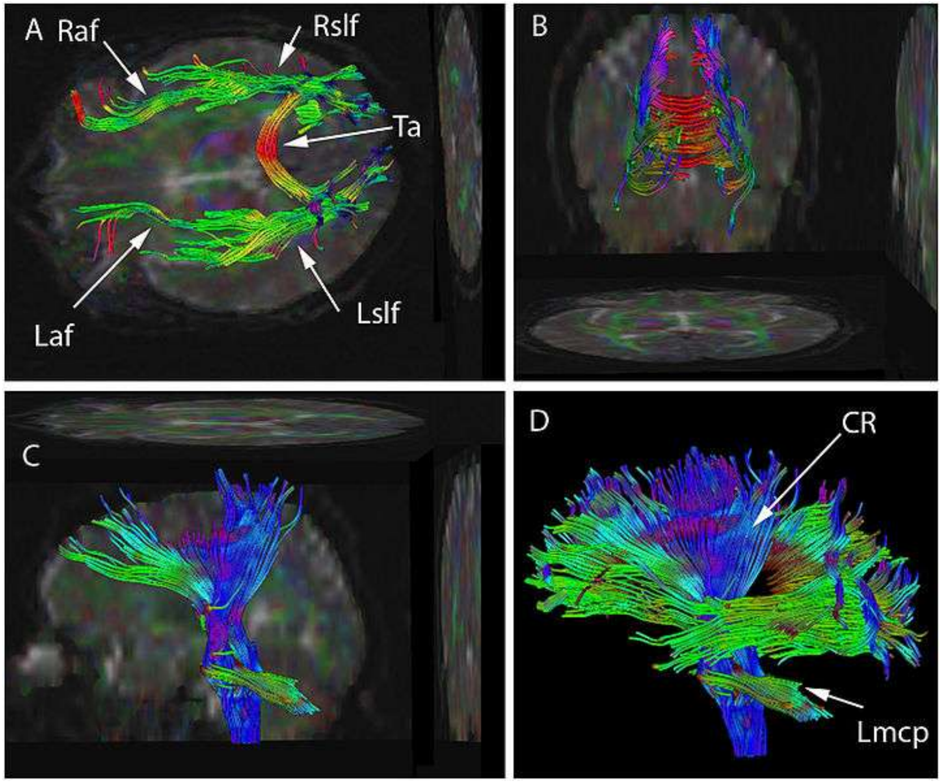
Imaging and Radiotherapy with Synchrotron X-rays

Rob Lewis

Other Modalities

- Ultrasound
  - ✓ Cheap
  - ✓ No radiation dose
  - ✗ Cannot penetrate bone or air
  - ✗ Spatial resolution degrades with depth
  - ✗ Scan times are minutes
- MRI
  - ✓ Fantastic soft tissue contrast
  - ✓ Minimal radiation dose
  - ✗ Expensive
  - ✗ Scan times are many minutes
  - ✗ Spatial resolution f(B)



MRI Accidents

MRI-CT Comparison

MRI

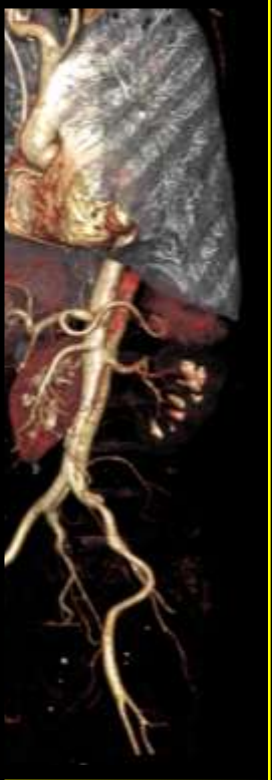
CT

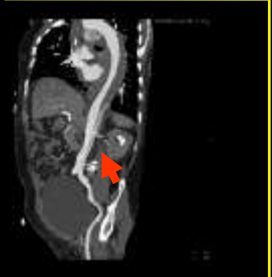
http://www.ct-scan-info.com/head-ct.html

Current Trends

- Preventative medicine is a good idea
- Medical imaging procedures can detect disease at a stage when it can be treated effectively
  - Funding bodies (public and private) will fund imaging procedures
- There is a trend towards more imaging, particularly screening
  - Mammography
  - Whole body CT scans
- Screening means go fast!

e lumen, very sharp





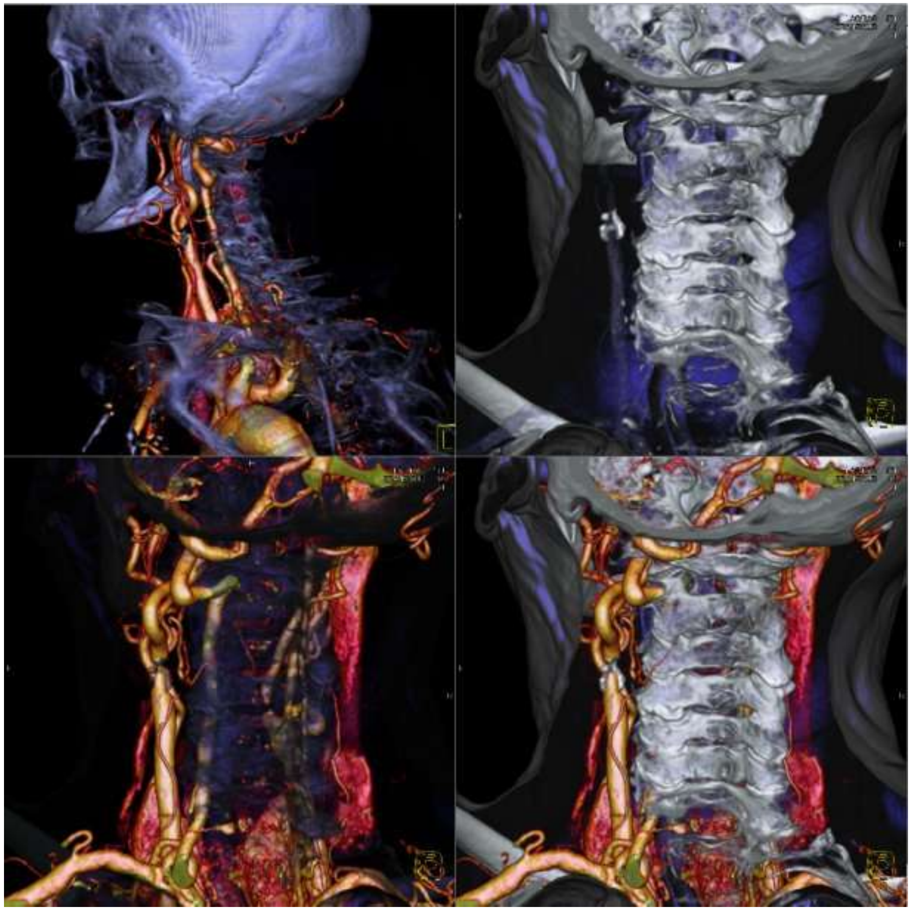
SOMATOM Definition Flash

Flash speed.
Lowest dose.

collimation: 128 x 0.6 mm
spatial resolution: 0.33 mm
scan time: 2.3 s
scan length: 613 mm
rotation time: 0.28 s
100kV, 183 effective mAs
6.2 mSv

Courtesy of Centre Cardio-Thoracique de Monaco / Monaco

Dual Energy CT

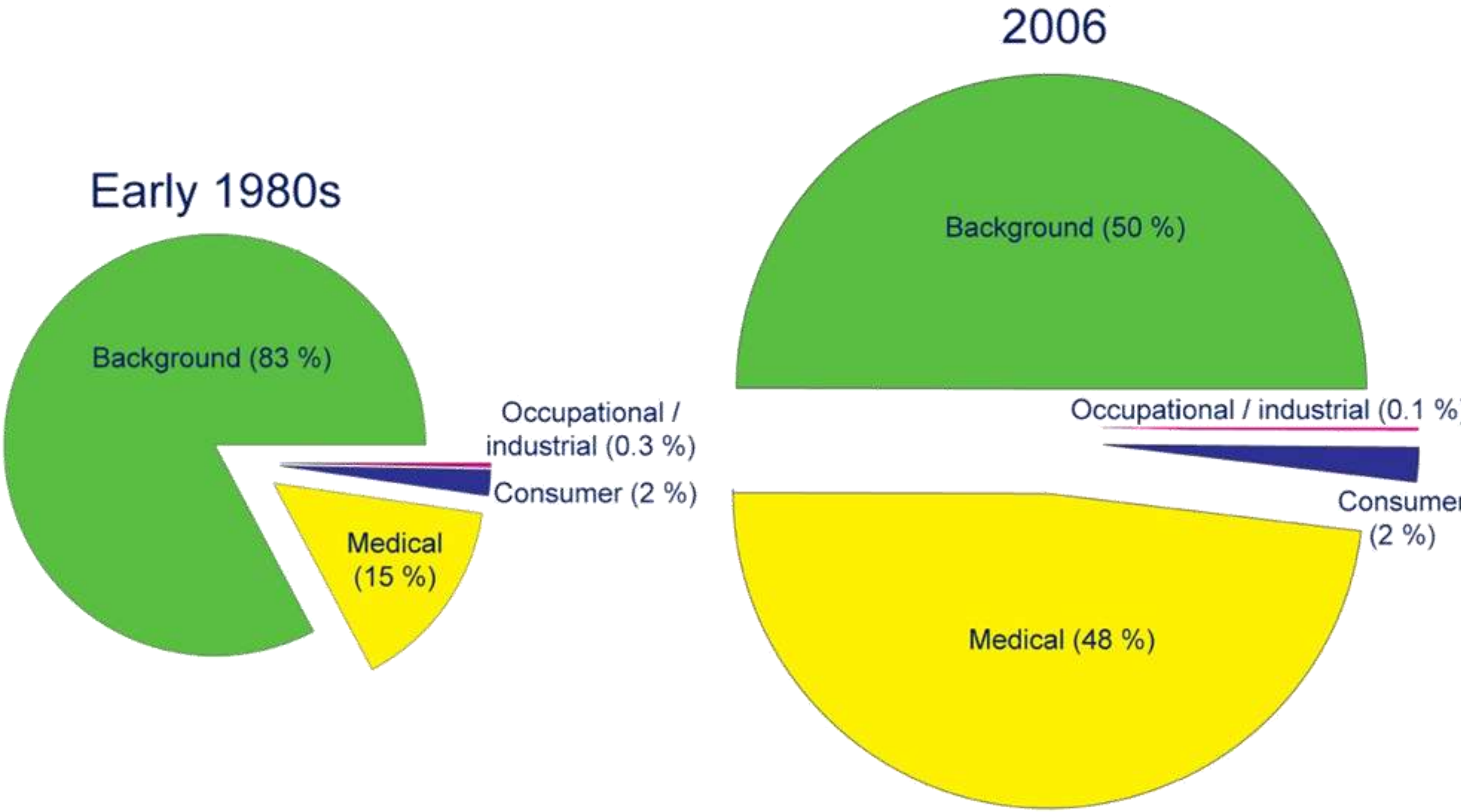


- Plaque in Carotid
  - 9 s for 348 mm
  - Spatial Res. 0.33
  - Rotation 0.33 s
  - 140/80 kV
  - 60/230 mAs (eff.)

What is the Risk from Radiation?

- A lifetime dose of 100mSv increases cancer risk by ~1%
  - 1000 chest x-rays
  - 100 mammograms
  - 50 head CT scans
  - 10 abdominal or pelvic CT scans
- Background Dose is ~ 2.4mSv/year
- It takes most radiation-induced cancers 10 to 20 years to develop in adults
- The average lifetime risk of developing cancer is 42%
- From early 1980s to 2006, 7× increase in population dose from medical procedures

Trends in Radiation Dose from Medical Imaging

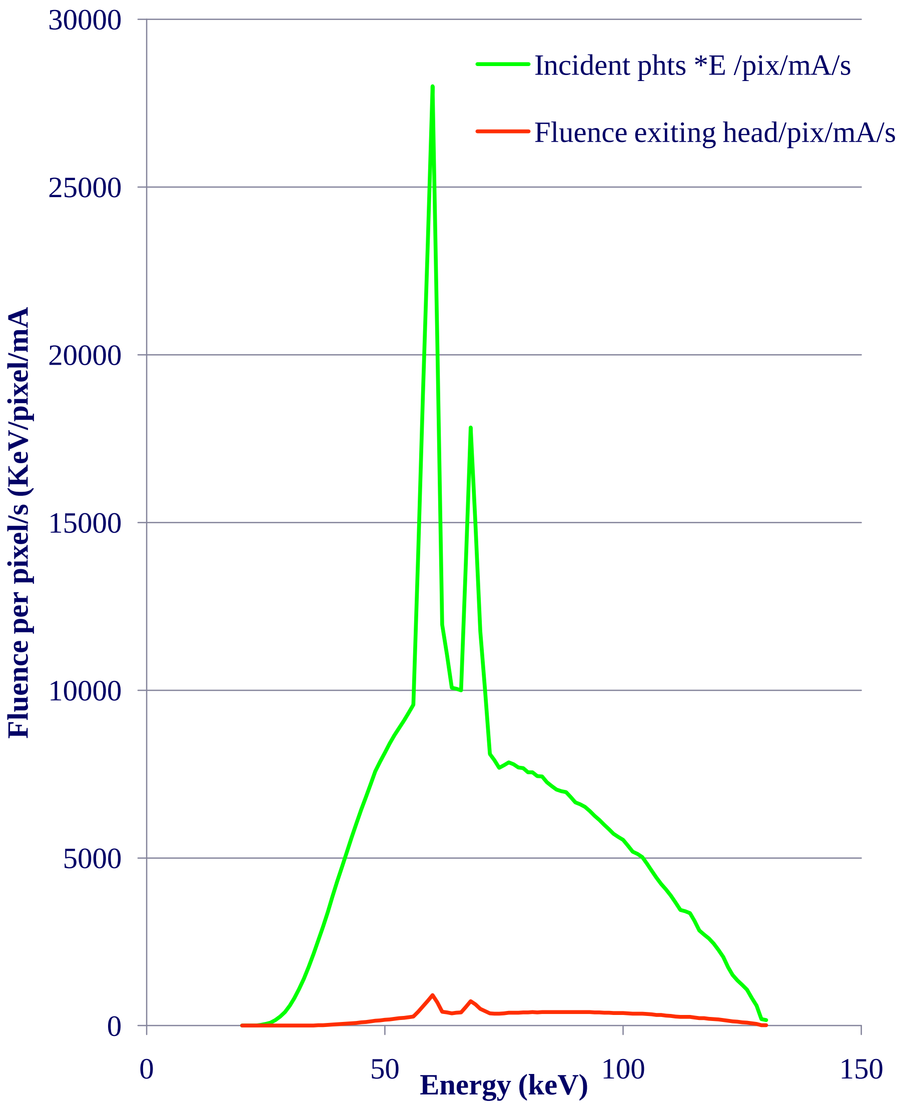


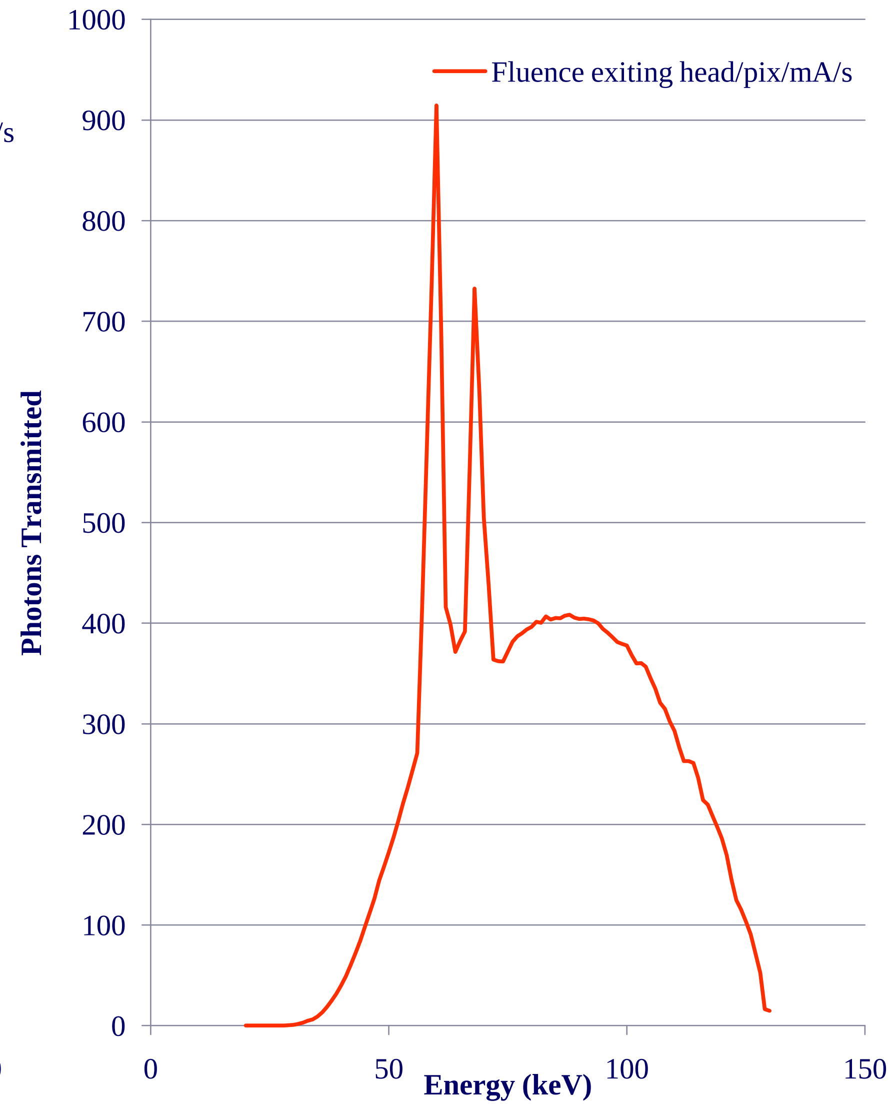
	Early 1980s	2006
Collective effective dose (person-Sv)	835,000	1,870,000
Effective dose per individual in the U.S. population (mSv)	3.6	6.2

