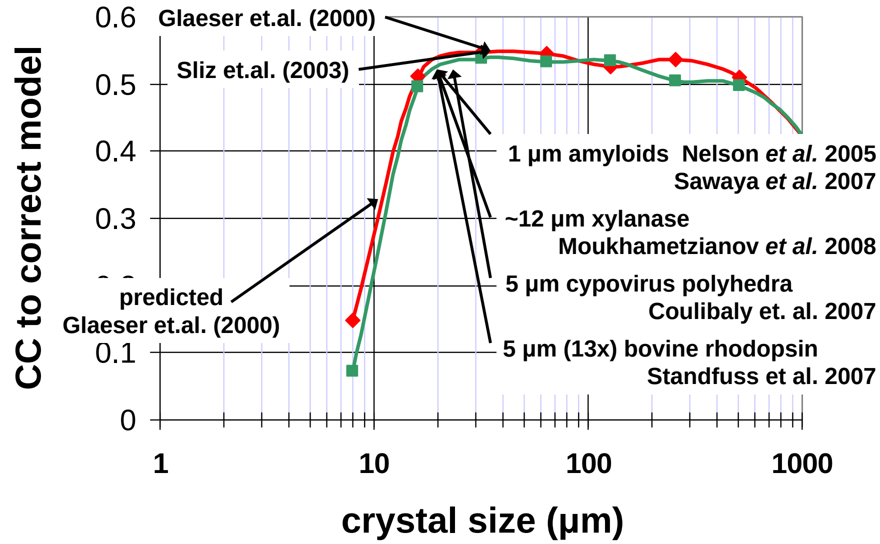

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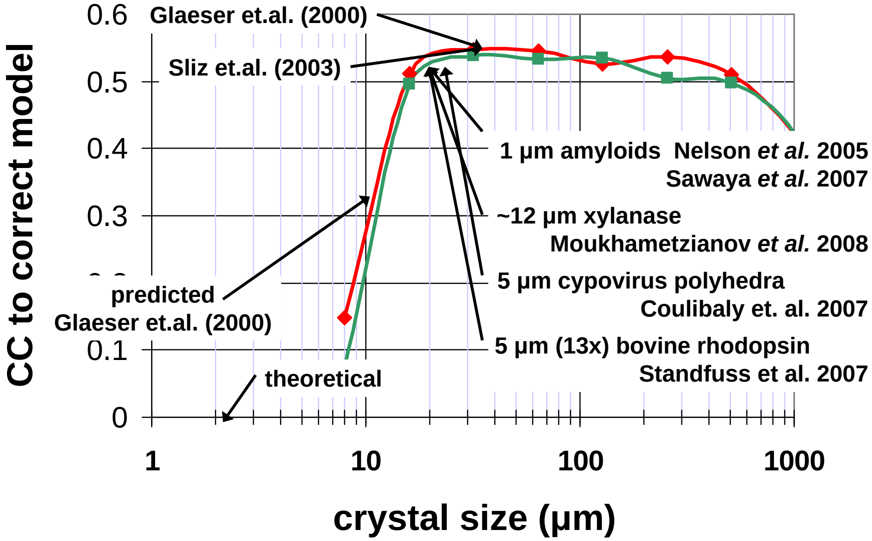


Theoretical limit for lysozyme:

$$< I_{max} > (s) \cong \frac{8 \cdot 10^{29}\, r_e^{\,2}\, \rho R^4 \lambda^4}{9\pi\, hc\, H\, s\, n_{ASU}\, M_r V_M^{\,2}} \left(\frac{1.05 \cdot \pi}{4\, s\, \lambda} - \frac{1}{2} \right) \cdot \frac{T_{sphere}(2\theta, \mu, R)}{1 - T_{sphere}(0, \mu_{en}, R)} \cdot \frac{< f_a(s) >^2 \exp(-2Bs^2)}{< M_a >}$$

Where:

$<I_{max}>$ (s)	- average damage-limited spot intensity (photons) at "s"
s	- sin(θ)/λ or 0.5/d if d is the d-spacing of interest (Å^{-1})
θ	- Bragg angle
r_e	- classical electron radius (2.818 x 10^{-15} m)
10^{29}	- conversion from m^4 to $Å^4$, g/cm³ to kg/m³ and MGy to Gy
ρ	- density of crystal (~1.2 g/cm³)
R	- radius of the spherical crystal (m)
λ	- x-ray wavelength (Å)
h	- Plank's constant (6.626 x 10^{-34} J·s)
c	- speed of light (299792458 m/s)
H	- Howells's coefficient (11 x 10^{-3} Å/MGy)
n_{ASU}	- number of proteins in the asymmetric unit
M_r	- molecular weight of the protein (Daltons or g/mol)
VM	- Matthews's coefficient (~2.4 Å³/Dalton)
$<f_a(s)>^2$	- number-averaged squared protein atom structure factor (electron units²)
$<M_a>$	- number-averaged atomic weight of a protein atom (~7.1 Daltons)
B	- average (Wilson) temperature factor (Å²)
μ	- attenuation coefficient of sphere material (m^{-1})
μ_{en}	- mass energy-absorption coefficient of sphere material (m^{-1})

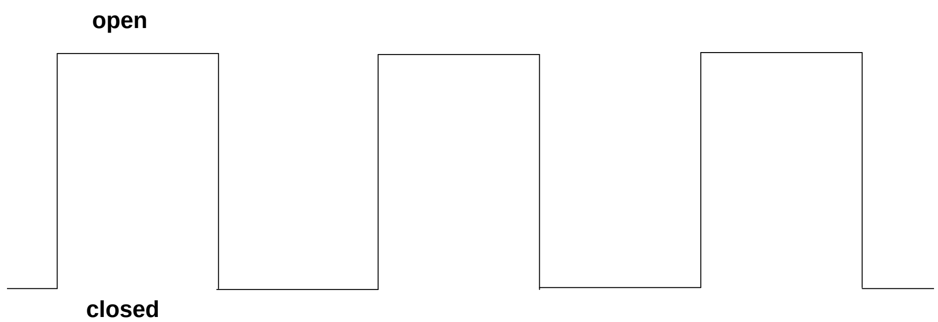
Theoretical limit for lysozyme:

$$1.0 \, \frac{\text{photon}}{\text{spot } \mu m^3}$$

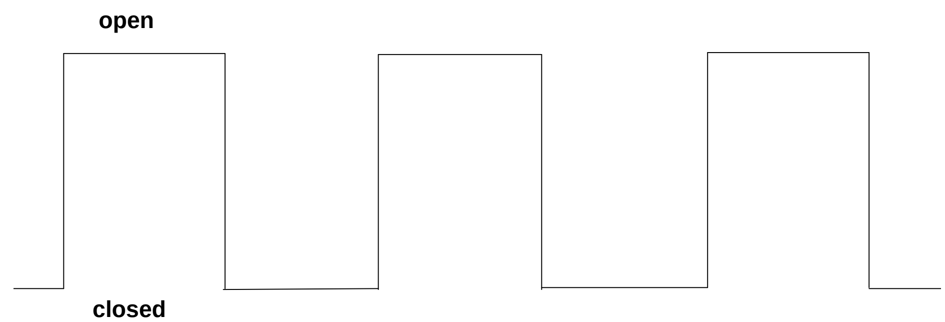
at ~2.4 Å

What if we had a "better" beamline?

Shutter Jitter



Shutter Jitter



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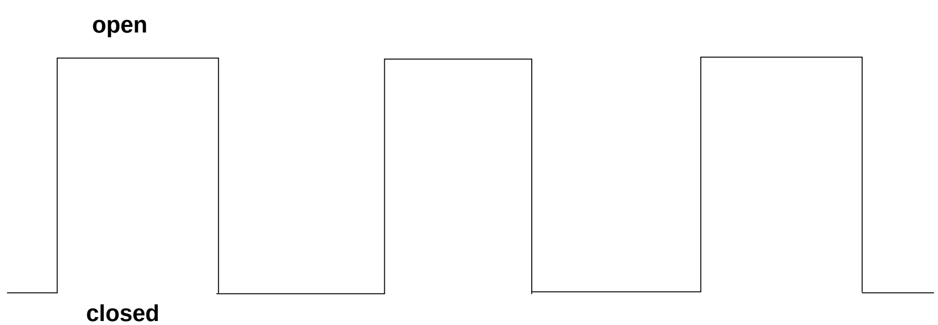

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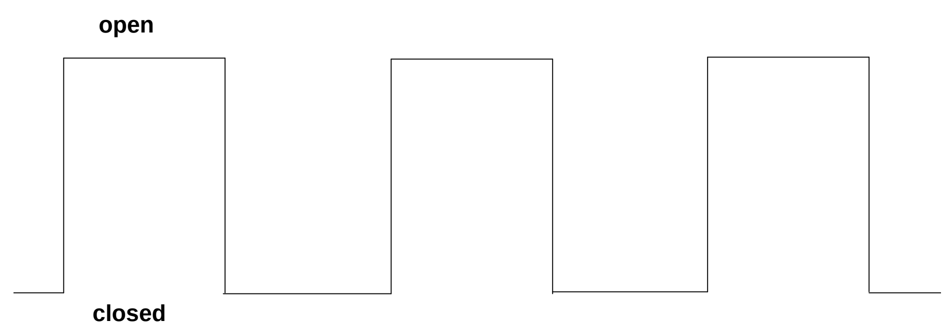

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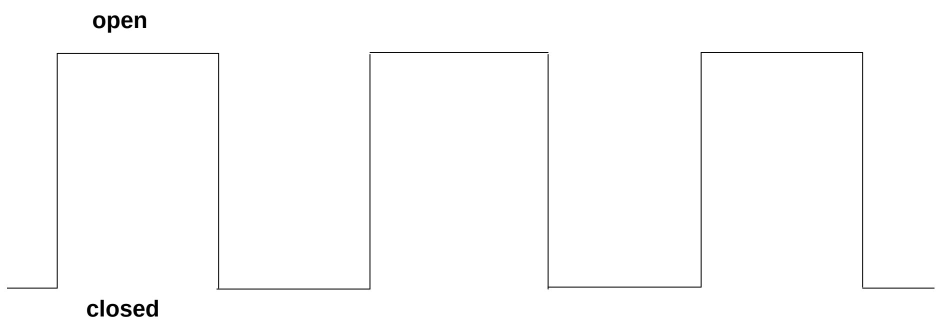

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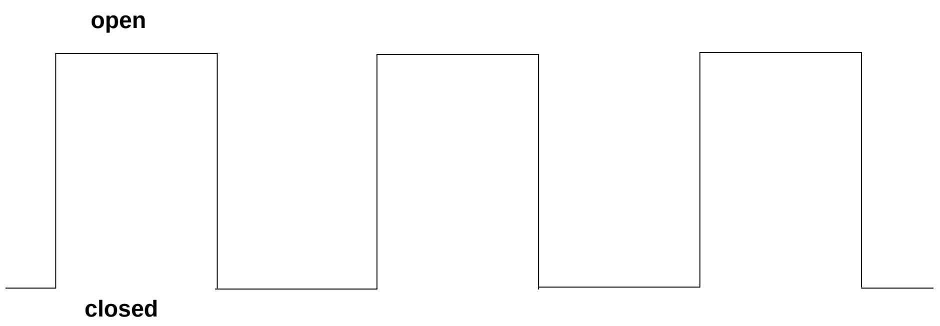