CT and Radiography Problems

1. X-ray Dose
2. Scatter
3. Beam Hardening
4. Cone Beam Artefacts

Fluence and Dose





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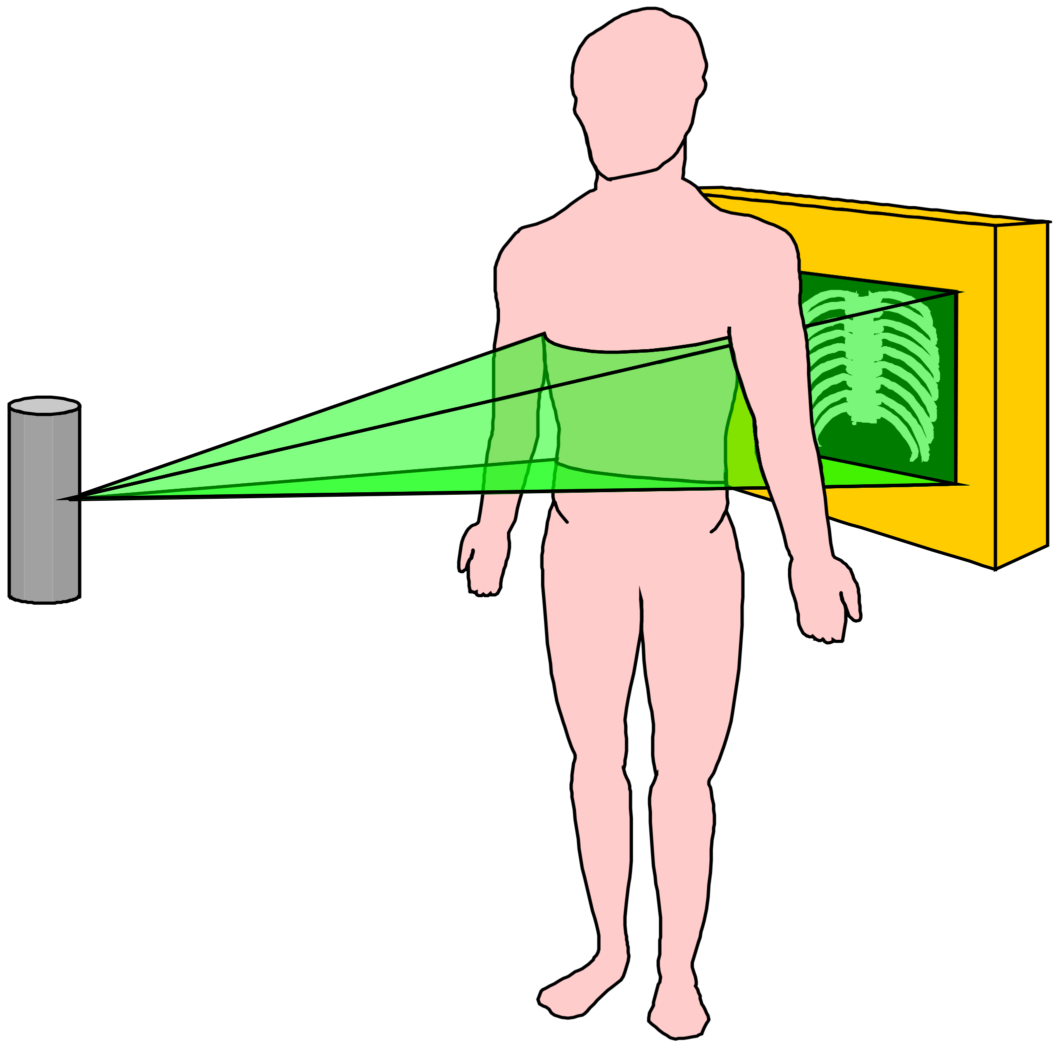
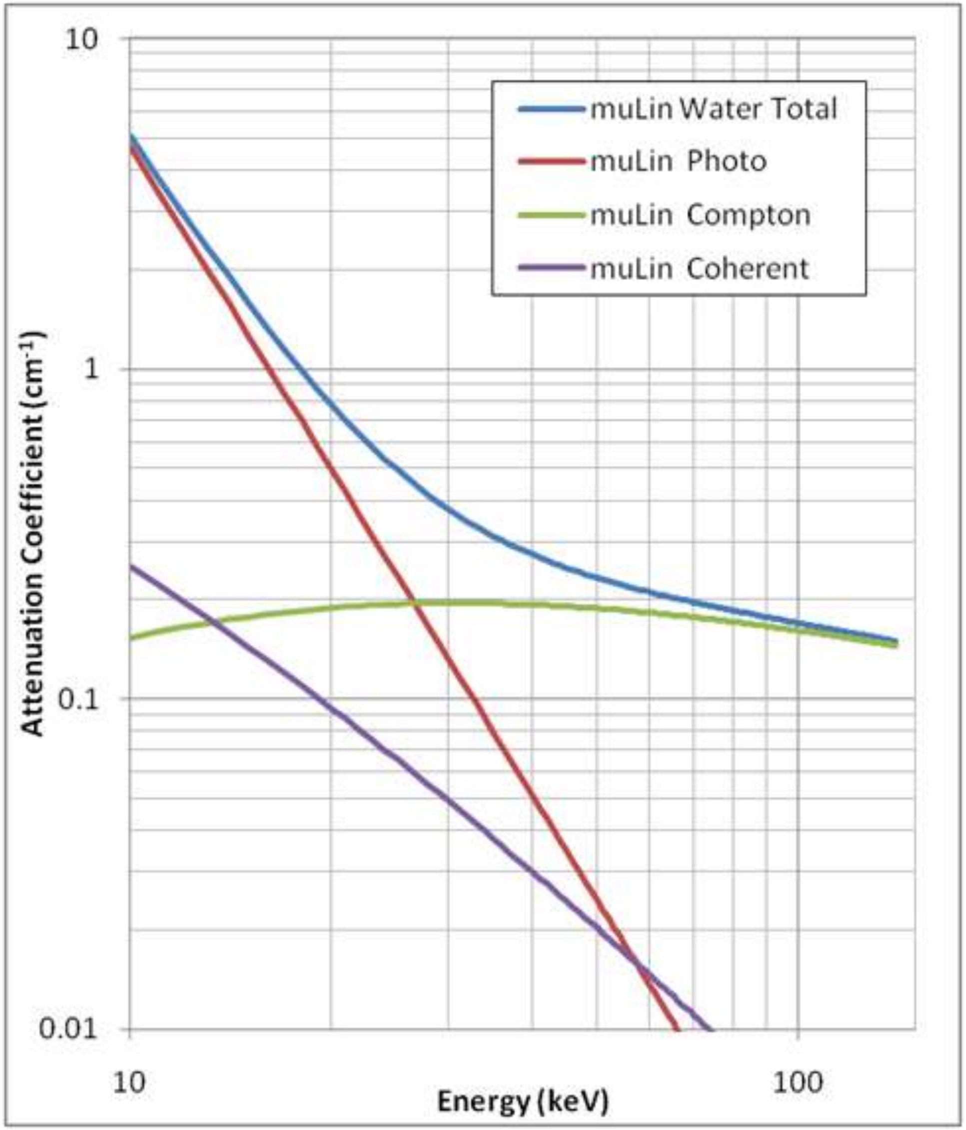
Conventional Radiography

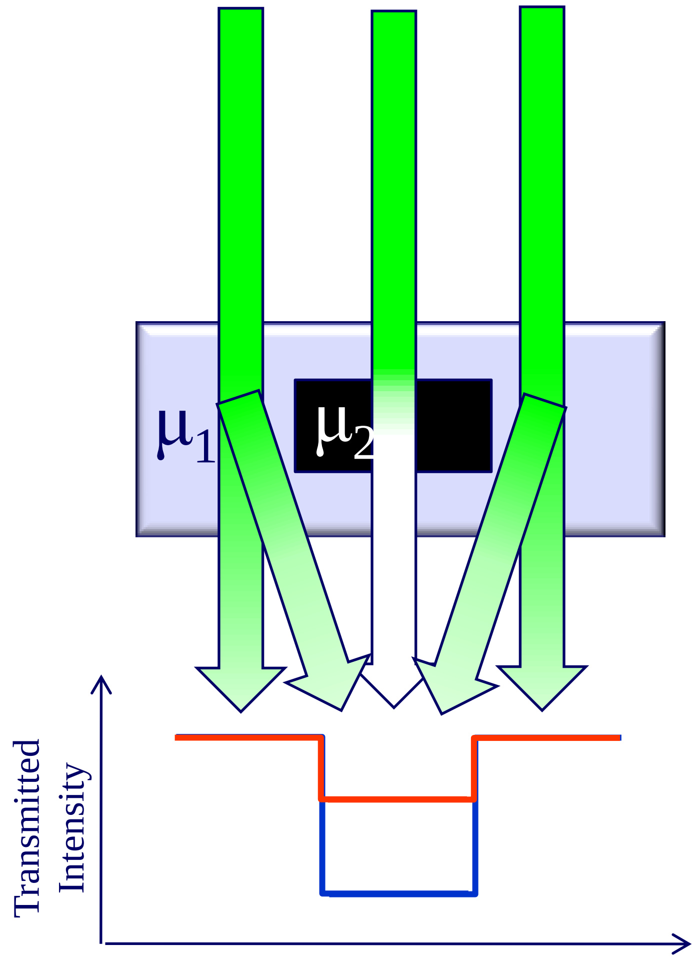


Water Attenuation Coefficients

- Photo electric falls rapidly with increasing energy
- Compton scattering roughly constant
- Coherent scattering falls with increasing energy but less rapidly than photoelectric (important see later)

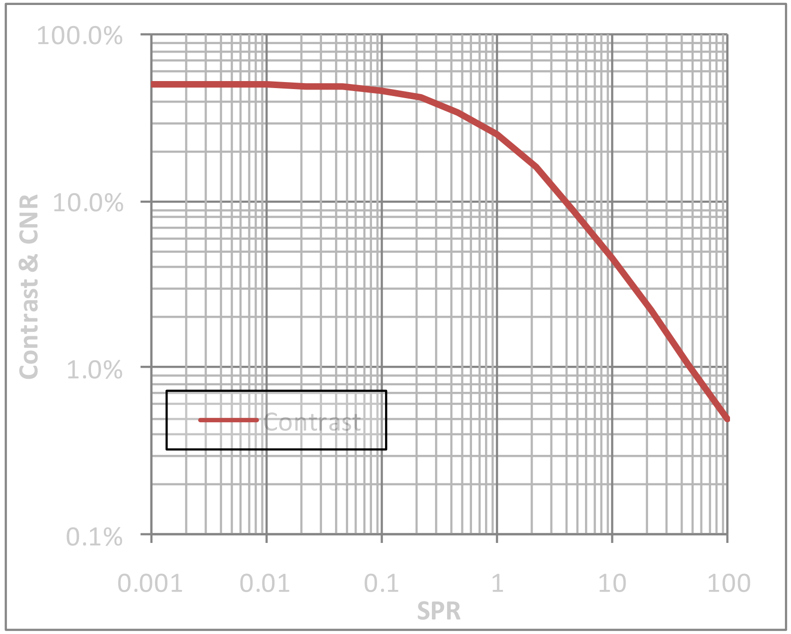


X-rays and Contrast



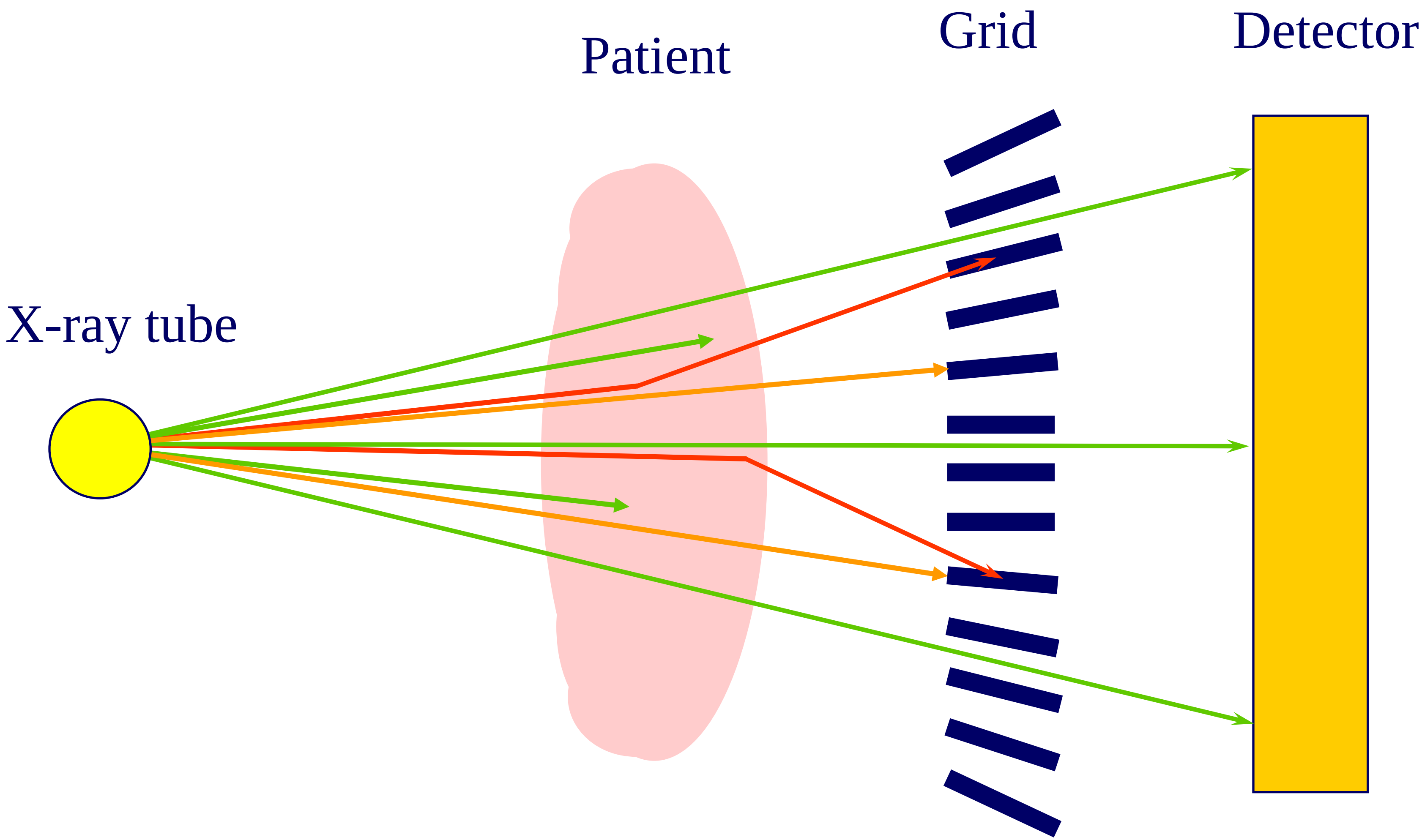
- Difference in attenuation coefficients generates contrast
- $\mu_1 < \mu_2$
- Scatter reduces contrast

Scatter in Medical Imaging



Examination	**Energy**	**Field Size (cm)**	**Antiscatter mechanism**	**$Scatter_{Total}$/ Primary**	**$Scatter_{Coherent}$ / $Scatter_{Total}$**
Chest	120 kVp	30 x 30	6.7 cm air gap	2.3	0.12
			20 cm air gap	1.2	0.11
Abdomen	80 kVp	17 x 17		2.7	0.26
			Grid	0.34	0.075
Mammography	30 kVp (Mo)	12 cm diam	Grid	0.6	0.24

Use of Grid to Remove Scatter



Effect of Antiscatter Grid

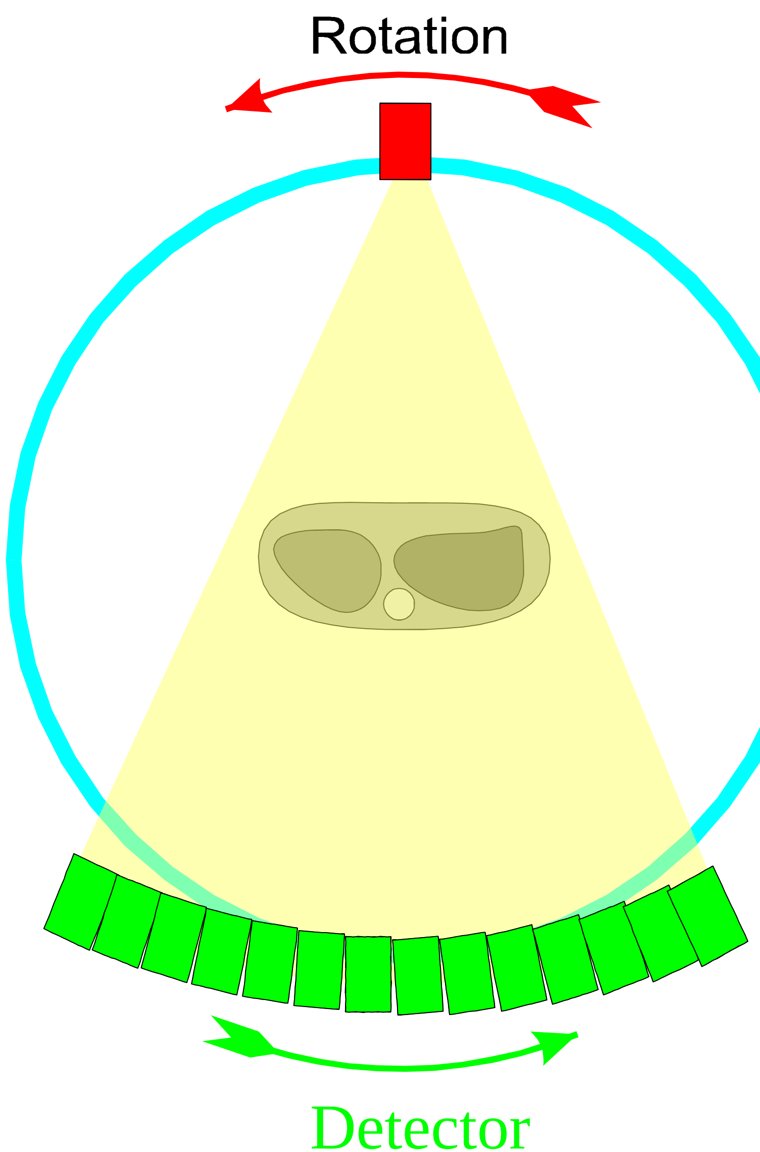
With Grid

Without Grid

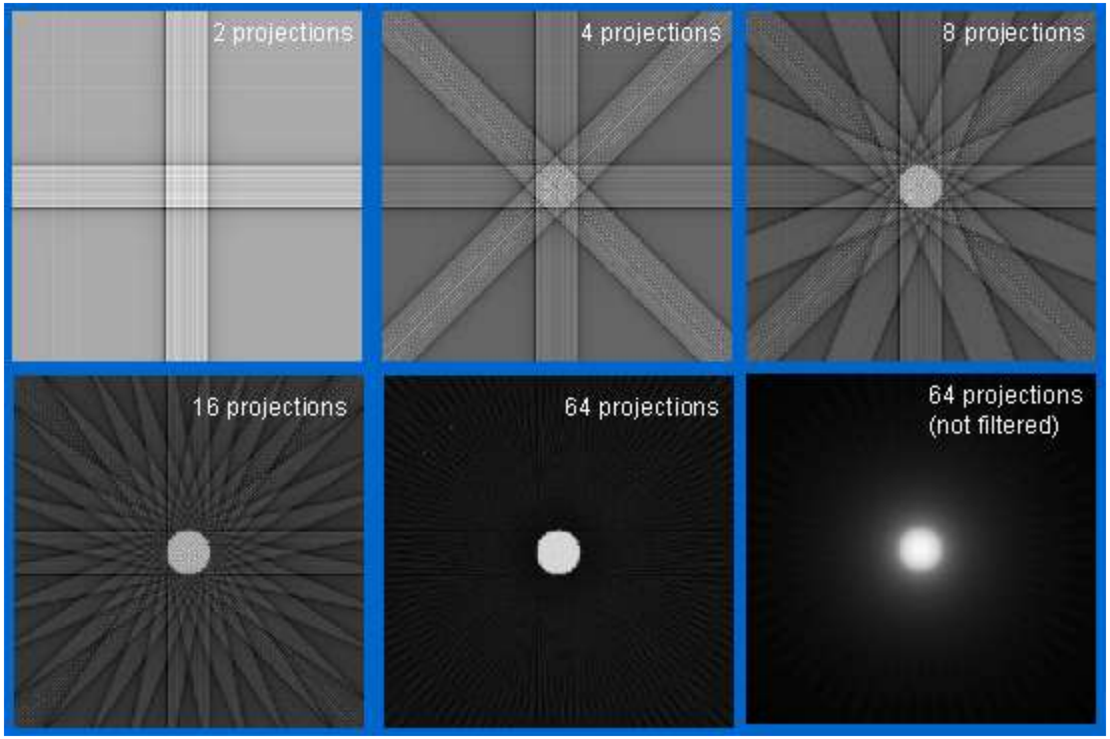
- 75 kVp
- Air Kerma incident on CR plate ~8 uGy in both cases.
- Left=3mAs; right=25mAs.
- Increase in dose = 8× but improvement in image is worth it

3rd Generation CT Scanner

- Multiple detectors
- Translation-rotation
- Large fan beam
- Patient stationary for each 2-D slice acquisition; about 1-2 seconds per slice
- kV = 120, mA = 500
- Image then reconstructed in about 1-2 seconds

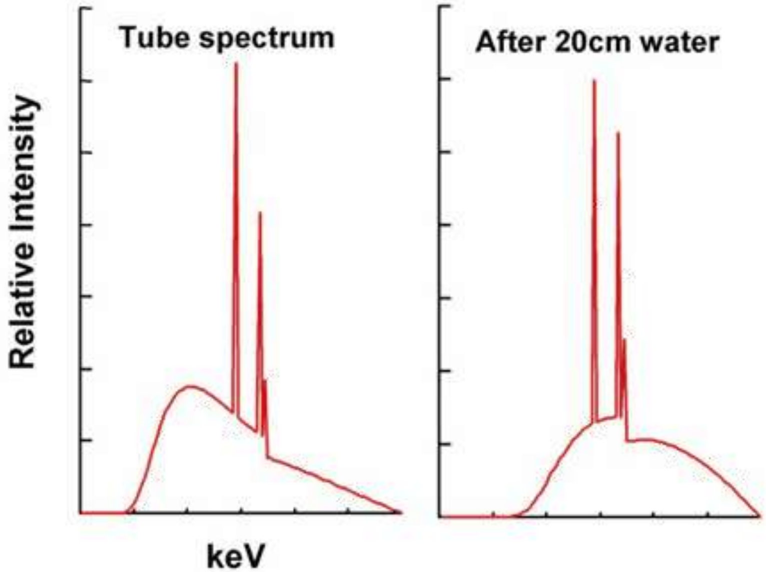


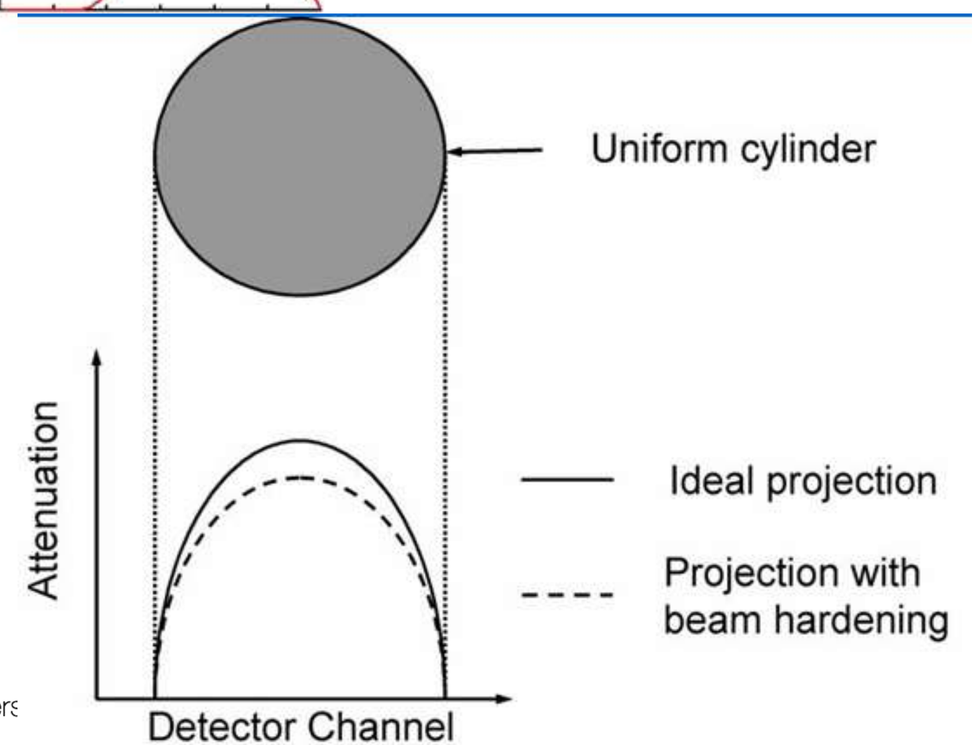
FBP in Practice



Volume CT image

Beam Harding Artefacts





Beam Harding Artefacts

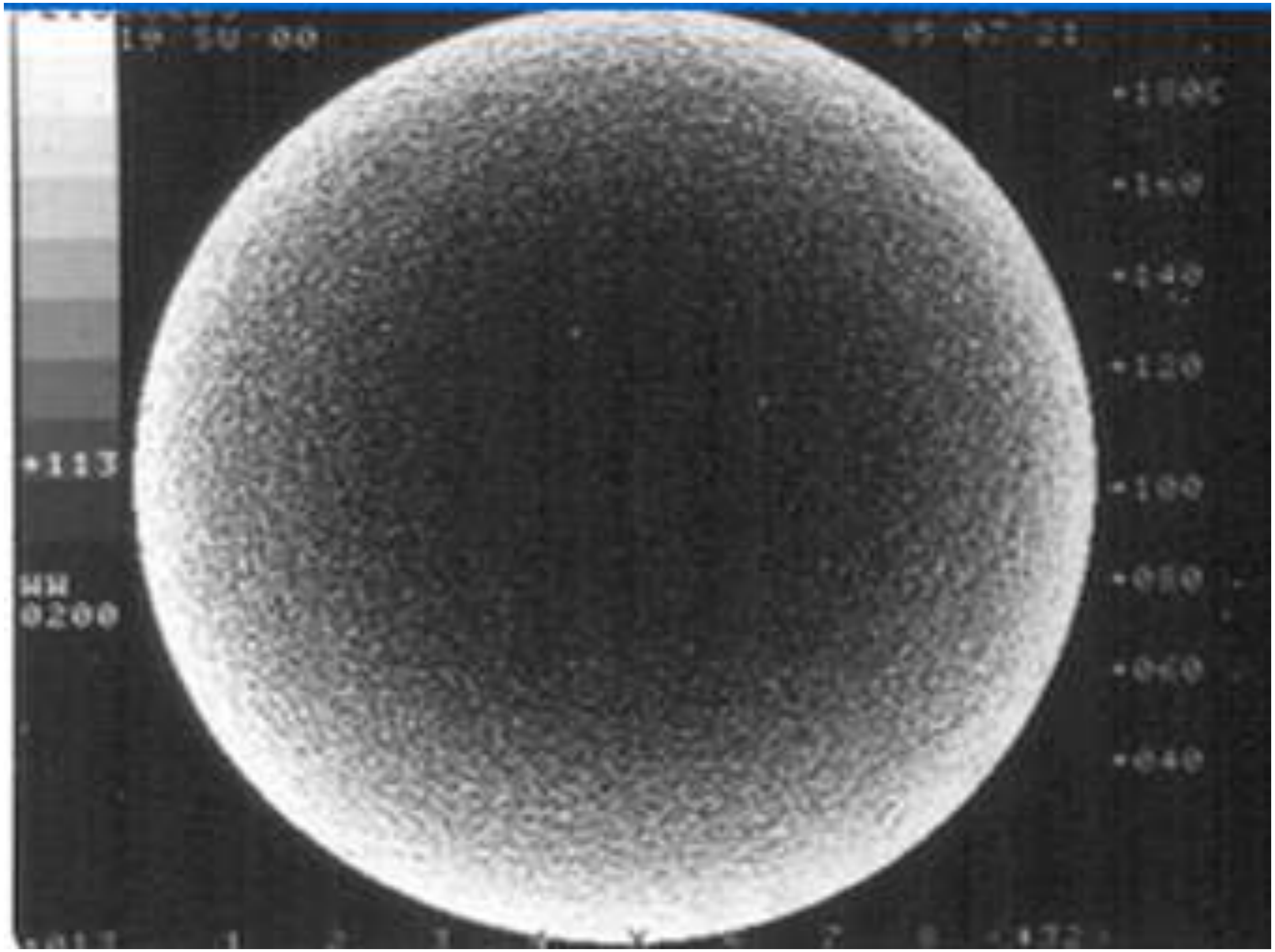
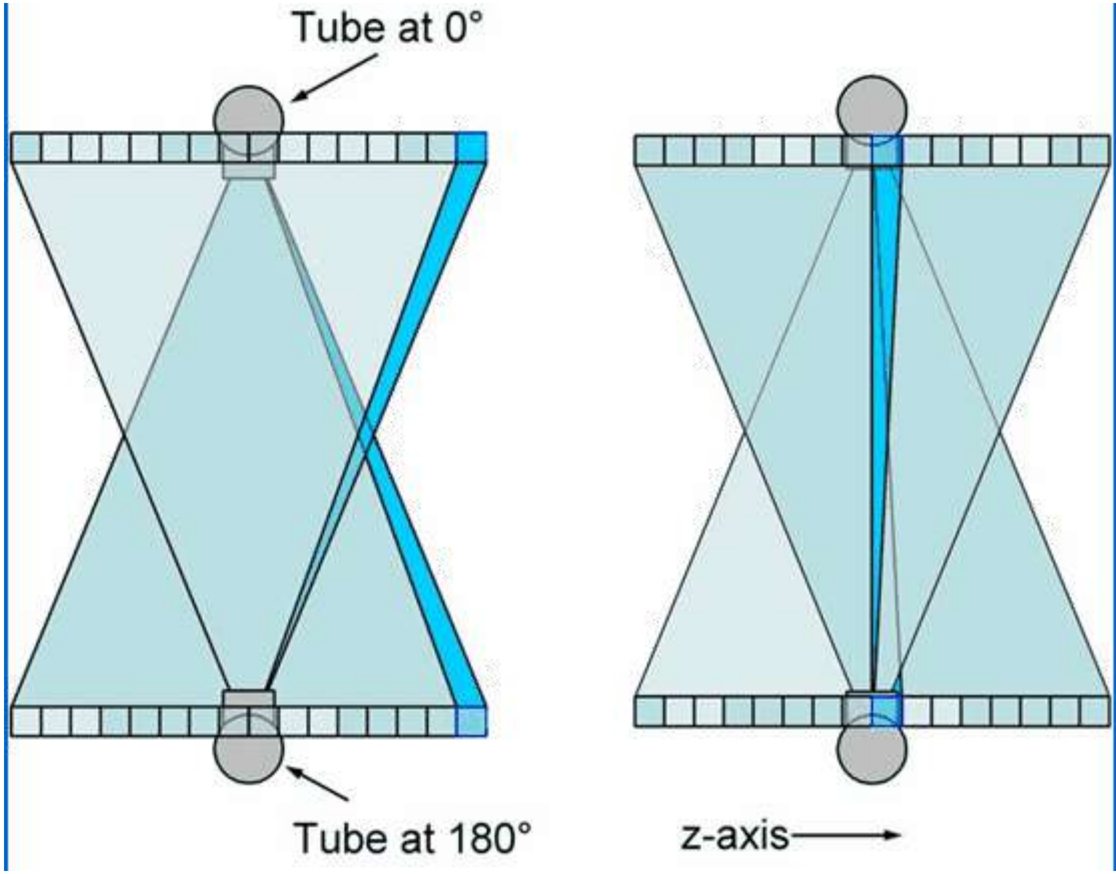
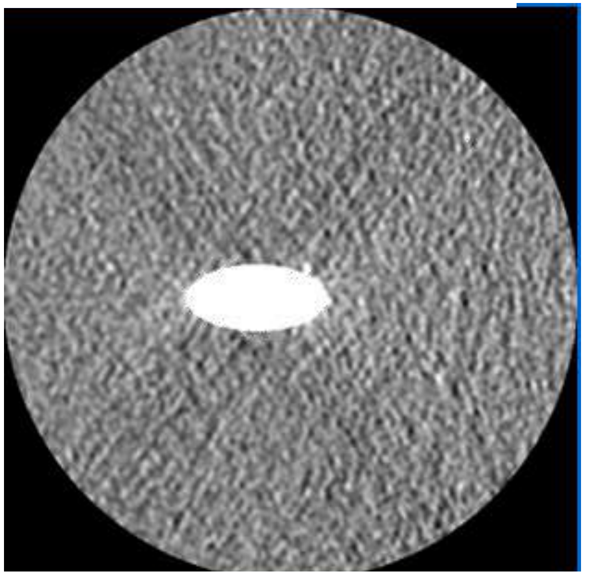