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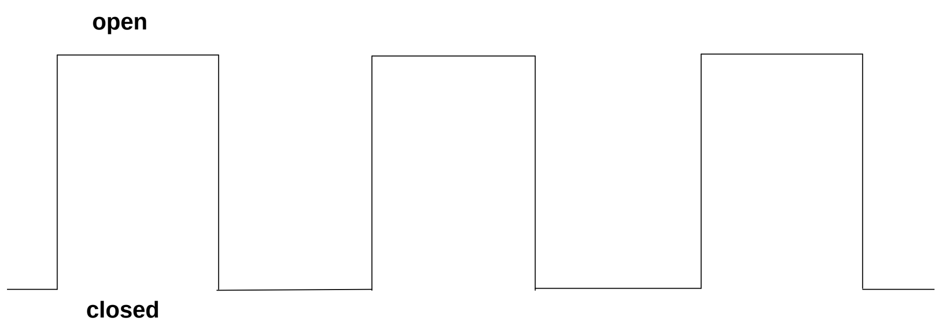

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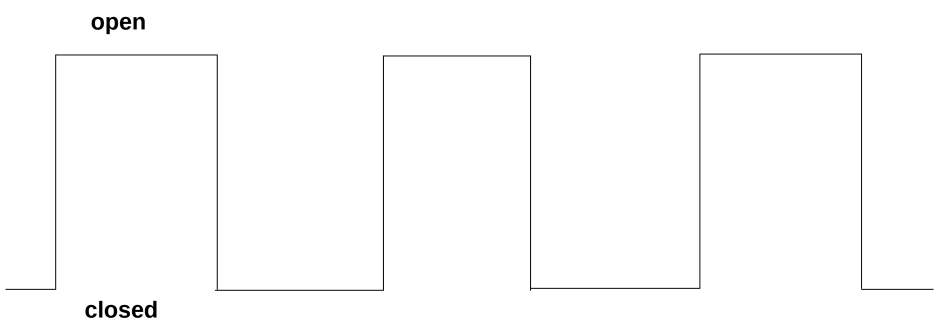

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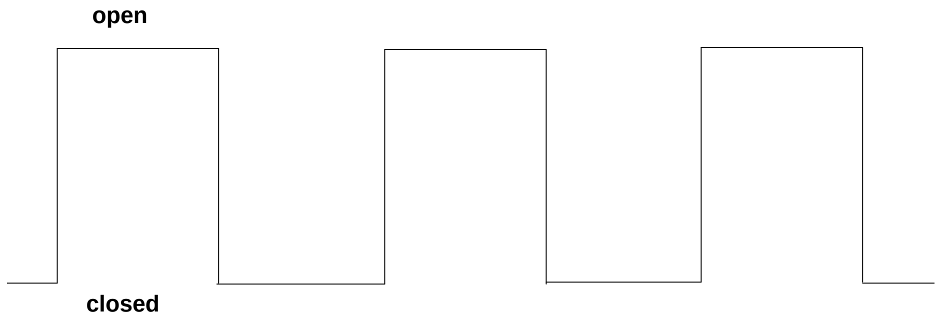

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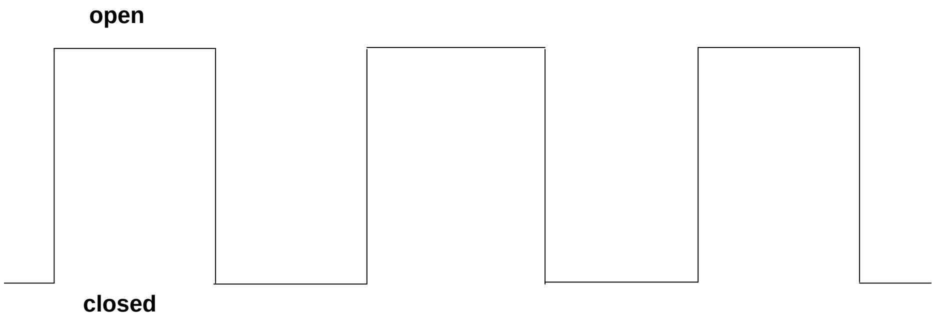

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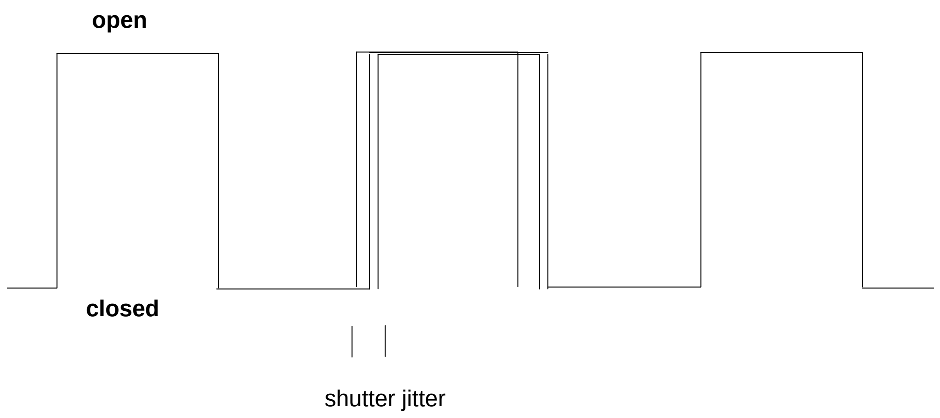

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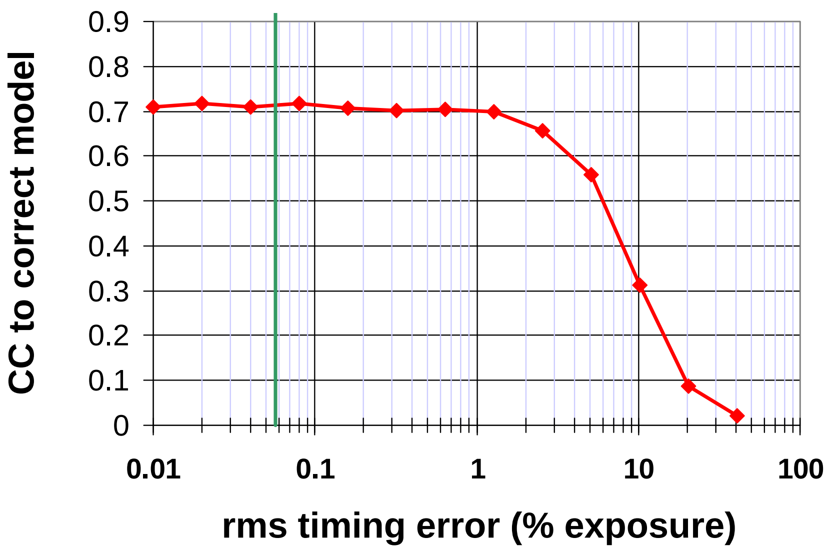


What about crystal vibration?

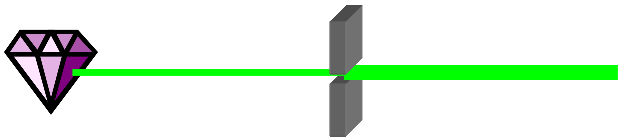
Beam Flicker

1/f noise or "flicker noise"

Beam Flicker

1/f noise or "flicker noise"

comes from everything



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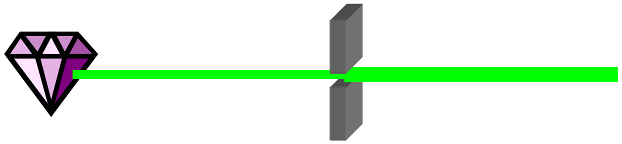

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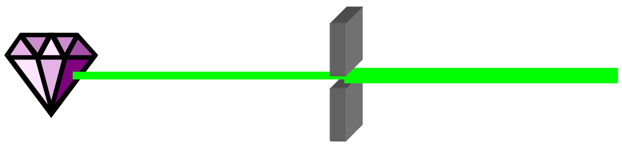

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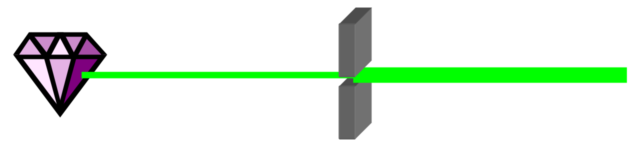

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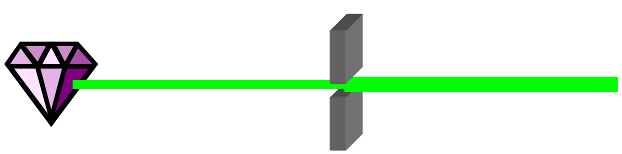

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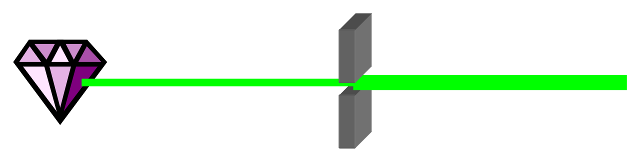

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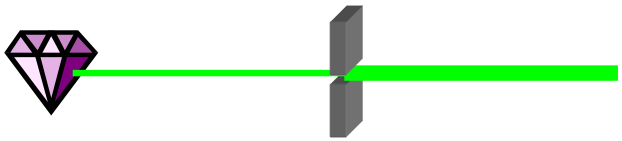

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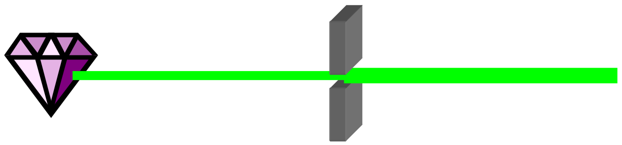

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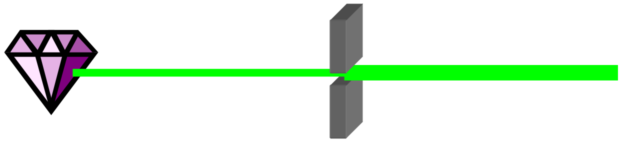

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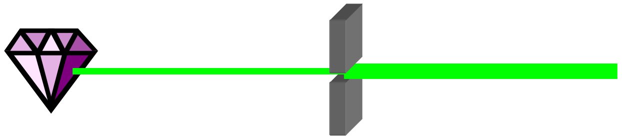

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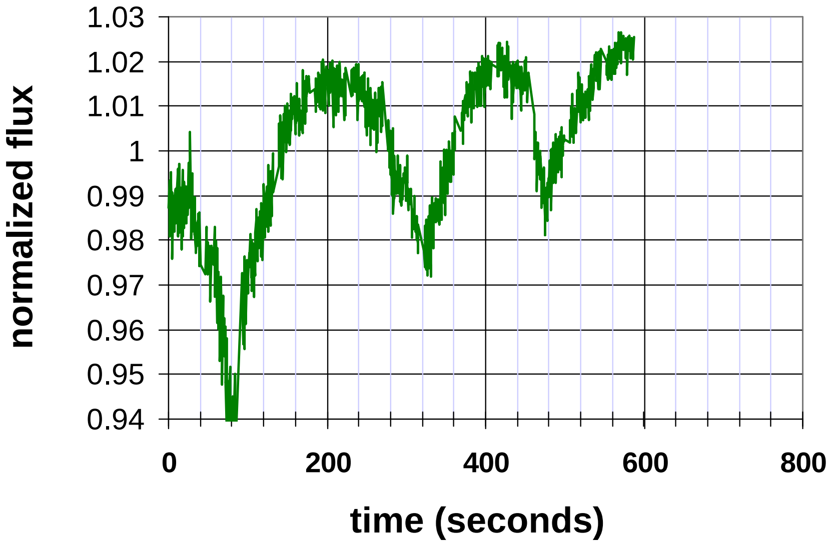

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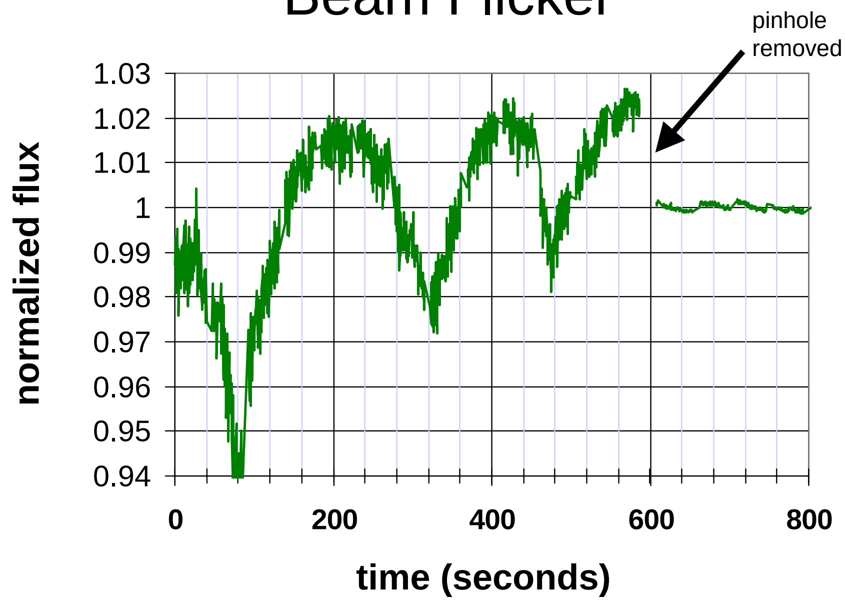

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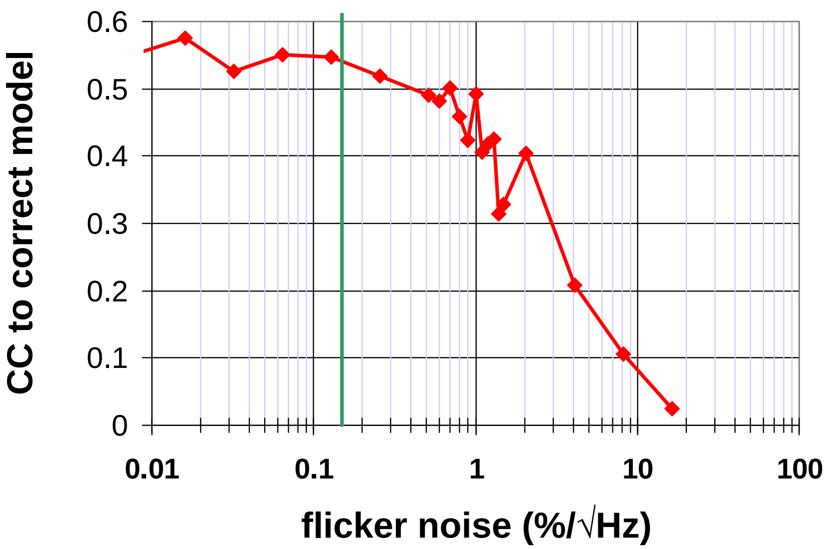
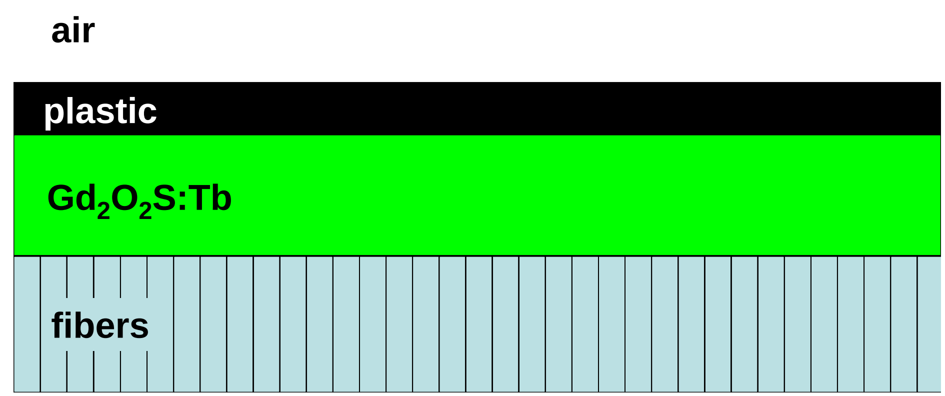


What about a better detector?

What if we had a perfect detector?

Detector model



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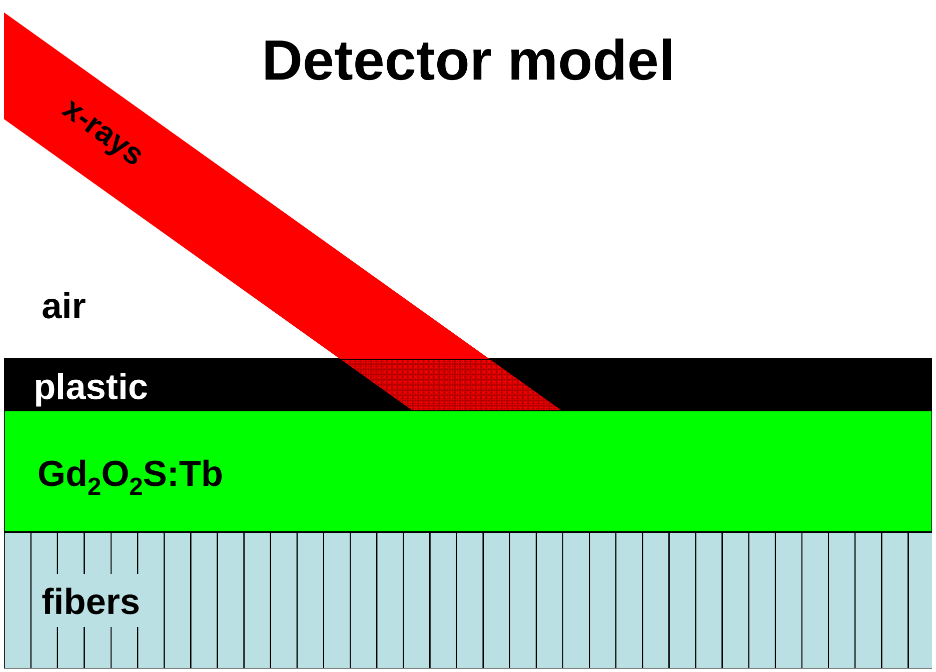

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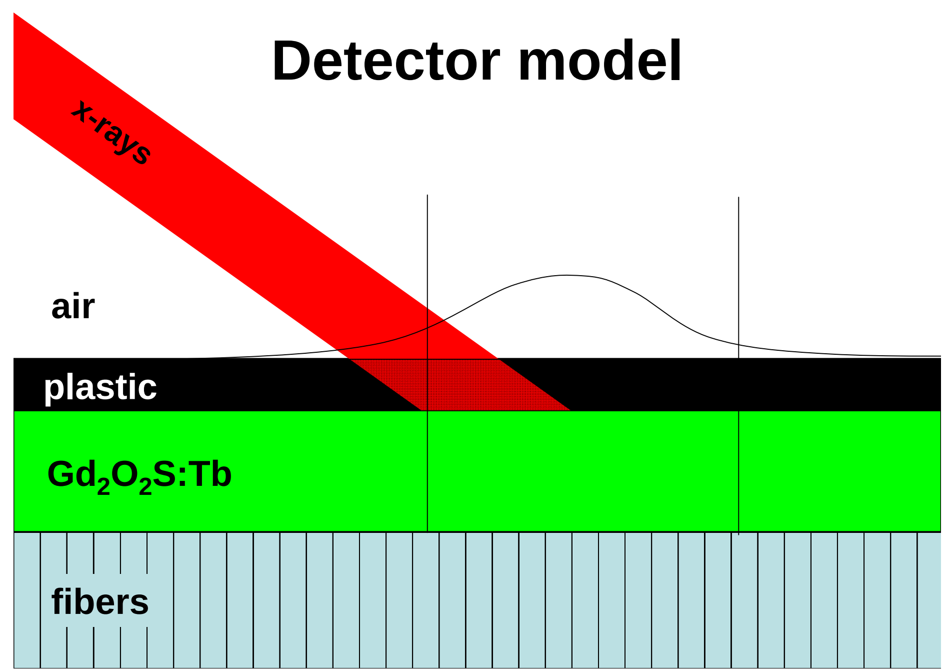
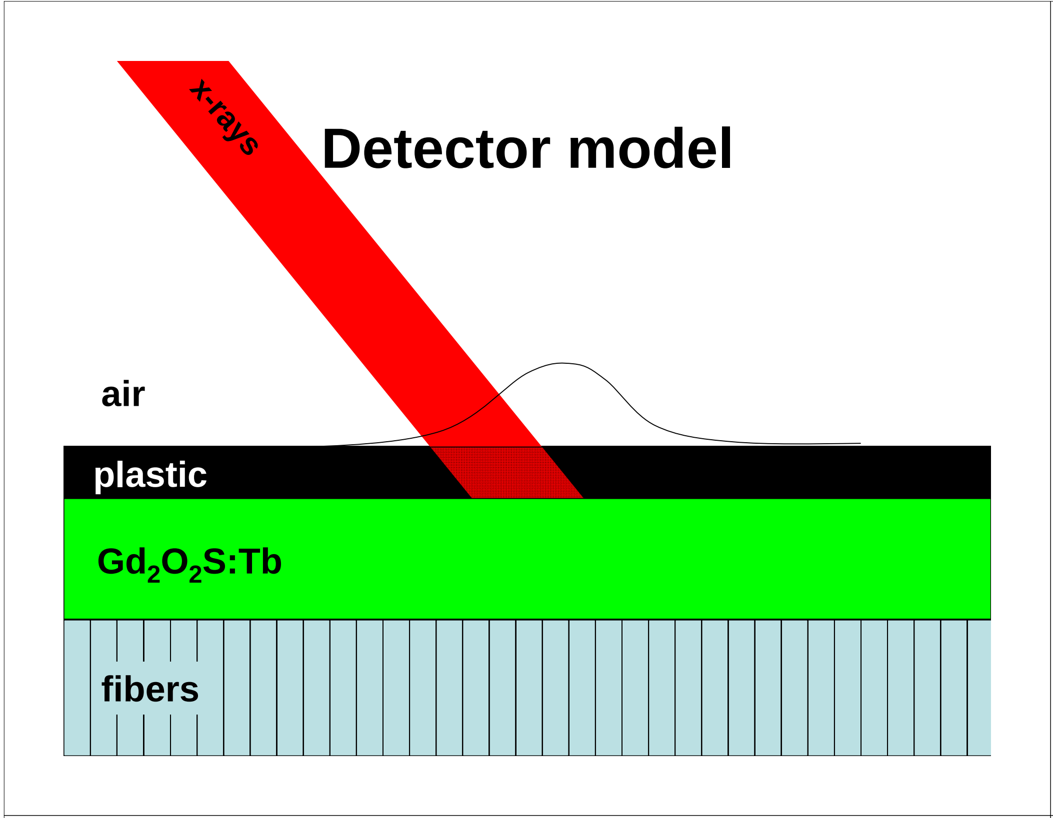
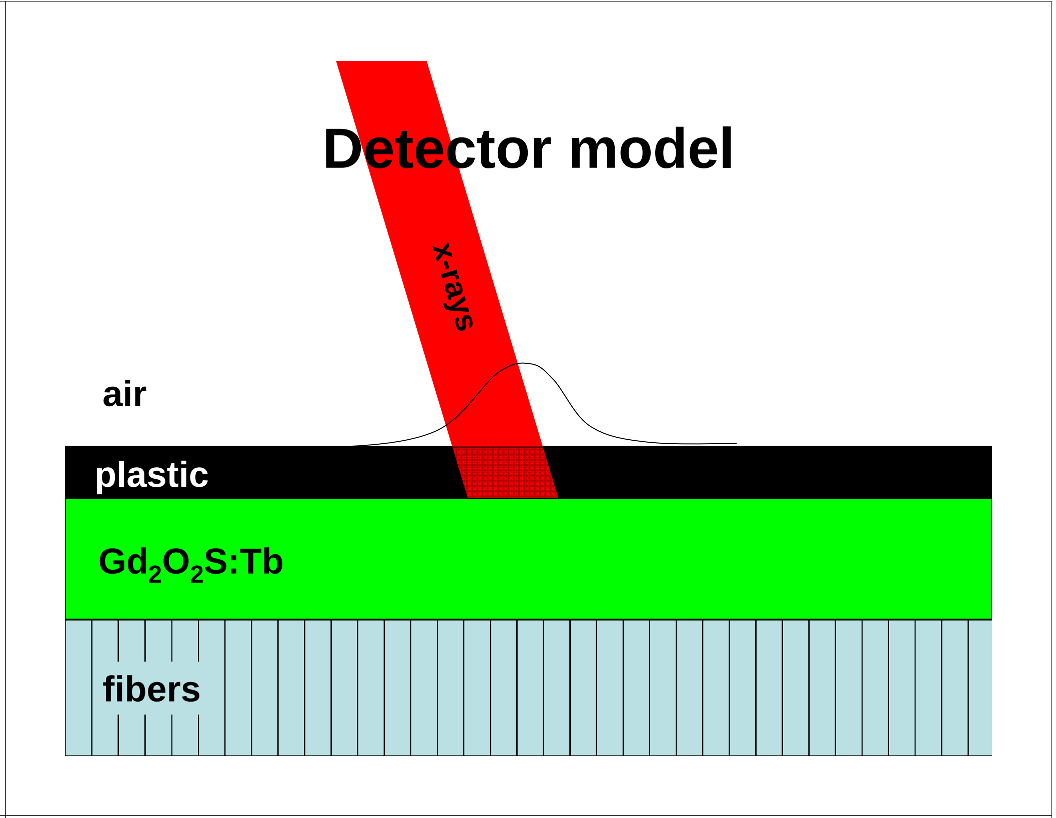