Image of uniform phantom

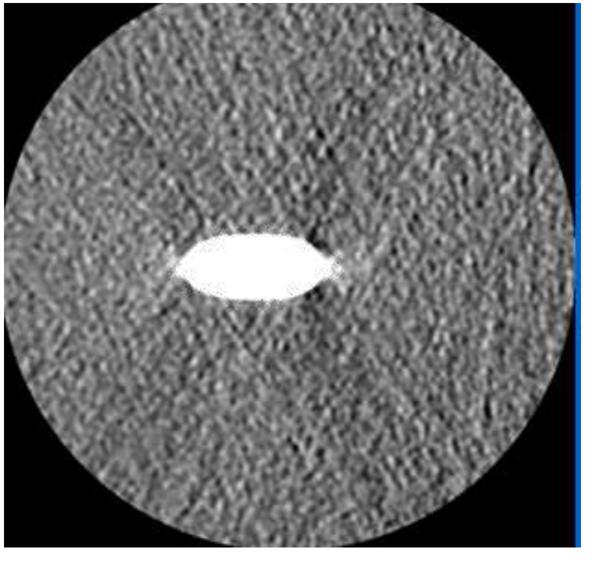
Cone Beam Artefacts



Inner detector row image



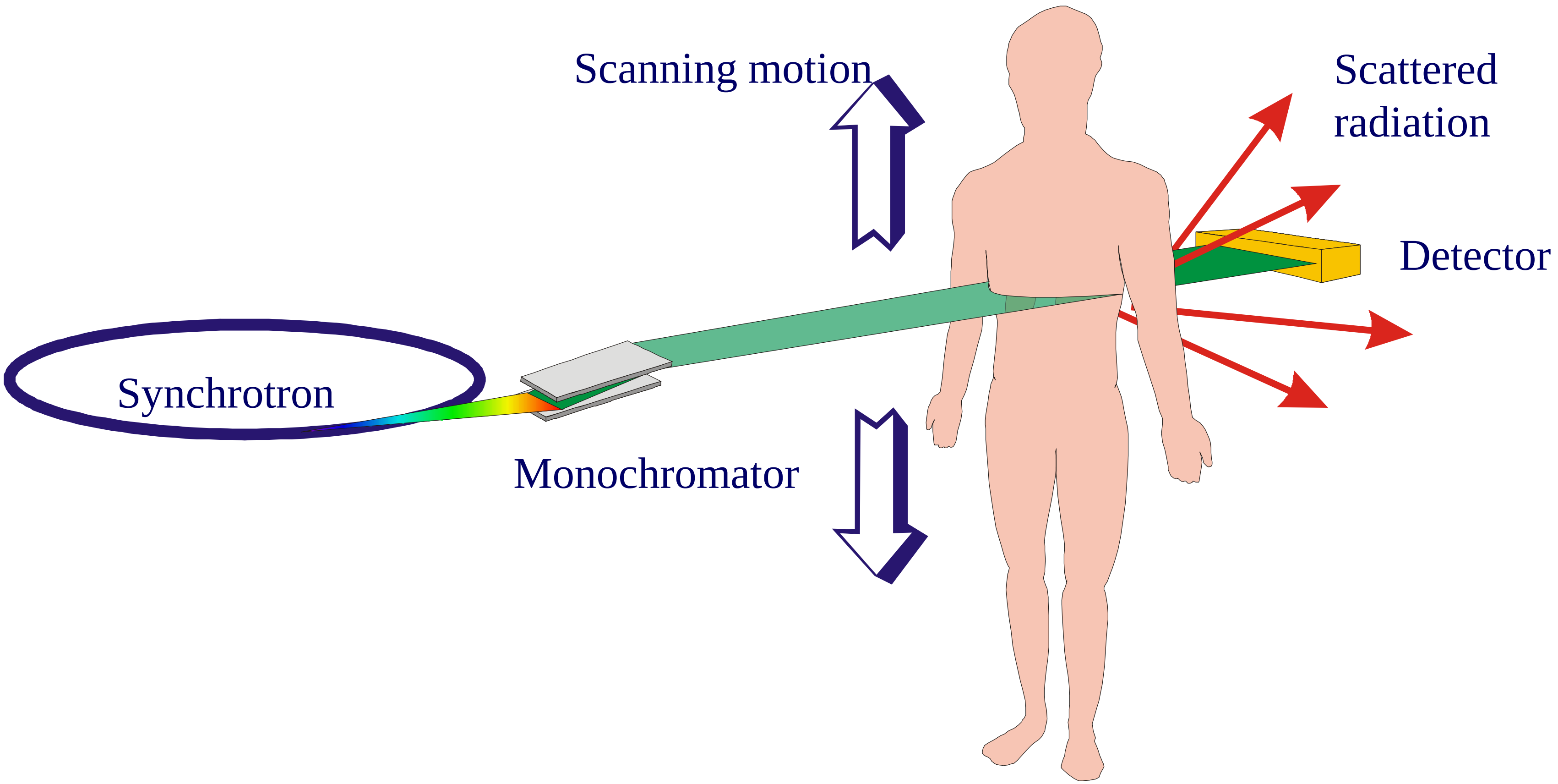
Outer detector row image



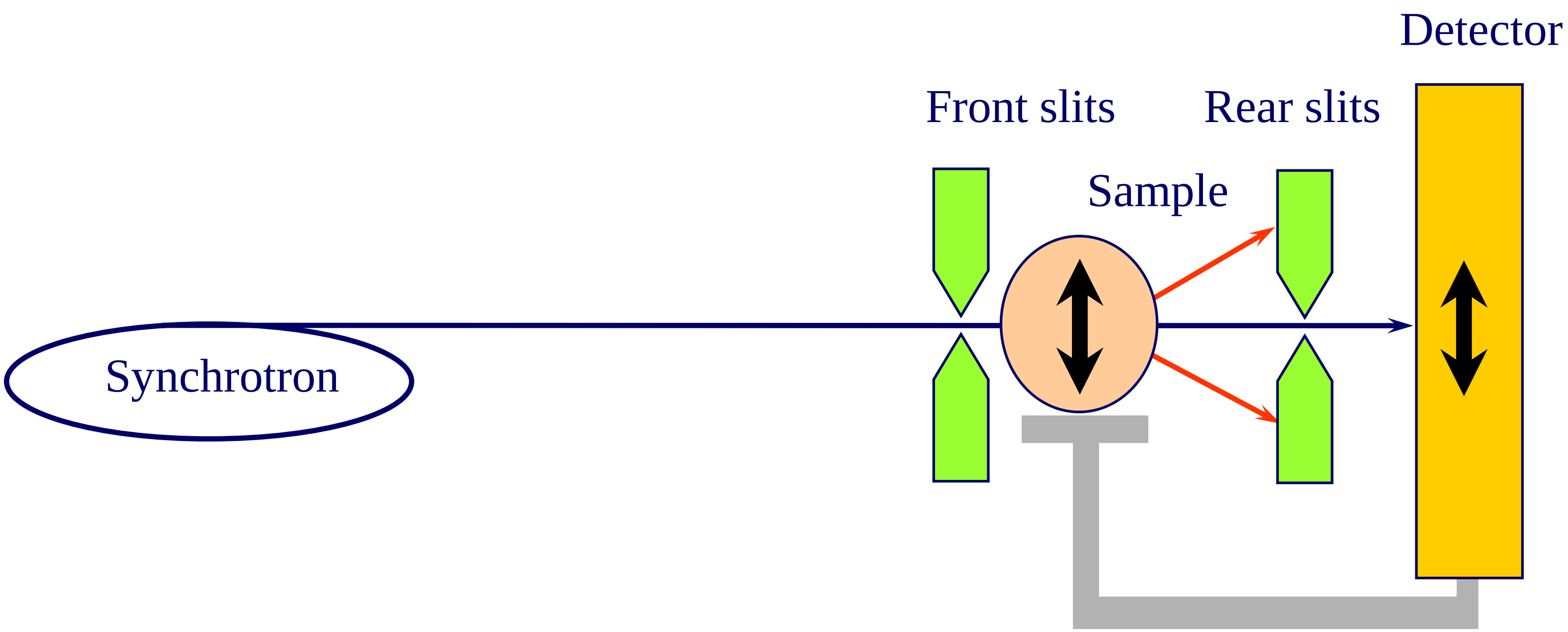
Exploit What Synchrotrons Are Good At

- Synchrotron is a great tool for performing medical physics studies
  - Synchrotron beams can be monochromated
    - No beam hardening
  - Synchrotron beams are almost parallel
    - No cone beam artefacts
    - Scatter removal with no dose penalty
- Allows studies of better x-ray imaging and developing new methodologies

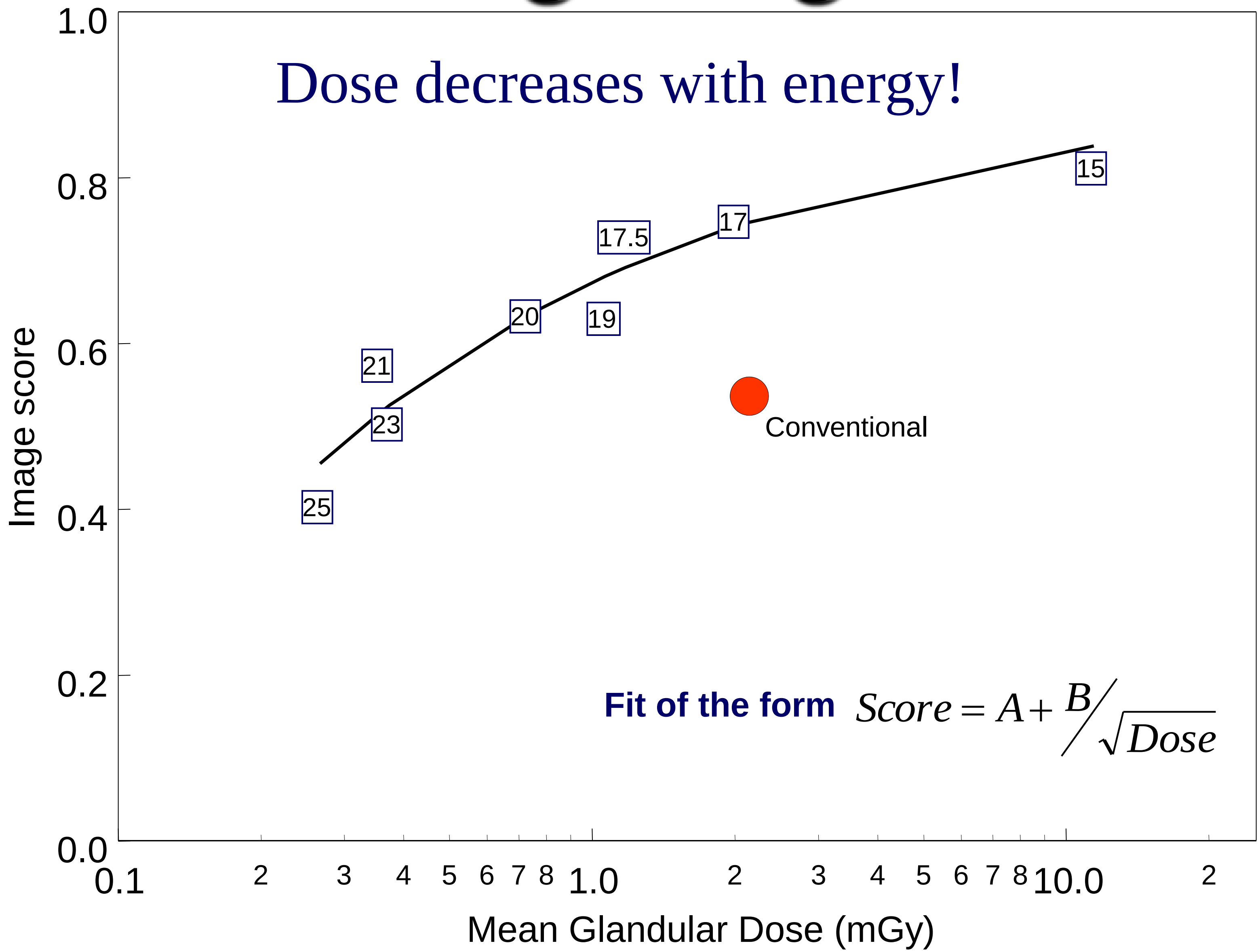
Synchrotron Radiography



SR Radiography



Slot Scanning Image Scores



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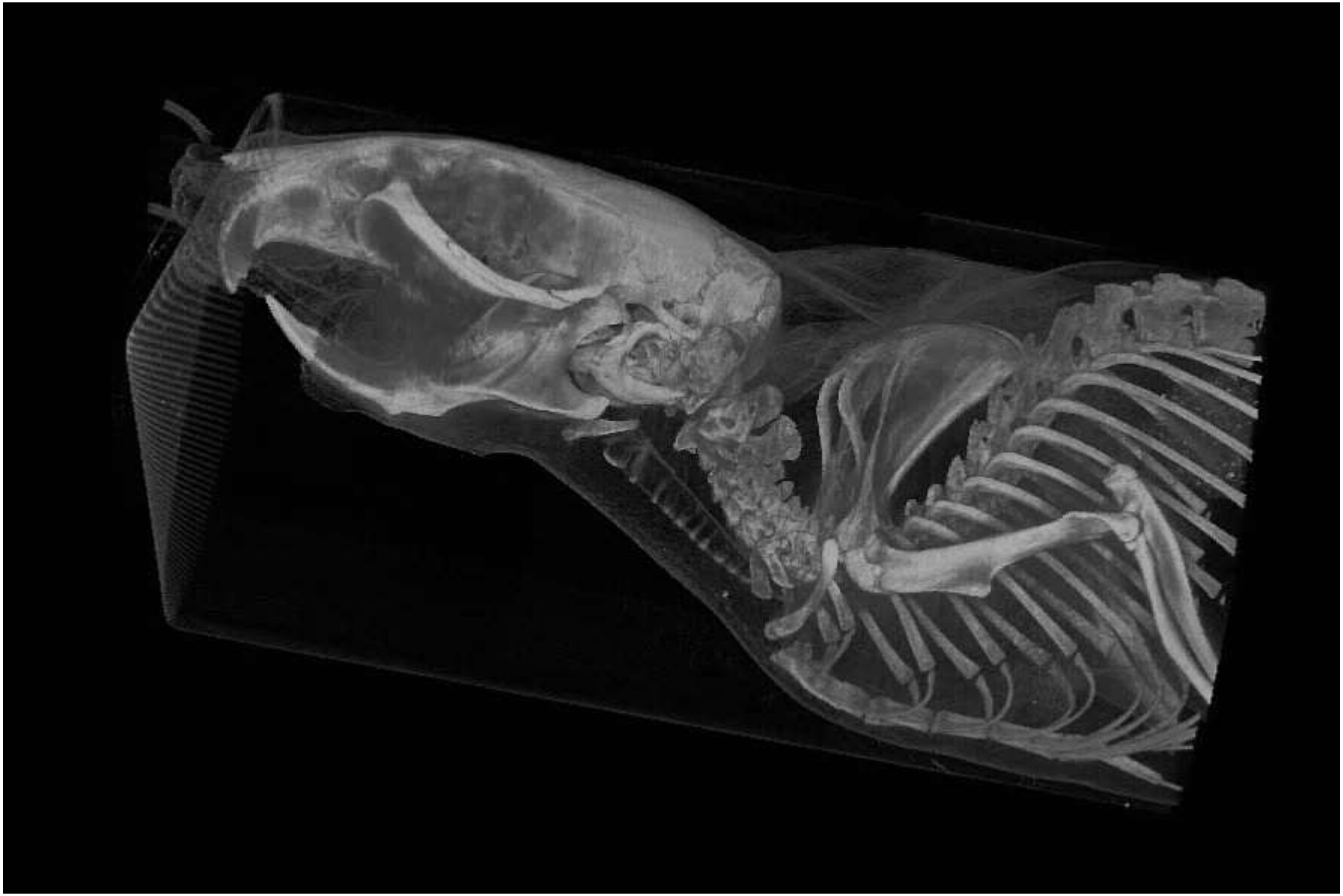
RA Lewis et al SPIE Vol. 4682 (2002) 286-297