Detector model
x-rays
air
plastic
Gd2O2S:Tb
fibers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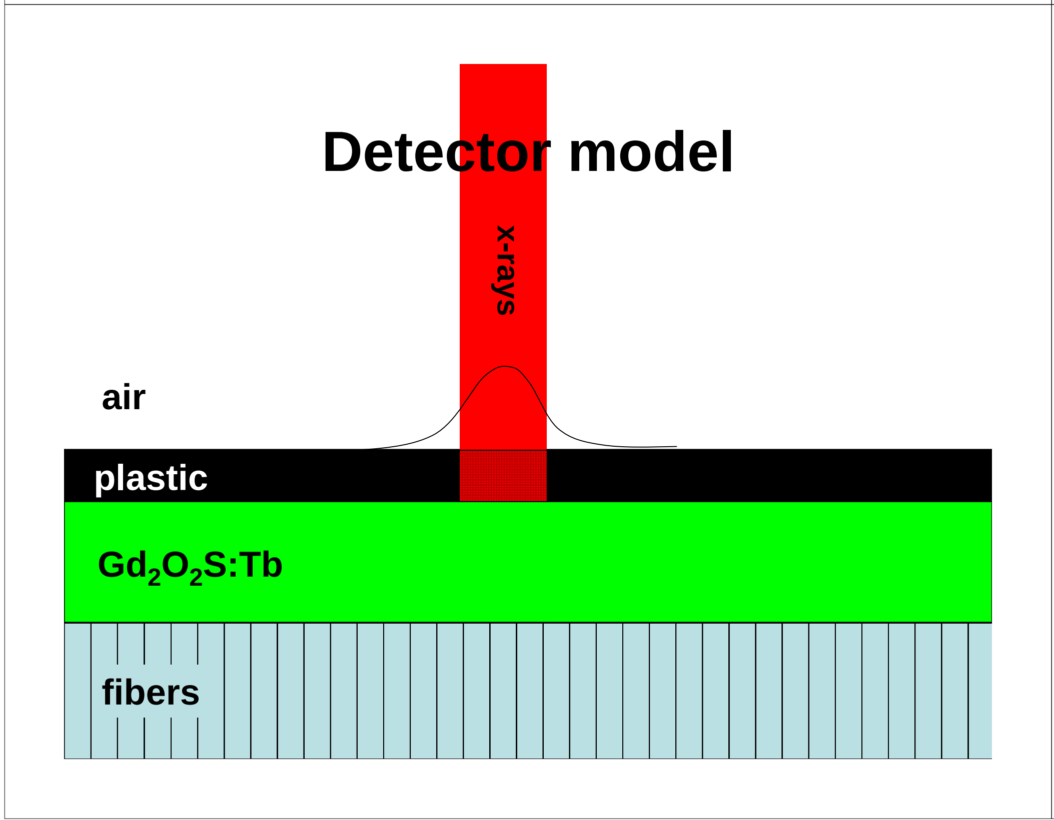
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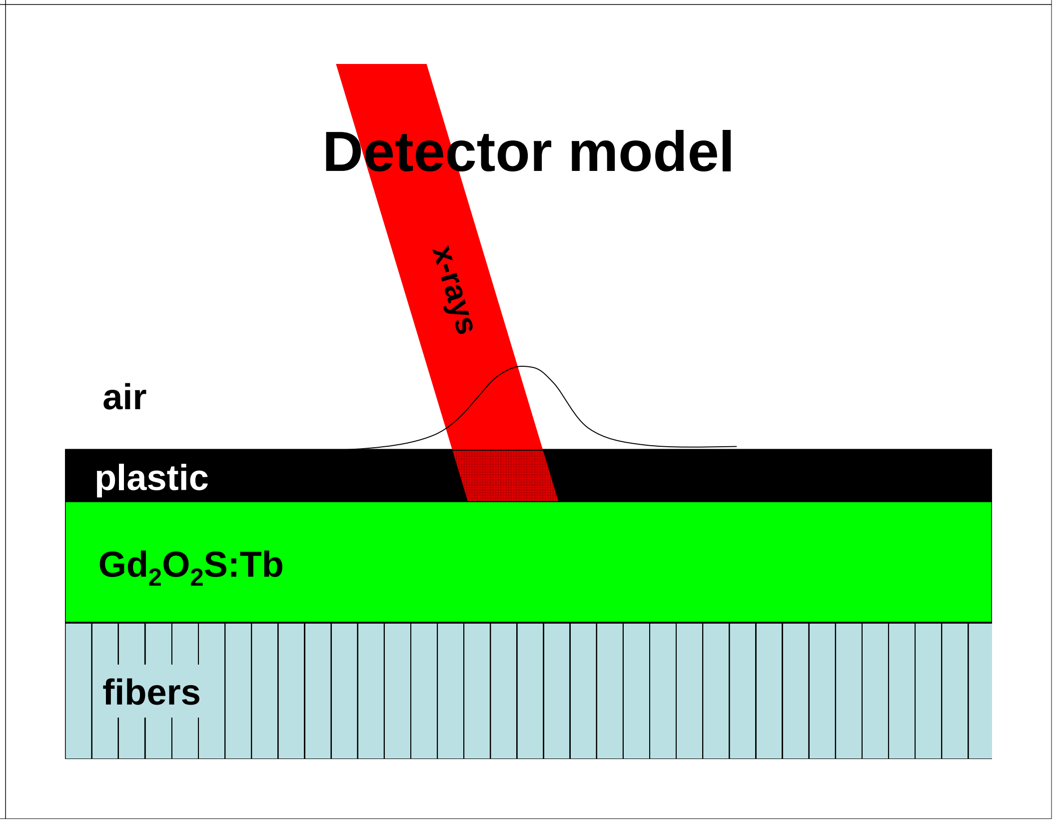
Detector model
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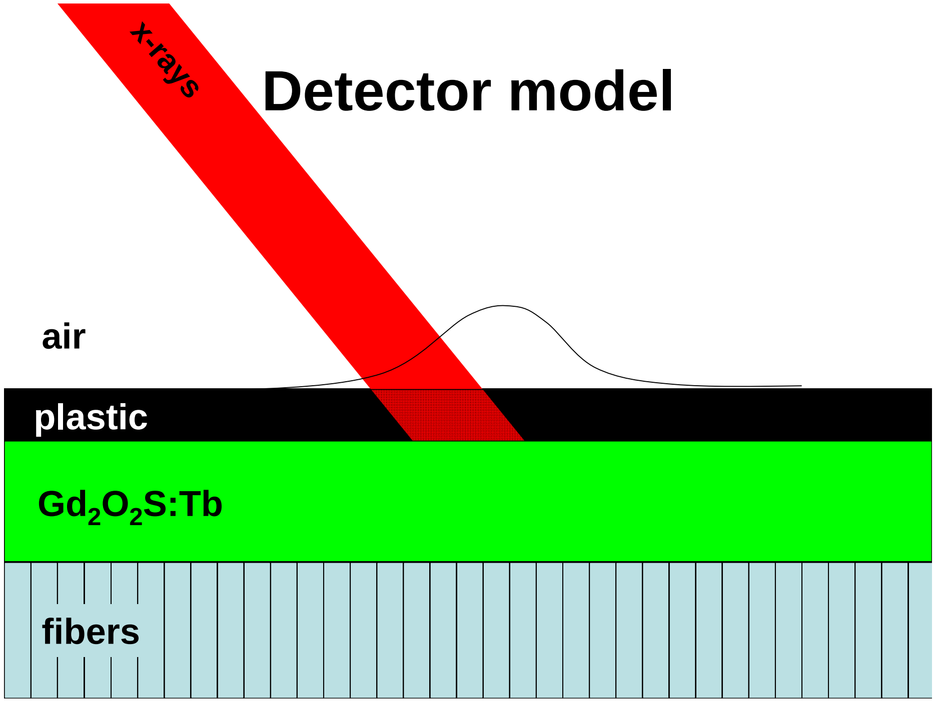
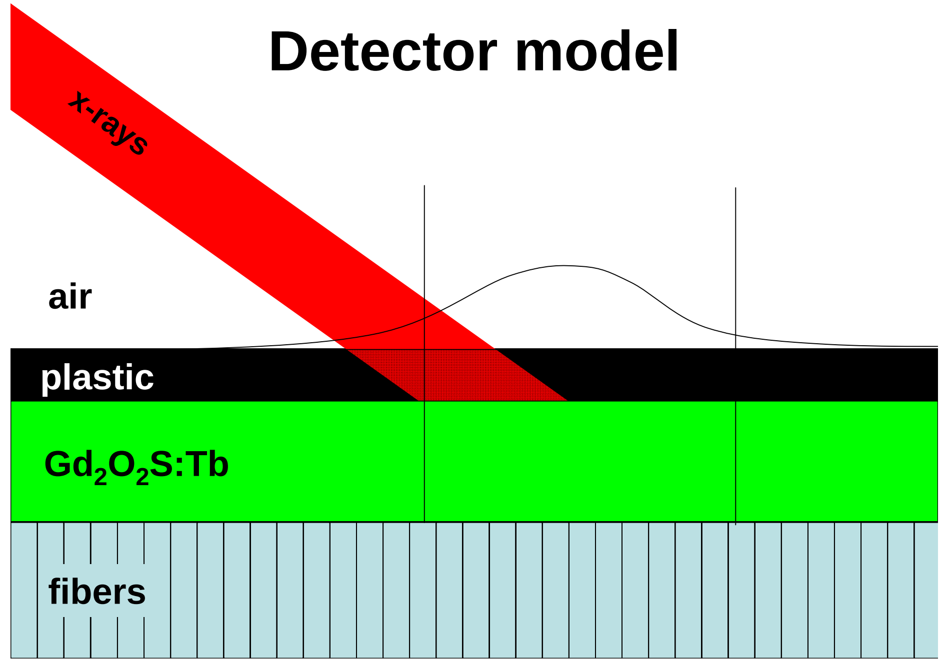
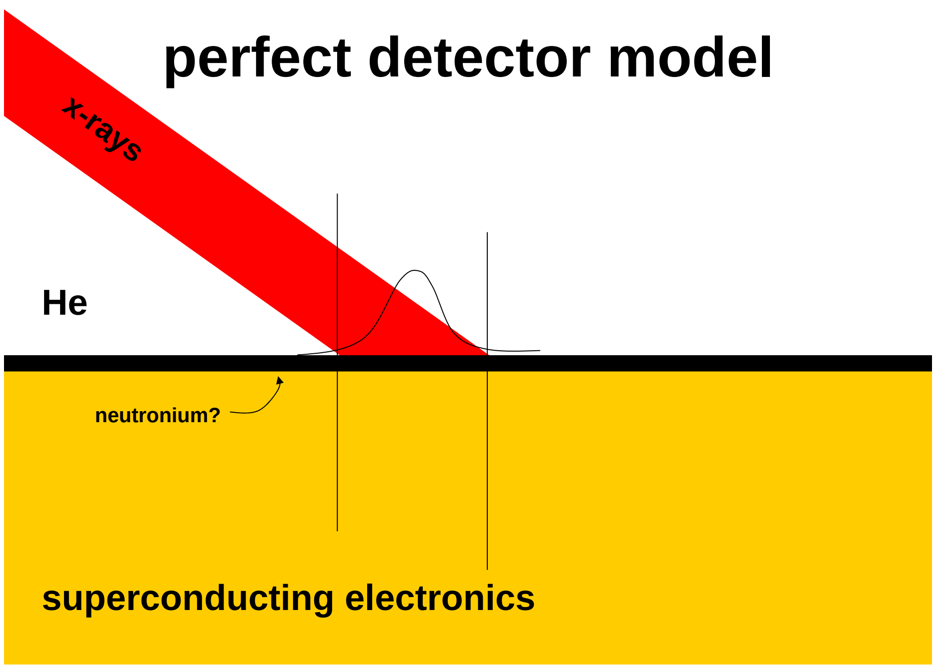
Detector model



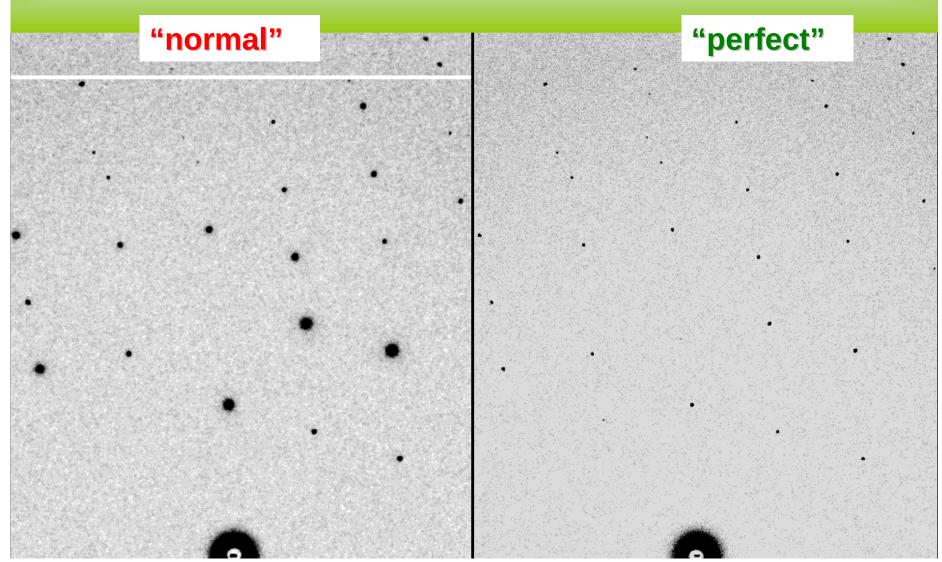
Detector model



perfect detector model



a perfect detector



normal	statistic	perfect
4.0%	R_{merge}	3.9%
24.3	I/sd	28.1
3.7	I/sd (1.4 Å)	7.3
1.37 3 0.02	SDCORR	0.98 11 0.05
38.01	PADFPH	35.16
4.104	mlphare f”	3.973
0.224	FOM	0.272
0.579	FOMDM	0.563
0.7113	CC(1H87)	0.7051
15.72	R_{cryst}	16.64
18.30	R_{free}	19.38

can we collect

shorter exposures with higher redundancy?

same total dose with high and low redundancy

dataset	1	2-11	12
exposure	1.0s	0.1s	1.0s
frames	100	100 x 10	100
R_{merge}			
R_{anom}			
I/sd			
I/sd (2.0 Å)			
redundancy			
PADFPH			
FOM			
FOMDM			
CC(1H87)			

same total dose with high and low redundancy

dataset	1	2-11	12
exposure	1.0s	0.1s	1.0s
frames	100	100 x 10	100
R_{merge}	5.6%	11.2%	4.7%
R_{anom}	4.8%	4.7%	4.7%
I/sd	29.5	43.4	33.3
I/sd (2.0 Å)	23.3	29.6	25.8
redundancy	7.6	75.7	7.6
PADFPH	36.69	37.11	37.93
FOM	0.342	0.343	0.366
FOMDM	0.698	0.711	0.726
CC(1H87)	0.418	0.492	0.468

same total dose with high and low redundancy

dataset	1	2-11	12
exposure	1.0s	0.1s	1.0s
frames	100	100 x 10	100
R_{merge}	5.6%	11.2%	4.7%
R_{anom}	4.8%	4.7%	4.7%
I/sd	29.5	43.4	33.3
I/sd (2.0 Å)	23.3	29.6	25.8
redundancy	7.6	75.7	7.6
PADFPH	36.69	37.11	37.93
FOM	0.342	0.343	0.366
FOMDM	0.698	0.711	0.726
CC(1H87)	0.418	0.492	0.468

same total dose with high and low redundancy

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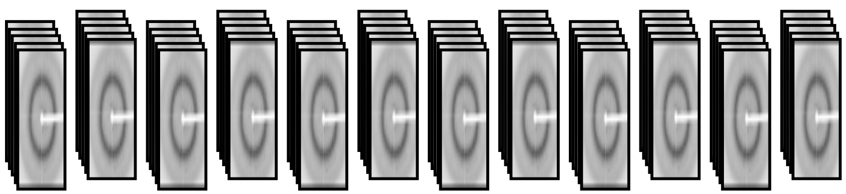
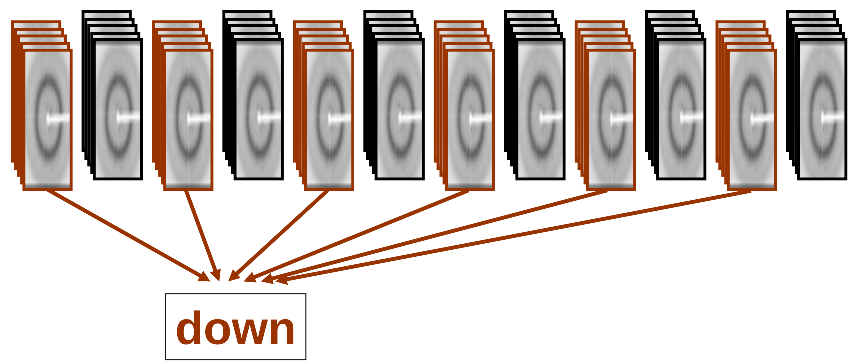
exposure	1.0s	0.1s	1.0s
frames	100	100 x 10	100
R_{merge}	5.6%	11.2%	4.7%
R_{anom}	4.8%	4.7%	4.7%
I/sd	29.5	43.4	33.3
I/sd (2.0 Å)	23.3	29.6	25.8
redundancy	7.6	75.7	7.6
PADFPH	36.69	37.11	37.93
FOM	0.342	0.343	0.366
FOMDM	0.698	0.711	0.726
CC(1H87)	0.418	0.492	0.468