Exploit What Synchrotrons Are Good At

- Synchrotrons allow fantastic spatial resolution

$$Dose_{skin} = \frac{2e^{\mu L} SNR_{out}^2}{DQE(f)\mu^2 size_{obj}^4 Contrast_{\mu}^2} E_{\gamma} (\frac{\mu}{\rho})$$

Mouse CT



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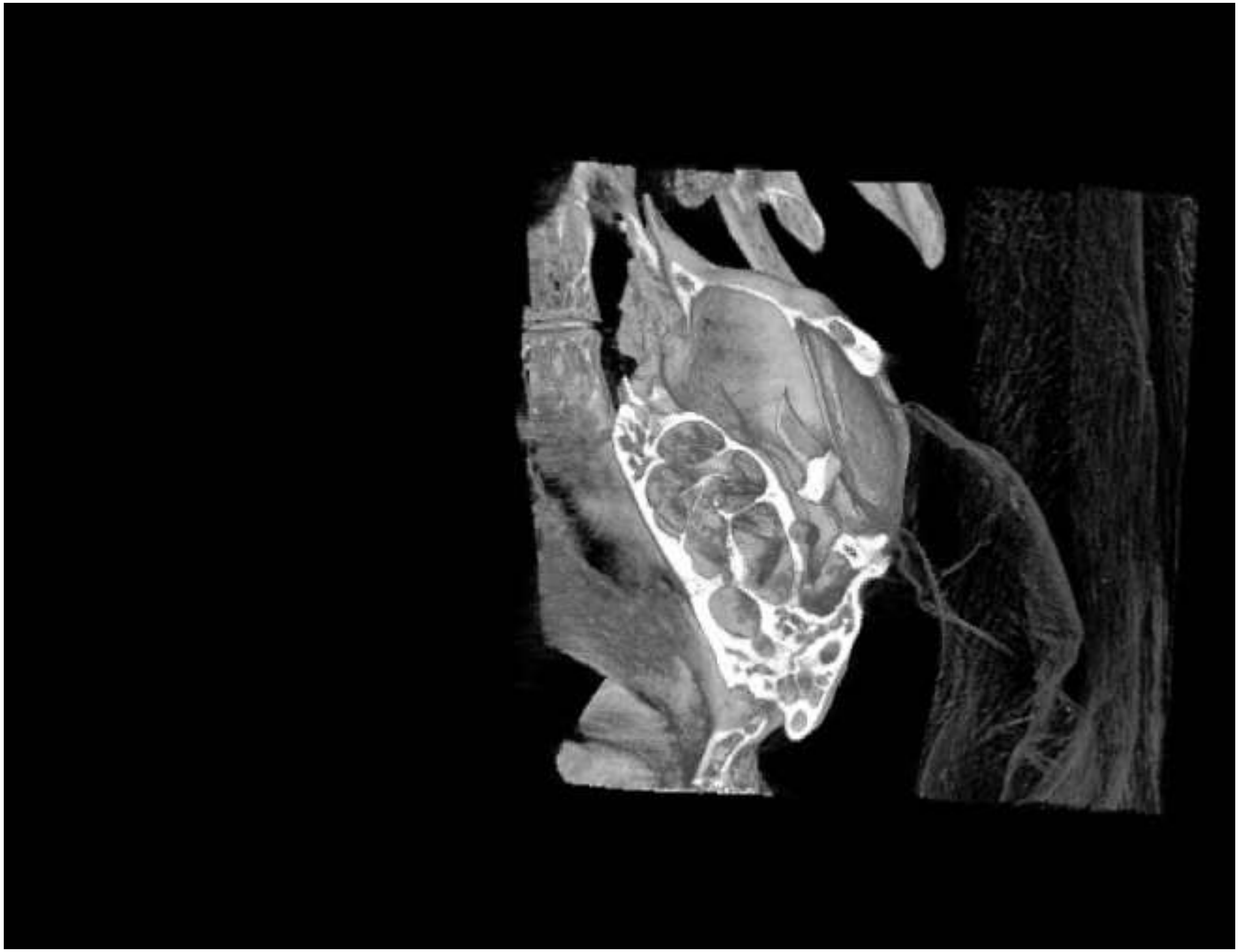
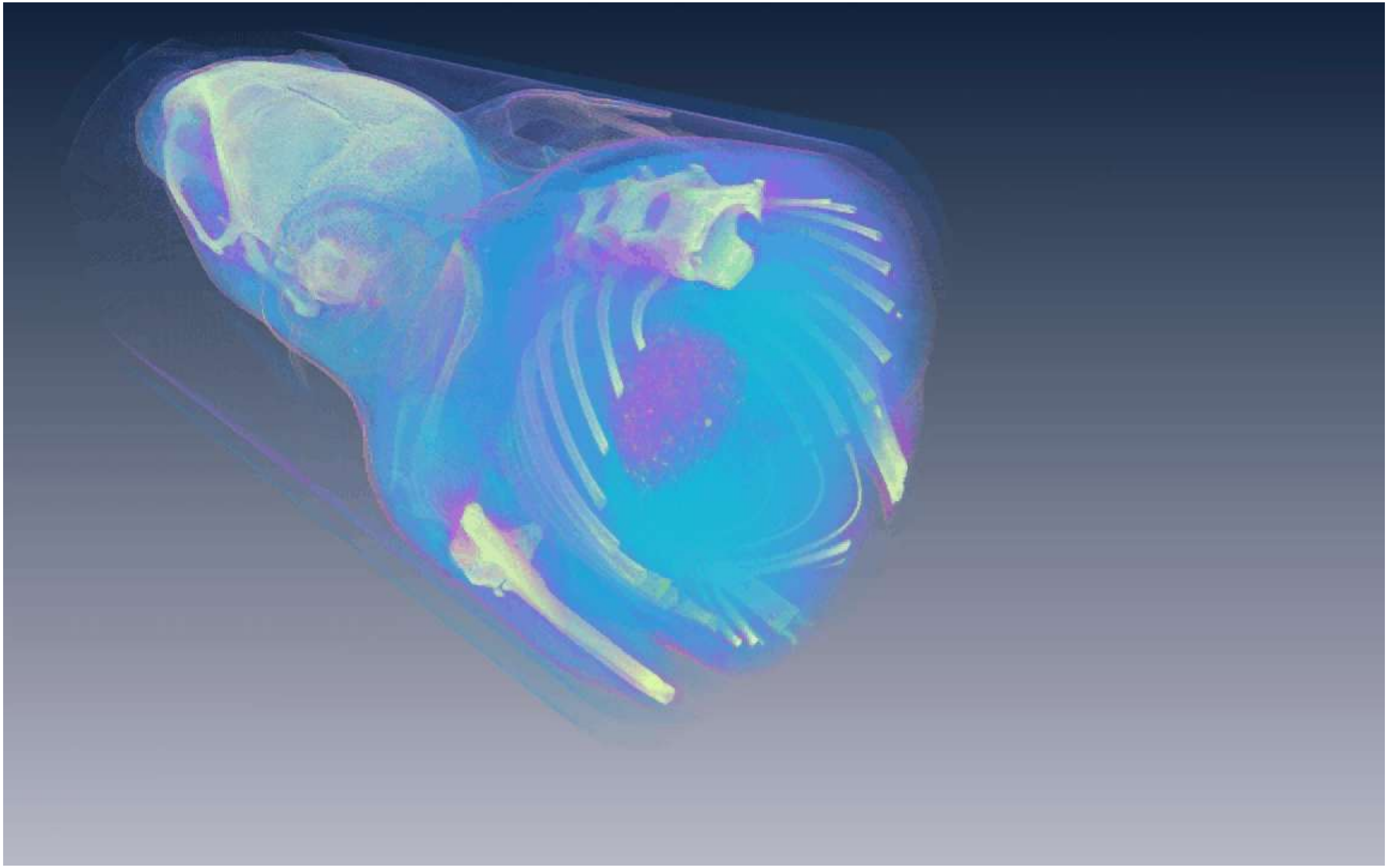
David Parsons and Karen Siu