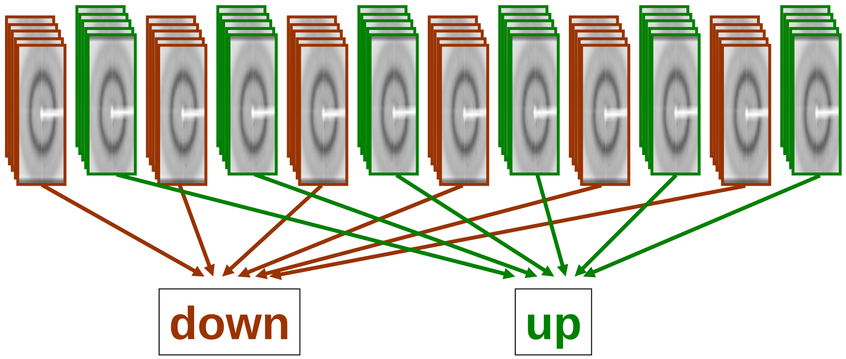
Spatial Noise



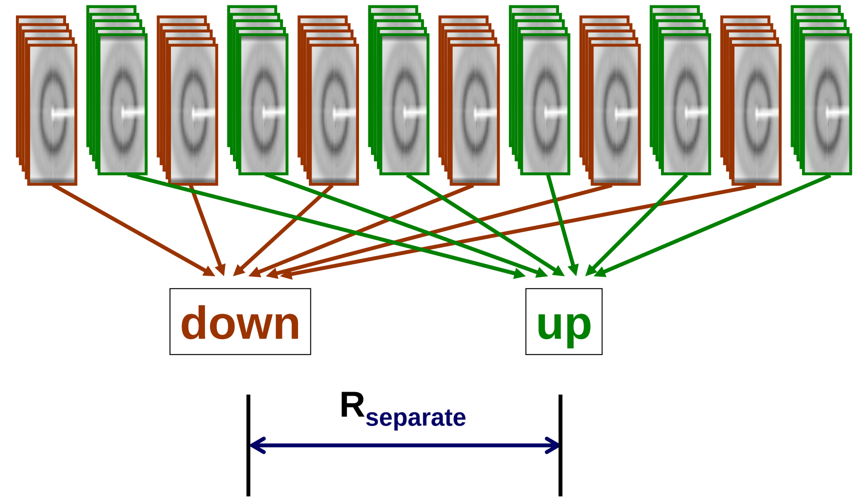
Spatial Noise



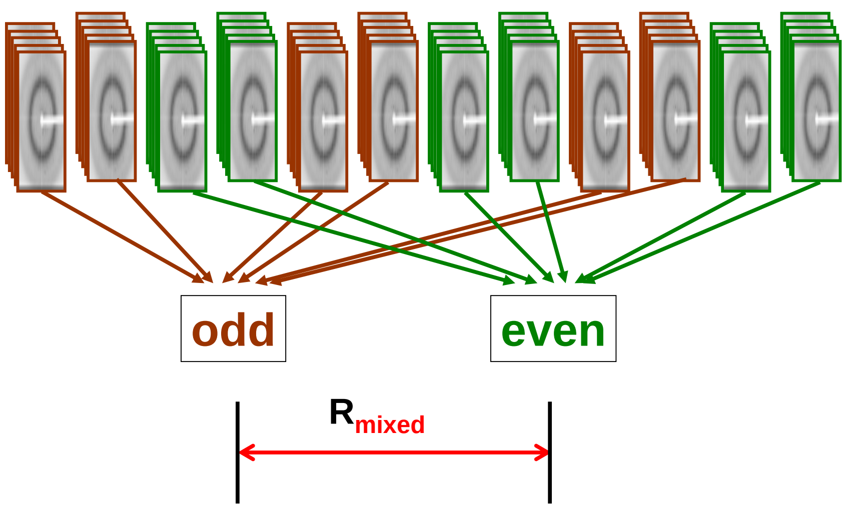
Spatial Noise



Spatial Noise



Spatial Noise



Spatial Noise

separate: 2.5%

Spatial Noise

separate: 2.5%

mixed: 0.9%

Spatial Noise

separate: 2.5%

mixed: 0.9%

$$2.5\%^2 - 0.9\%^2 = 2.3\%^2$$

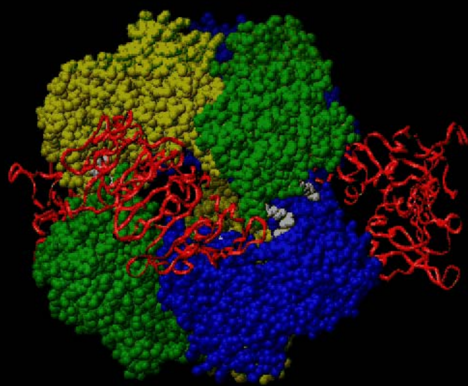
Spatial Noise

$$\text{mult} > \left(\frac{2.3\%}{<\Delta F/F>}\right)^2$$

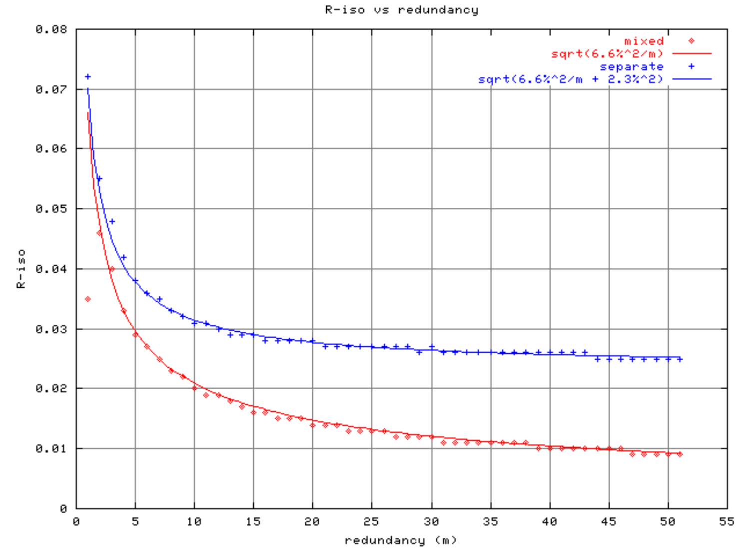
Spatial Noise

$$\text{mult} > \left(\frac{R_{merge}}{<\Delta F/F>}\right)^2$$

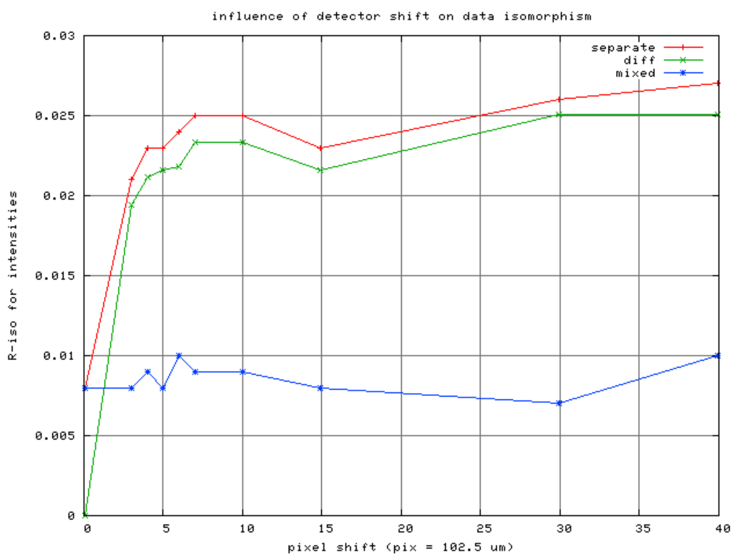
Proteins move



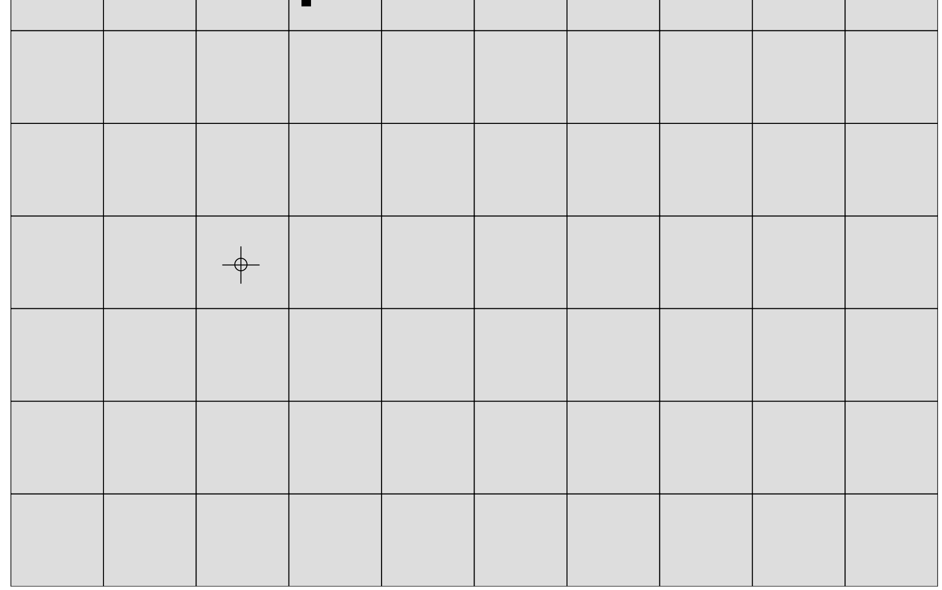
Spatial Noise



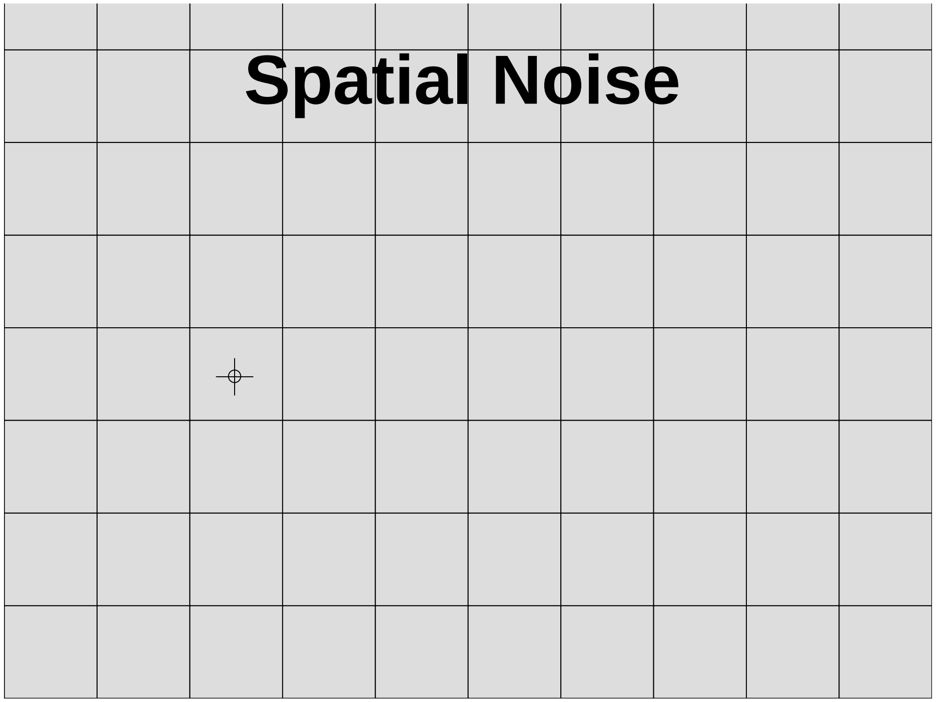
Spatial Noise



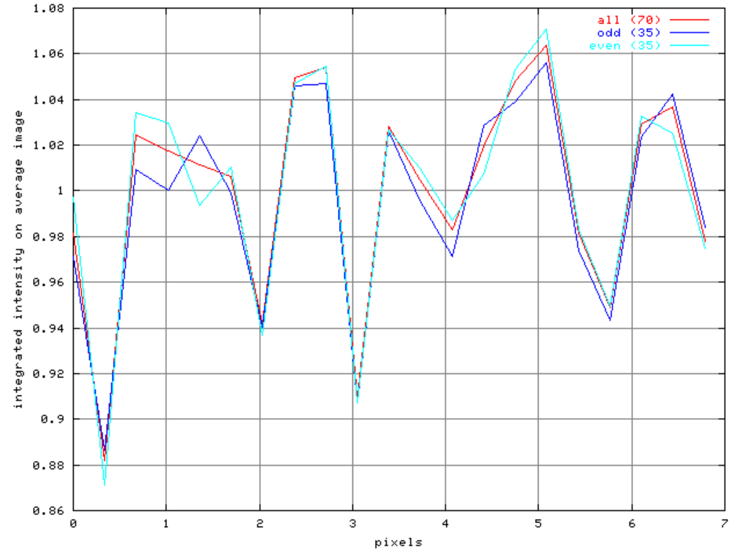
Spatial Noise



Spatial Noise



Spatial Noise



Summary

98% screening

short exposures FIRST

“dose slicing”

site damage is unpredictable

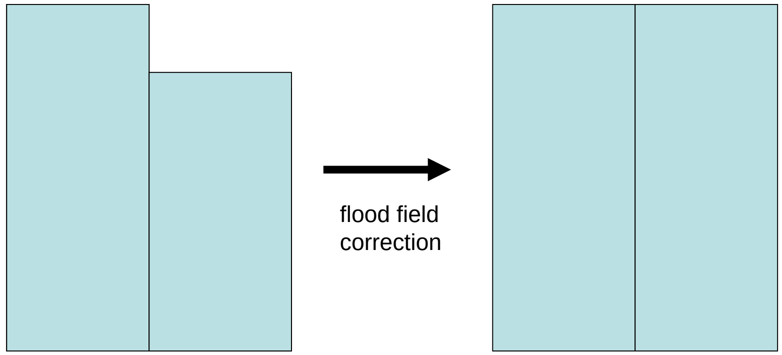
Development Snapshot

http://bl831.als.lbl.gov/~jamesh/mlfsom/
development_snapshot.tar.gz

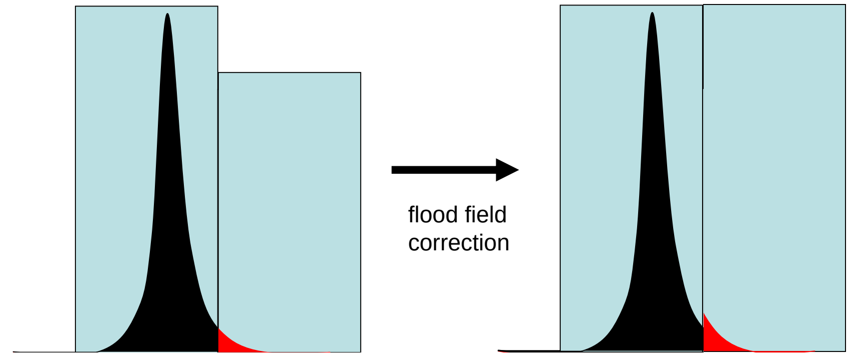
http://bl831.als.lbl.gov/~jamesh/
xtalsize.html

http://bl831.als.lbl.gov/~jamesh/
powerpoint/ACA_2009.ppt

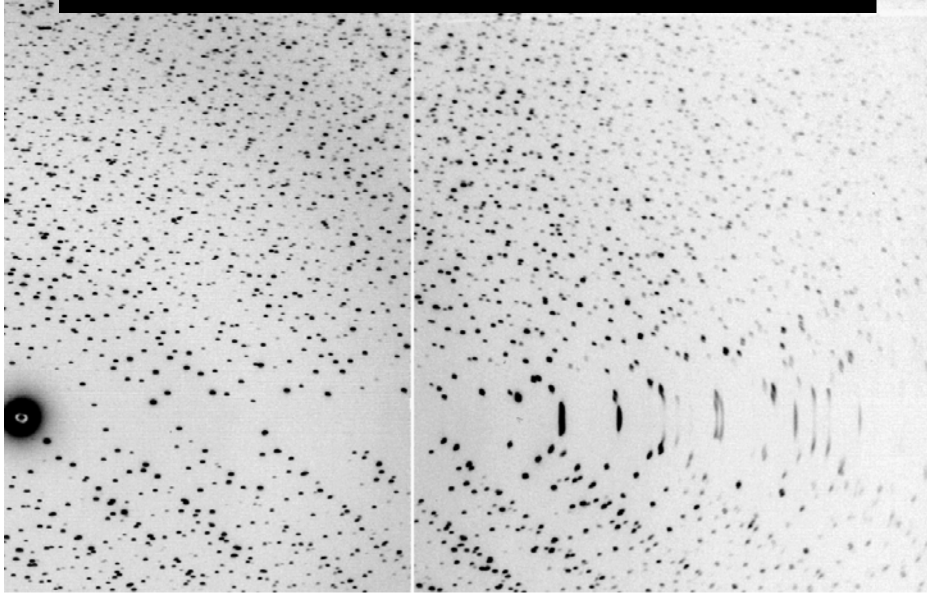
Spatial Noise



Spatial Noise

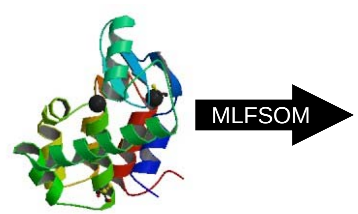


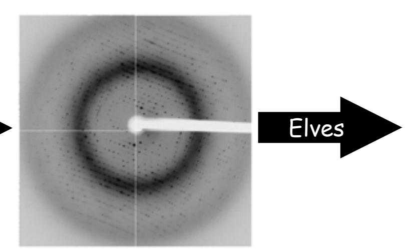
The “Lorentz zone”



The R-factor Gap

multi-conformer PDB file





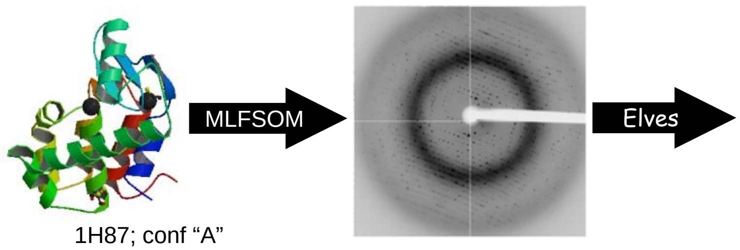
R_{merge} = 6%

R_{cryst} = 17%

R_{free} = 20%

The R-factor Gap

single-conformer PDB file



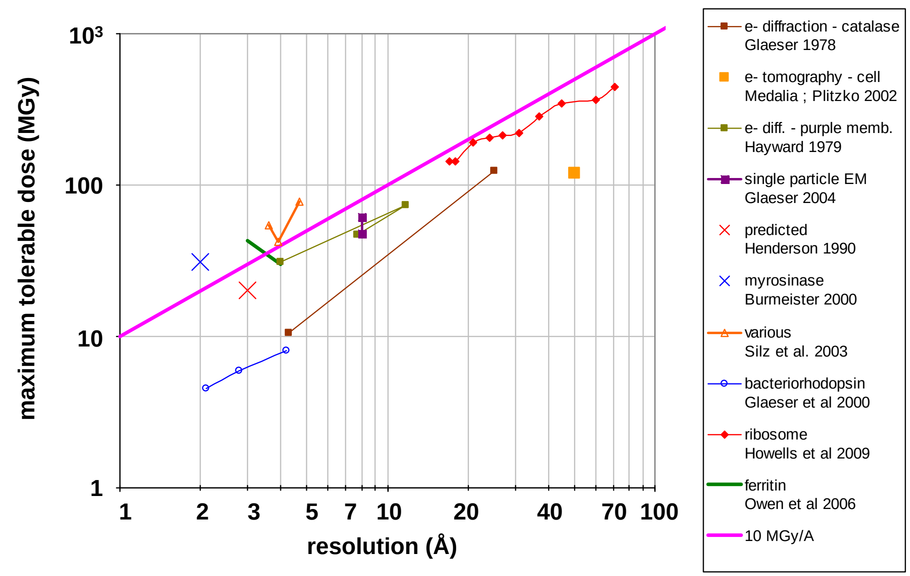
1H87; conf "A"

R_{merge} = 6%

R_{cryst} = 7%

R_{free} = 8%

Howells *et al.* (2009)
J. Electron. Spectrosc. Relat. Phenom. **170** 4-12



Radiation Damage Model

global (lattice) damage

$$|F_{used}| = |F_{undam}| \exp\left(-\ln(2)\frac{\text{dose}}{d\cdot H}\right)$$

F_{used} - structure factor used for spot

F_{undam} - structure factor of undamaged crystal

dose - absorbed dose (MGy)

H - 10 MGy/Å

d - resolution of spot (Å)

Radiation Damage Model

global (lattice) damage

$$F = F_0 \exp(-A\cdot s)$$

F - structure factor used for spot

F_0 - structure factor of undamaged crystal

A - something Debye said was zero

s - 0.5/**d**

d - resolution of spot (Å)

Radiation Damage Model

global (lattice) damage

$$F = F_0 \exp(- A \cdot s)$$

F - structure factor used for spot

F_0 - structure factor of undamaged crystal

A - something Debye said was zero

s - 0.5/**d**

d - resolution of spot (Å)

Radiation Damage Model

global (lattice) damage

$$F = F_0 \exp(- A \cdot s - B \cdot s^2 - C \cdot s^3 - \ldots)$$

A - something Debye said was zero

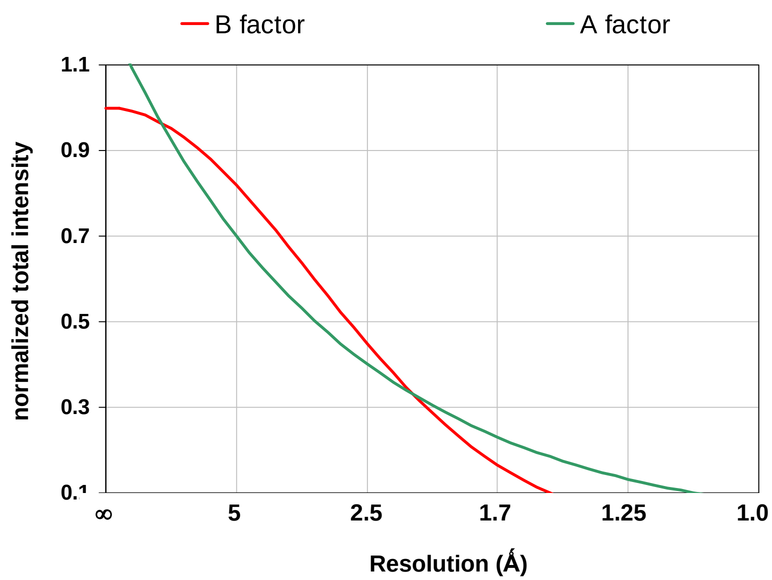
B - canonical Debye-Waller factor

C - something else Debye said was zero

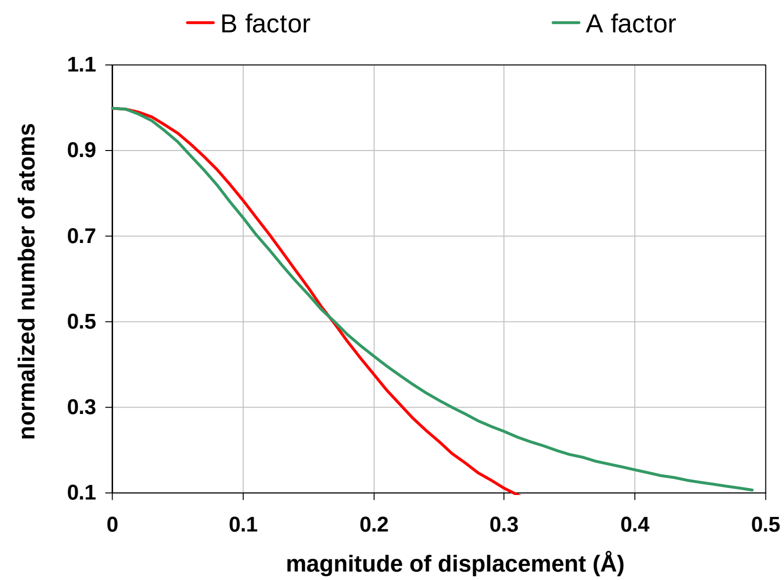
s - 0.5/**d**

d - resolution of spot (Å)