Mouse Cochlea

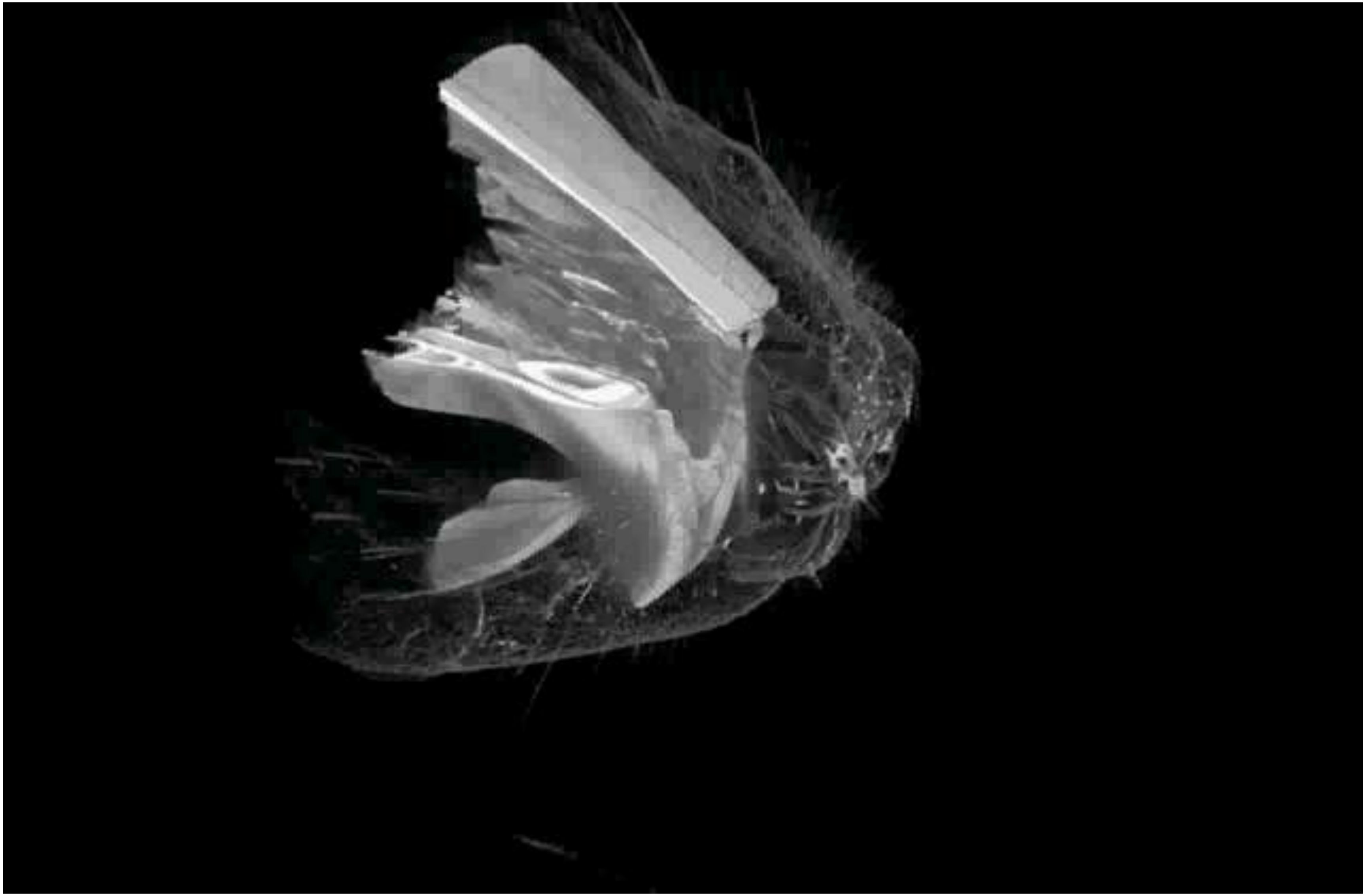


Mouse Fly Through

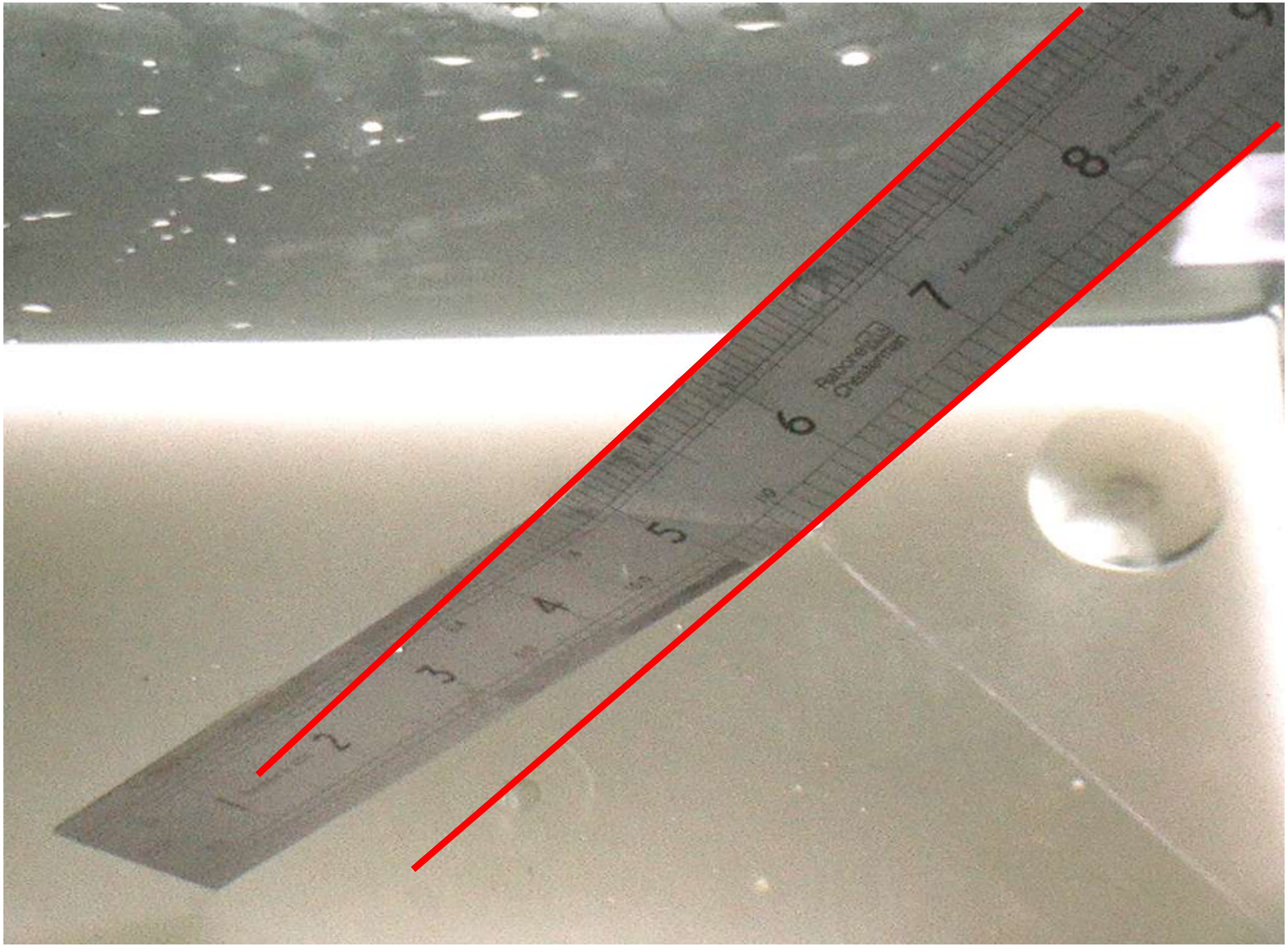


Kaye Morgan, Karen Siu, David Parsons

Mouse CT

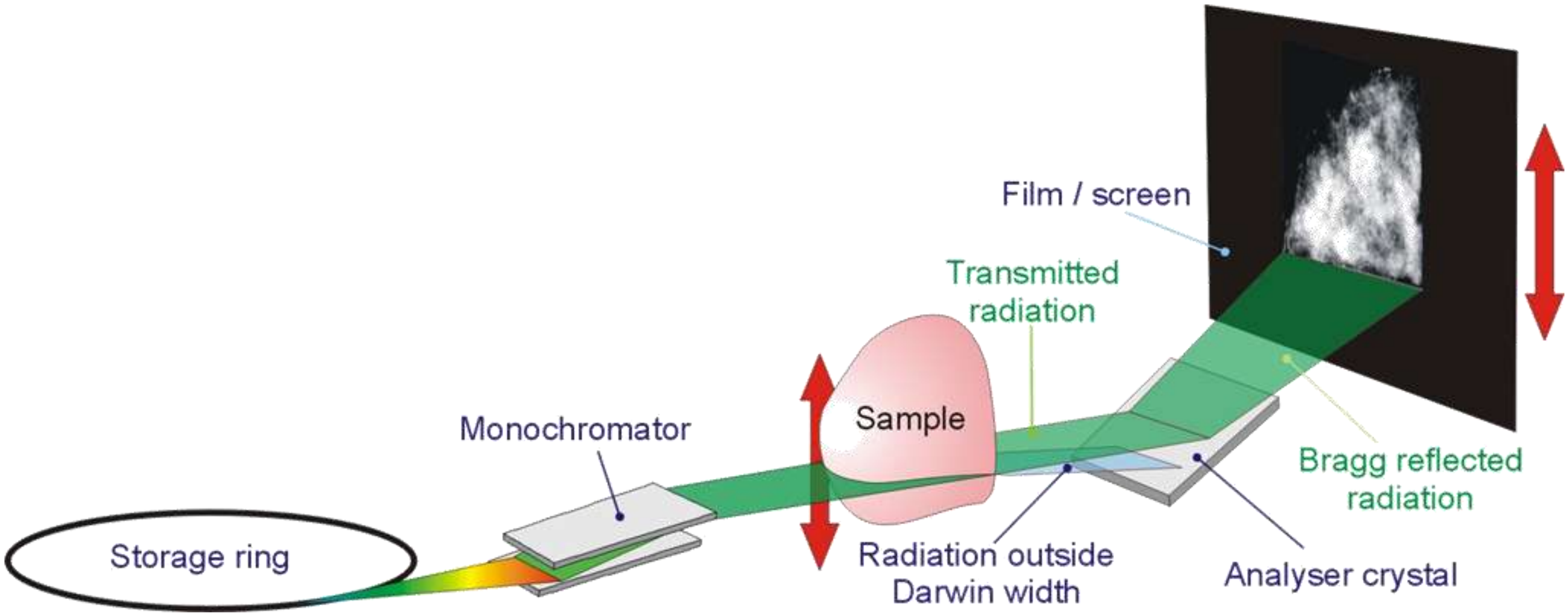


Refraction

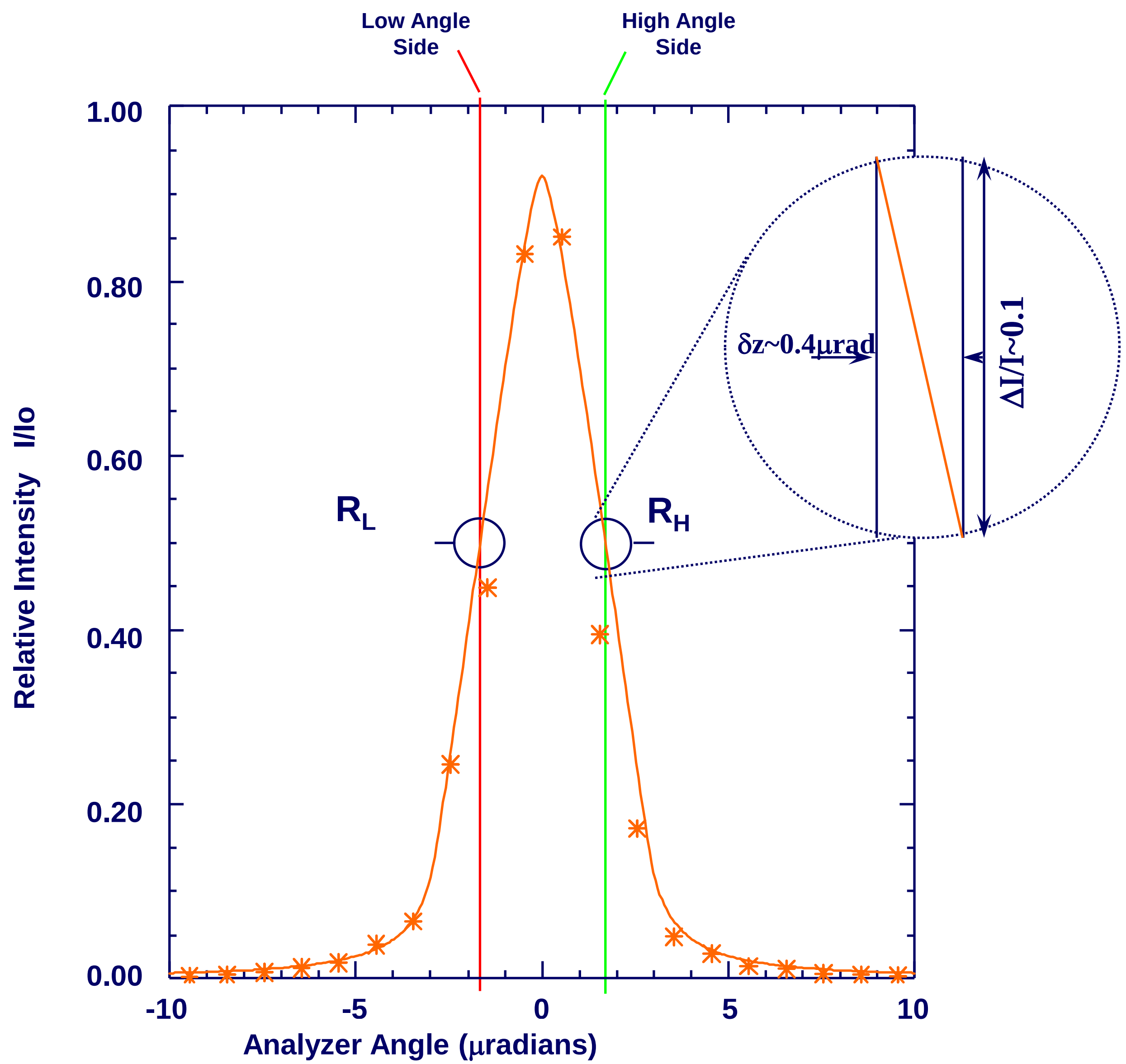


Analyser Based Imaging

Sometimes called Diffraction Enhanced Imaging



Crystal Rocking Curve



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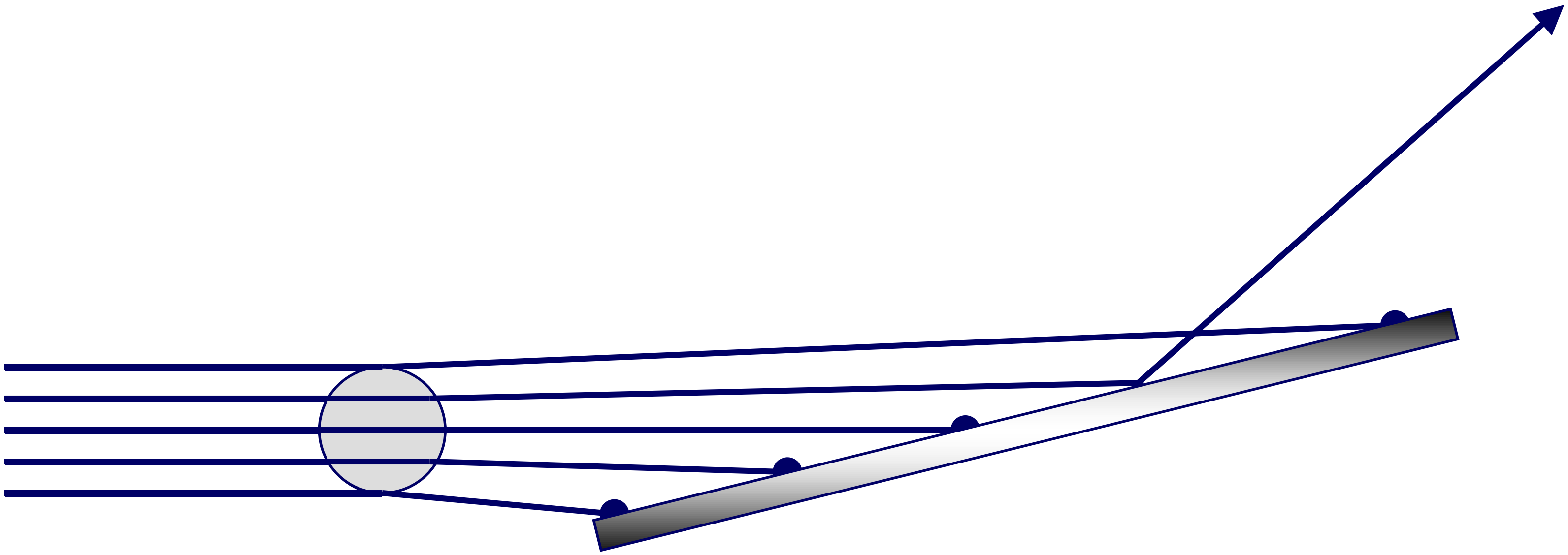
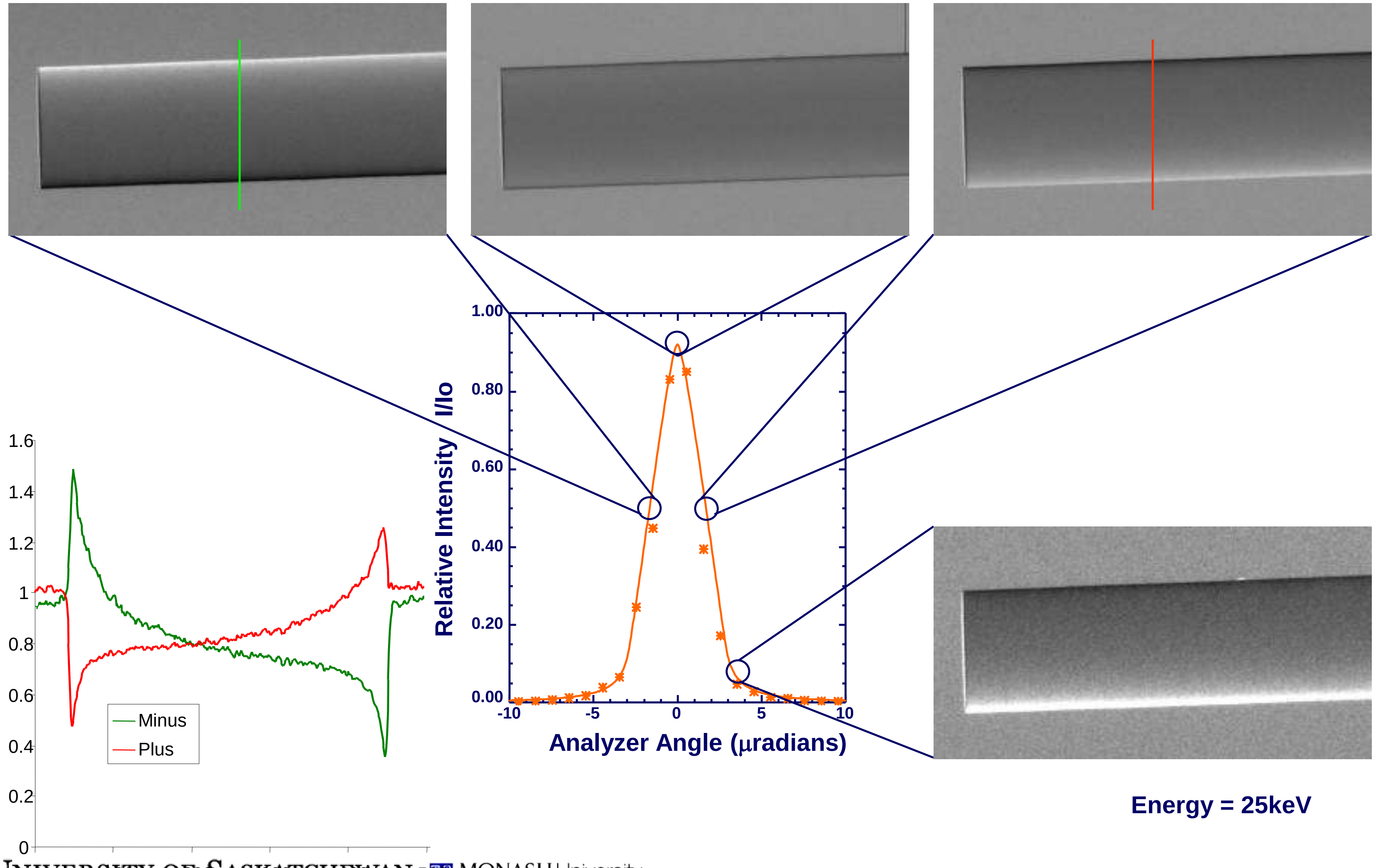
Rocking Curve



Refractive index for X-rays is less than 1 by about 1 part in a million

ABI How it works



ABI Mathematics

- I_L & I_H = Intensities on low and high angle sides of rocking curve
- $Grad_L$ & $Grad_H$ = Gradients of low and high angle sides of rocking curve
- I_R is intensity
- $\Delta\theta_z$= refraction angle