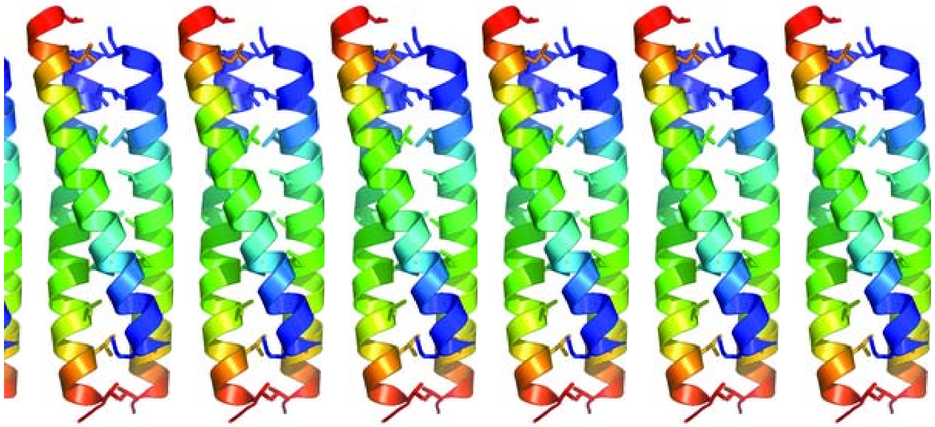
Radiation Damage Model



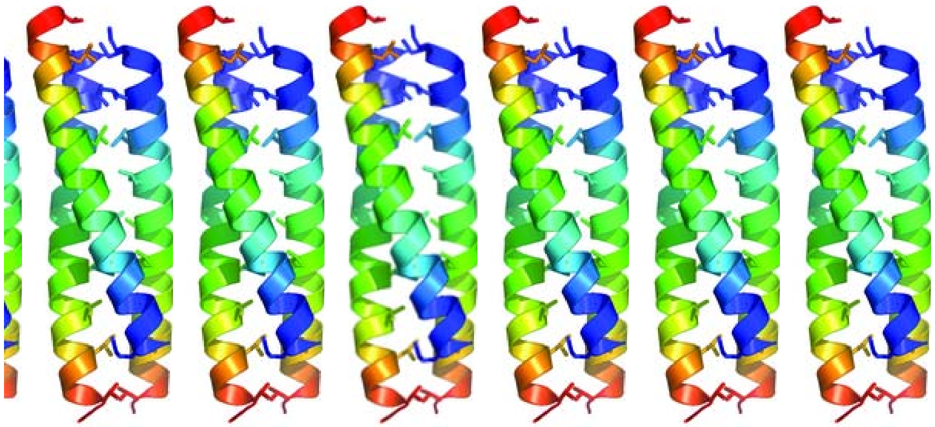
Radiation Damage Model



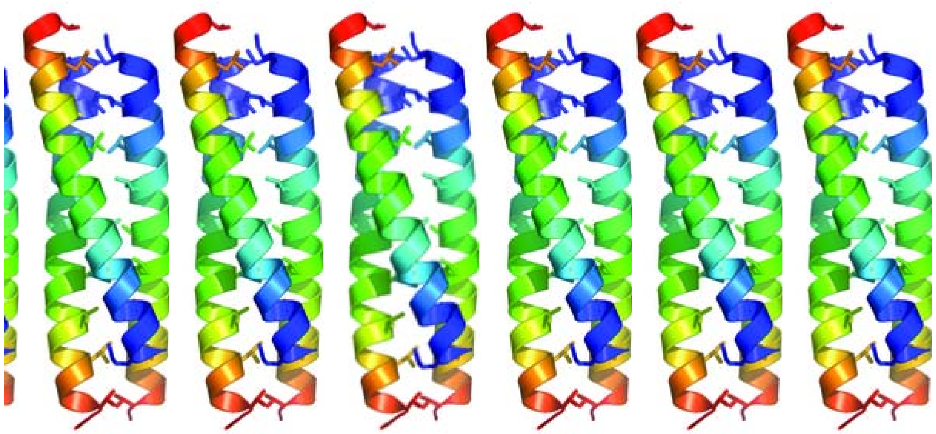
Radiation Damage Model



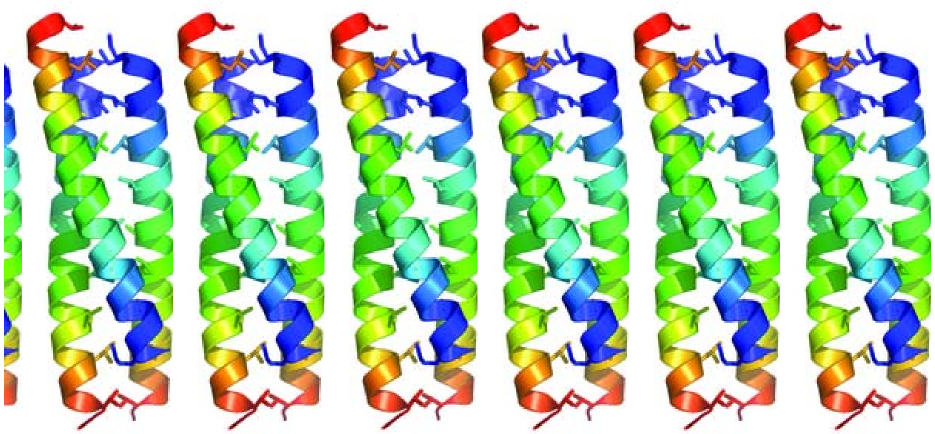
Radiation Damage Model



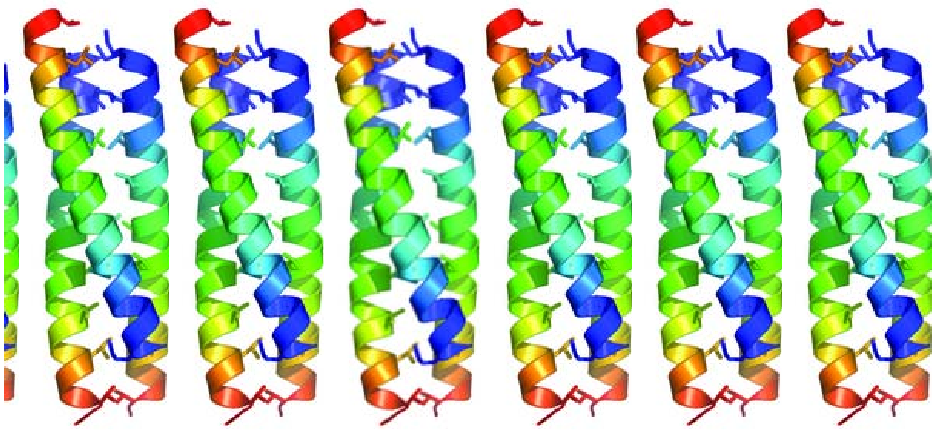
Radiation Damage Model



Radiation Damage Model

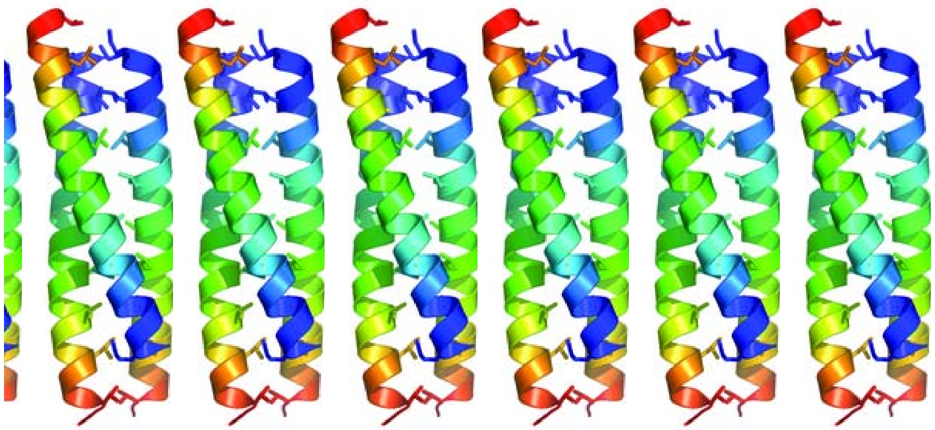


Radiation Damage Model



Kanzaki 1957

Radiation Damage Model



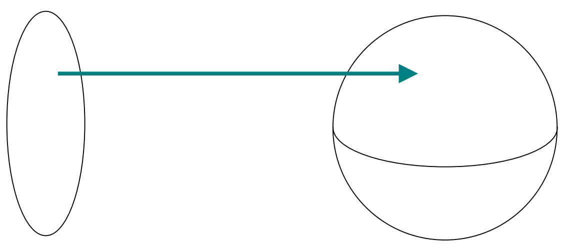
Kanzaki 1957

Radiation Damage prediction

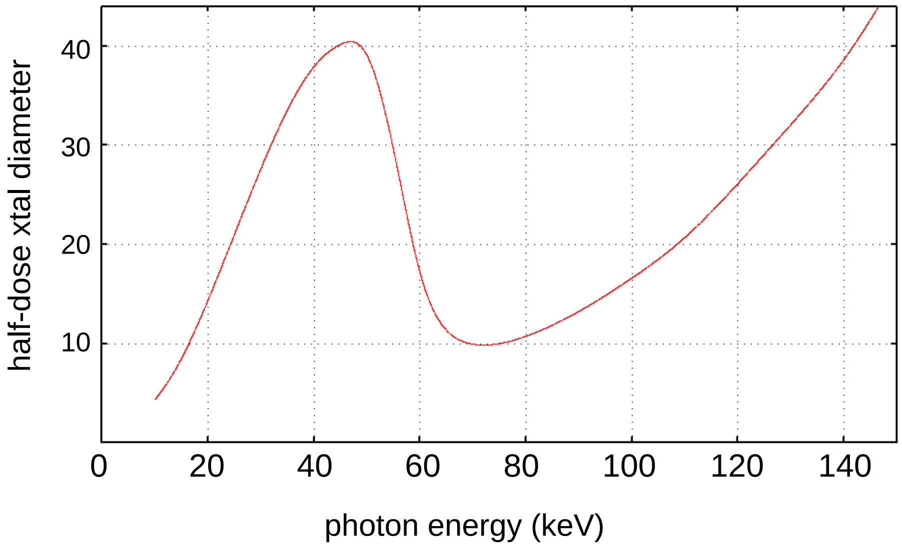
$$\frac{\text{data}}{\text{damage}} \approx k + \left(\frac{2\ \text{ps}}{\text{exposure}}\right)^3$$

particle transport simulation using MCNP

(other codes exist: EGSnrc)



Nave-Hill effect



Nave-Hill effect