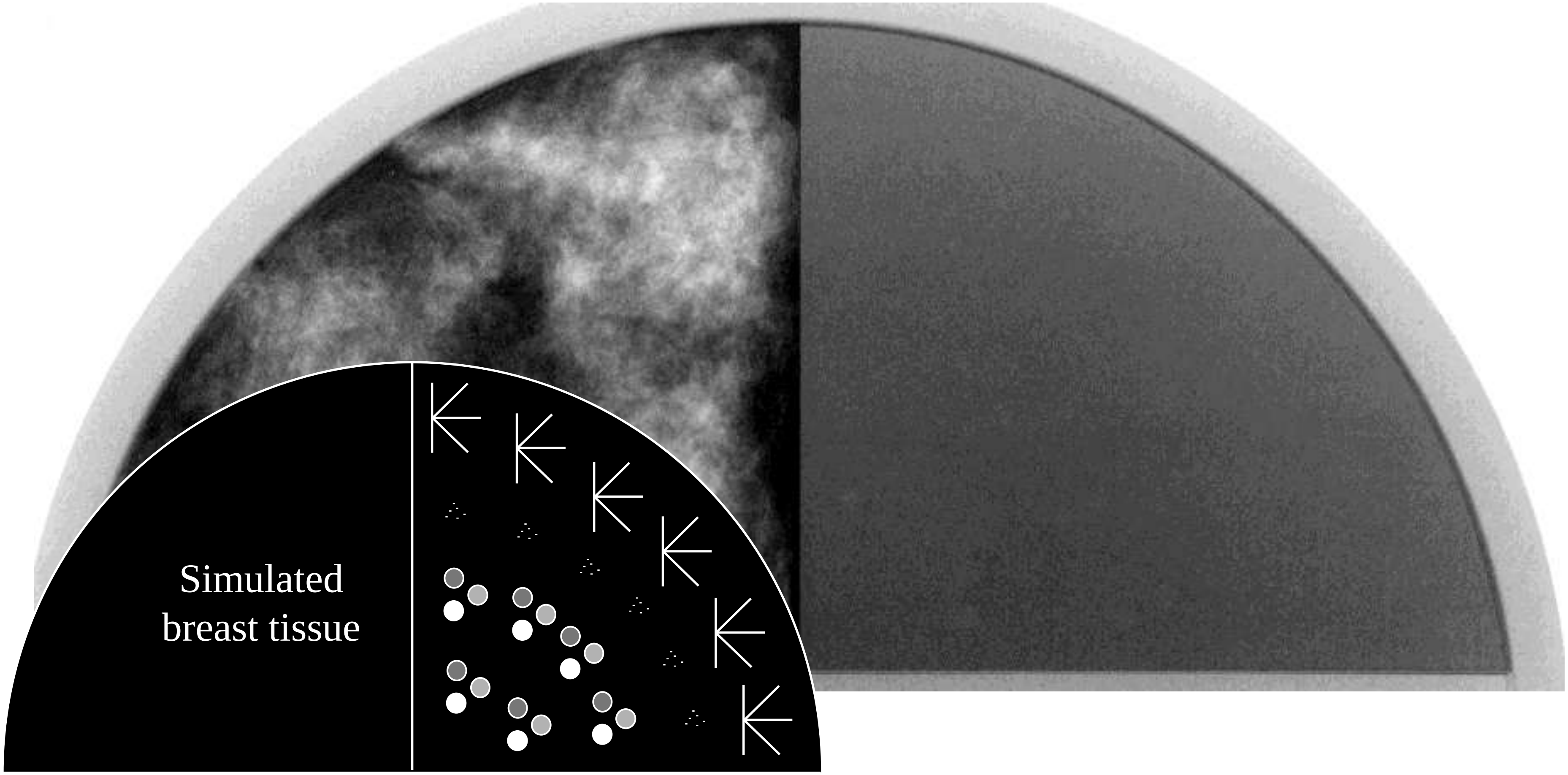
Given

$$I_L = I_R \cdot \left(R_L + Grad_L \cdot \Delta\theta_Z\right)$$

$$I_H = I_R \cdot \left(R_H + Grad_H \cdot \Delta\theta_Z\right)$$

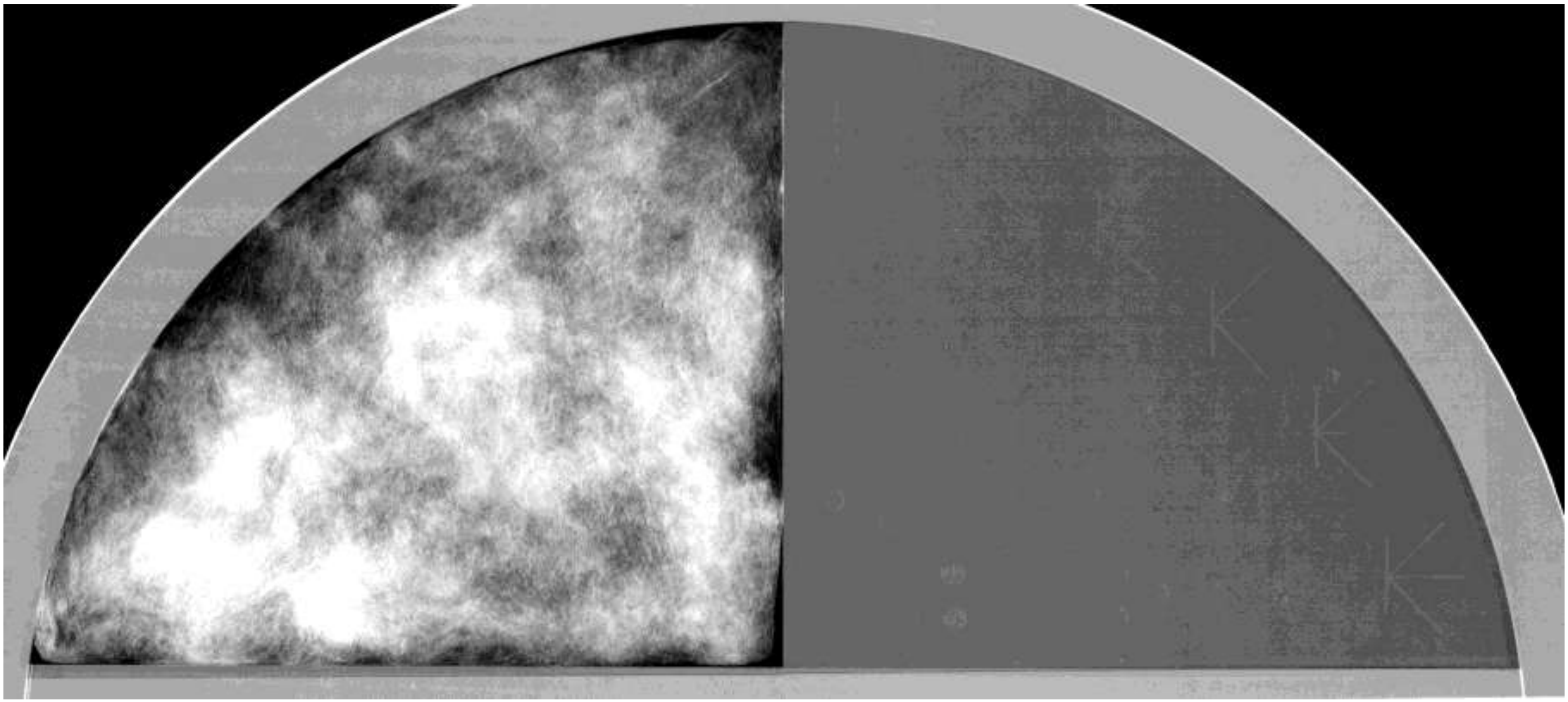
$$\mathrm{Find}\left(I_R, \Delta\theta_Z\right) \rightarrow \begin{pmatrix} \dfrac{Grad_H \cdot I_L - Grad_L \cdot I_H}{Grad_H \cdot R_L - Grad_L \cdot R_H} \\ \dfrac{I_H \cdot R_L - I_L \cdot R_H}{Grad_H \cdot I_L - Grad_L \cdot I_H} \end{pmatrix}$$

TORMam Conventional



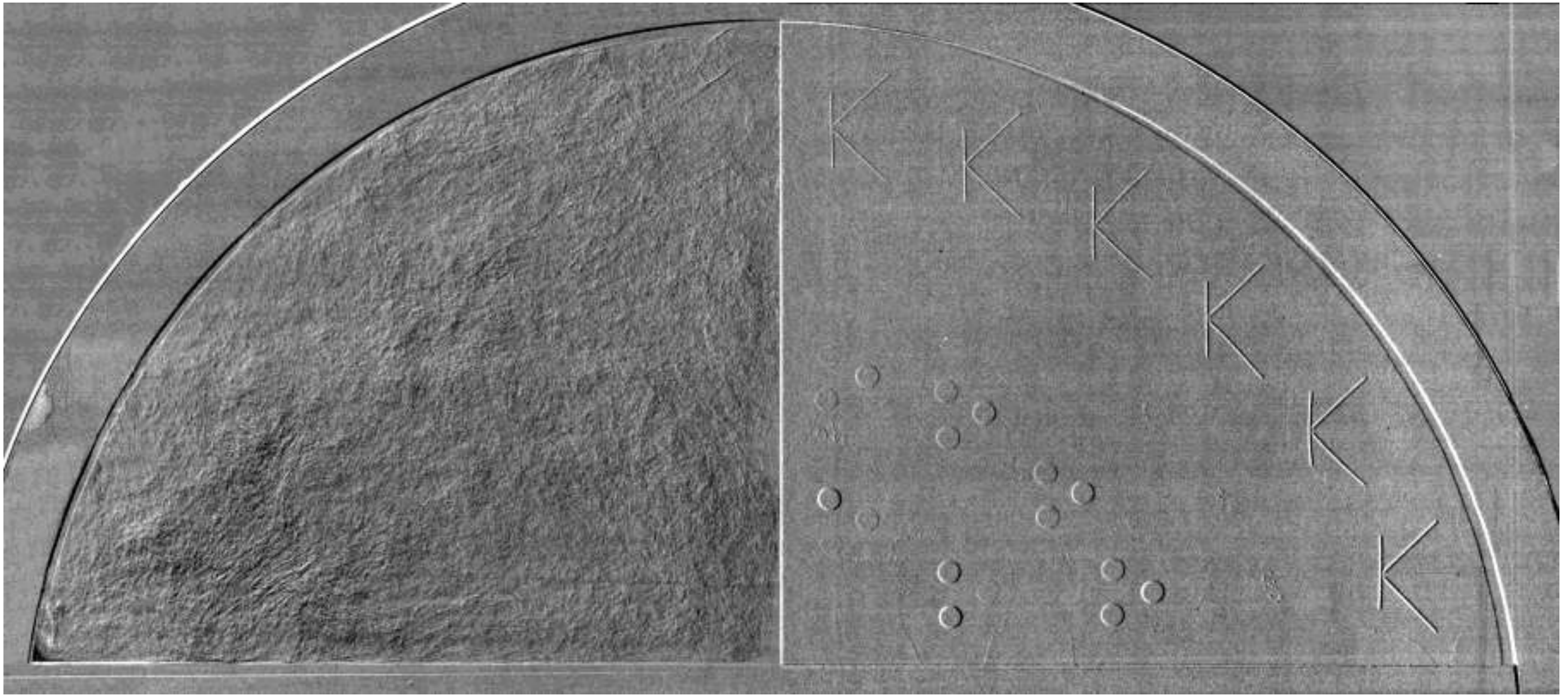
Spectrum = Mo:Mo 28kVp

TORMAM Peak



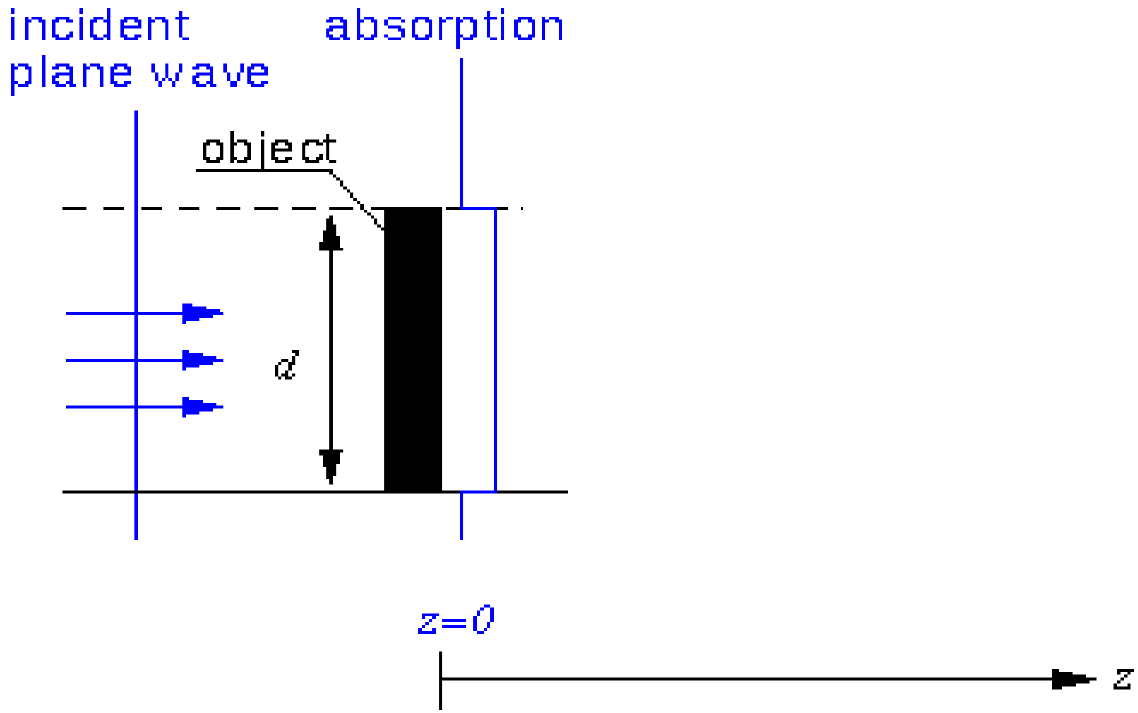
Energy = 20keV

TORMAM Refraction



Energy = 20keV

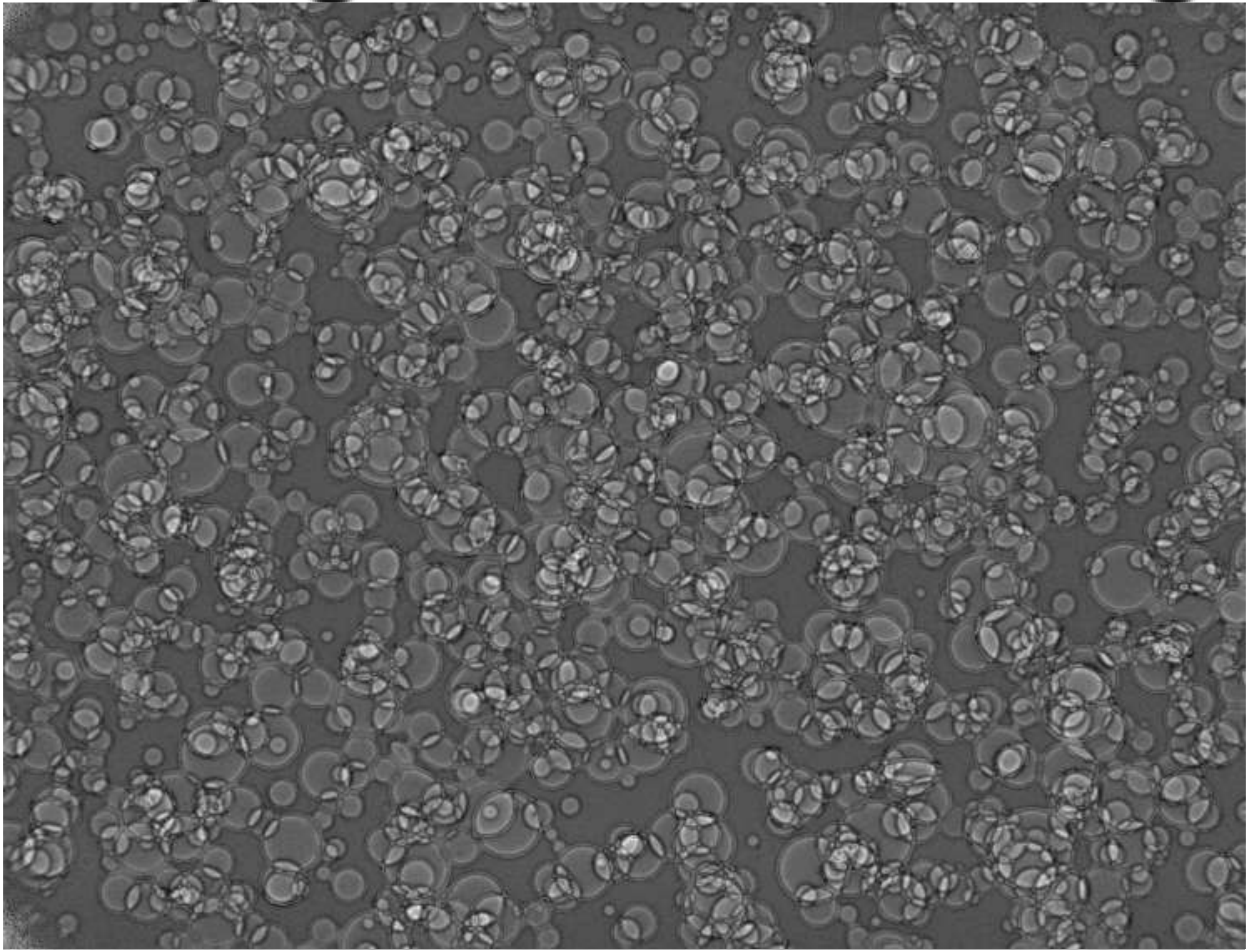
Phase Contrast



$$N_F = \frac{d^2}{\lambda z}$$

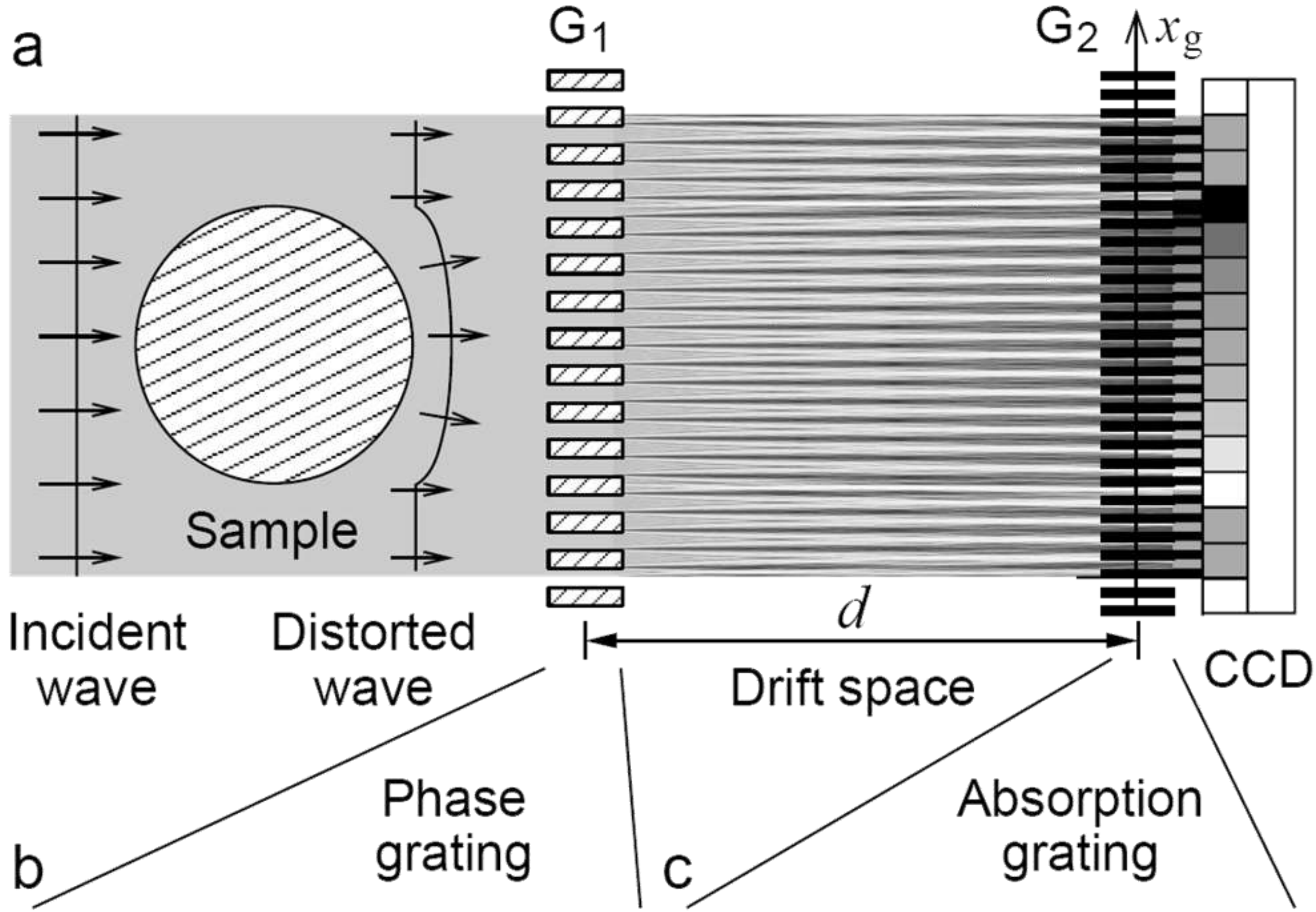
- **Contact:** **$N_F >> 1$** **Geometric approximation**
  - The intensity distribution is a pure absorption image.
- **Near field:** **$N_F >> 1$** **Geometric approximation**
  - Contrast is given by sharp changes in the refractive index, i. e. at interfaces.
- **Intermediate field:** **$N_F \sim 1$** **Fresnel approximation**
  - The image loses more and more resemblance with the object.
- **Far field:** **$N_F << 1$** **Far: Fraunhöfer approximation**
  - The image is the Fourier transform of the object transmission function

Propagation Based Imaging



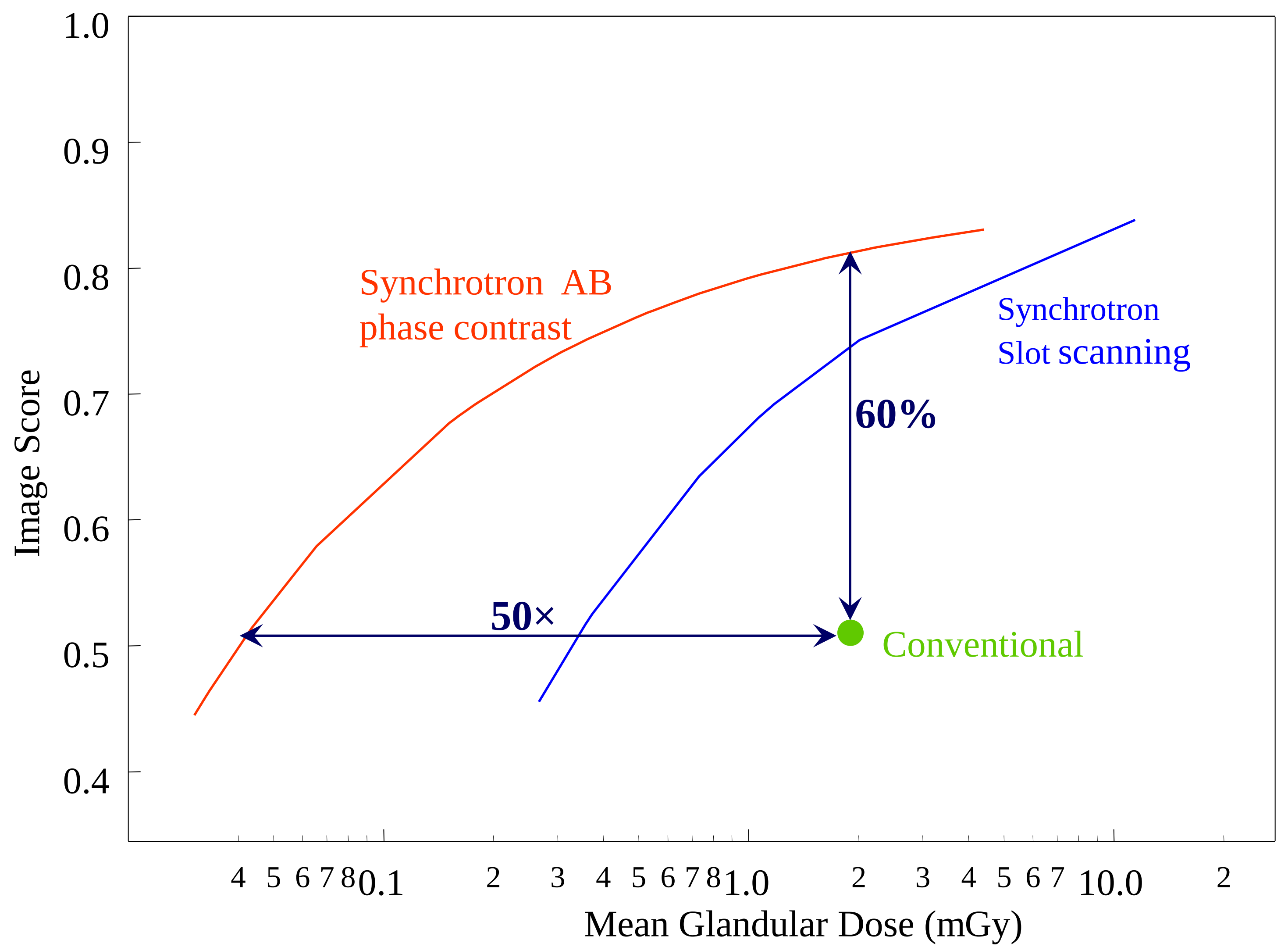
147cm

Grating Interferometry



Timm Weitkamp et al Vol. 12, No. 16 / OPTICS EXPRESS 6296

Phase Contrast Dose Advantage



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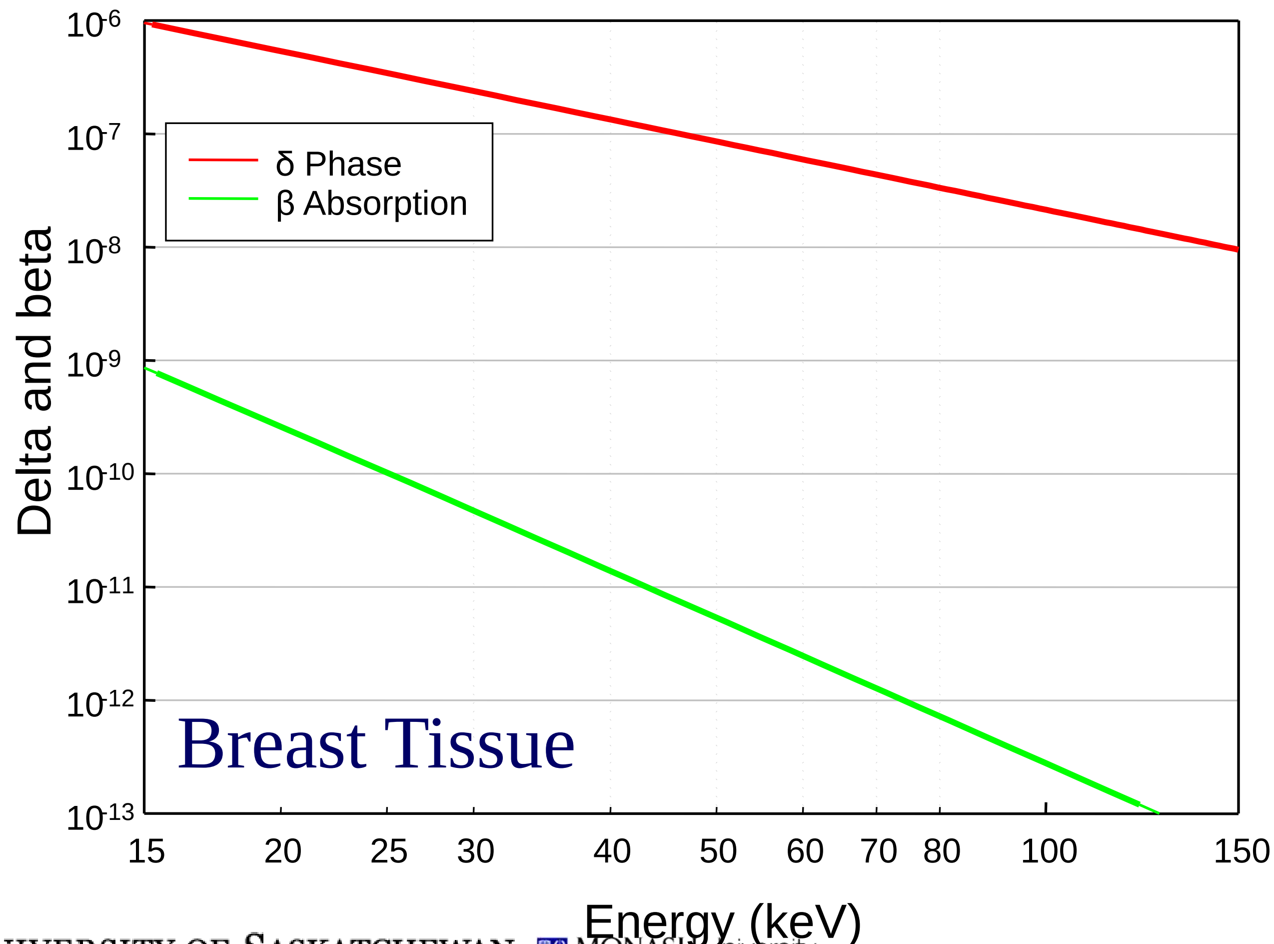
Complex Refractive Index

- Coherence properties enable phase contrast
- Contrast arising from phase effects does not require dose to be deposited in the object



Refractive index
$\eta = 1- \delta - i\beta$

Where β = absorption
δ = phase shift

Nb.
$\delta \sim 1000\ \beta$
$\delta \sim E^{-2}$
$\beta \sim E^{-4}$

CT and Radiography Problems

- X-ray Dose
  - Phase Contrast Helps. Synchrotron easy. Gratings?
- Scatter
  - Greatly reduced by slot scanning. Both conventional and synchrotron can use this.
- Beam Hardening
  - Eliminated by monochromatic radiation. Synchrotron only
- Cone Beam Artefacts
  - Eliminated by parallel beam. Synchrotron only.

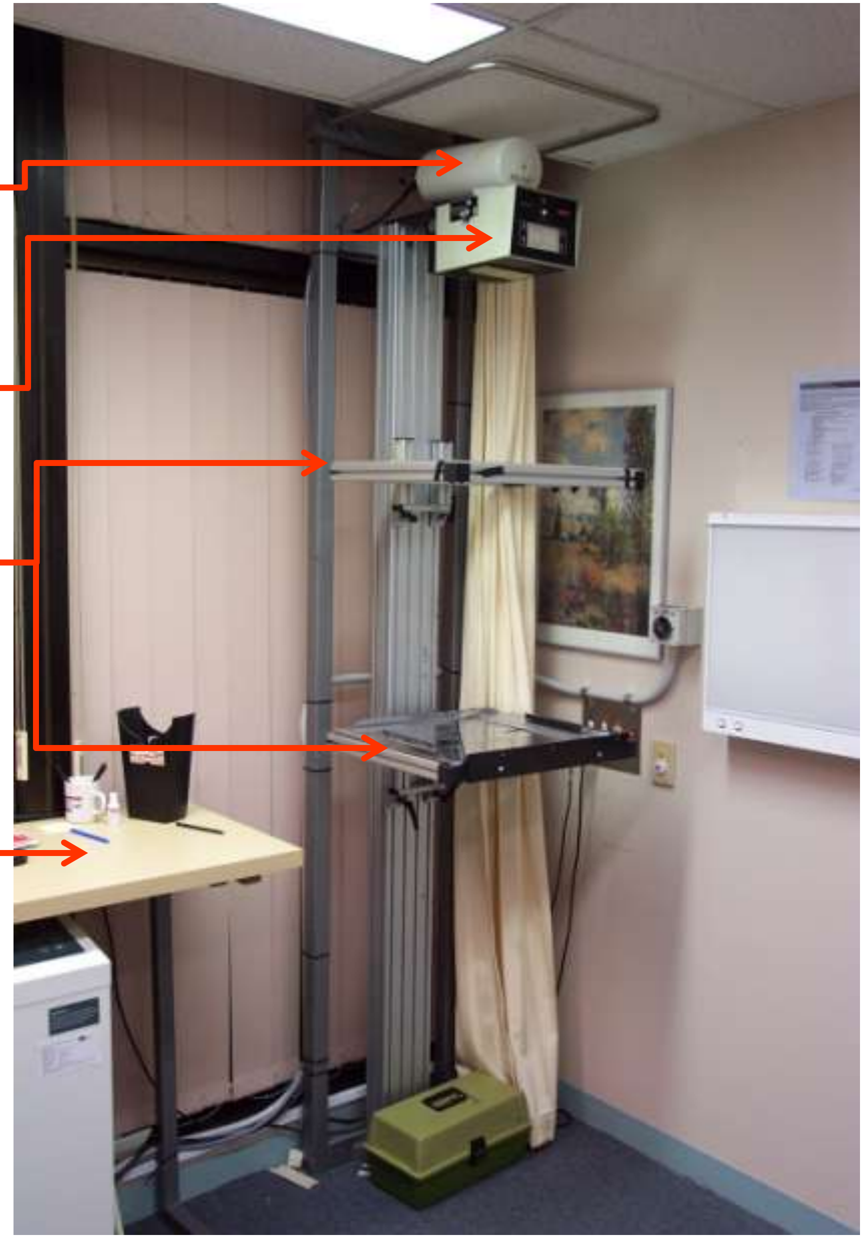
Phase Contrast at Monash Medical Centre

X-ray tube

Collimator

Moveable Trays

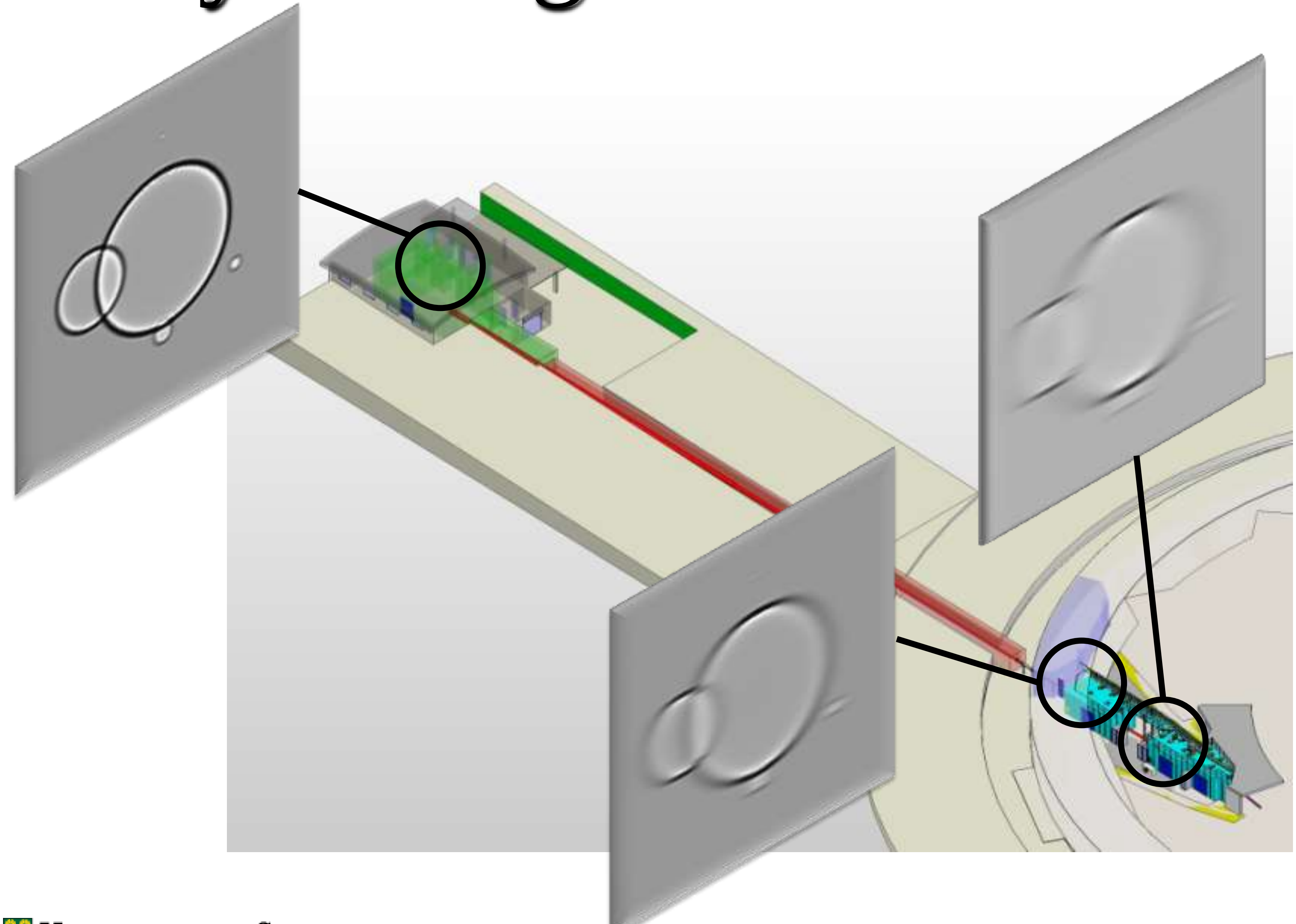
Control Desk



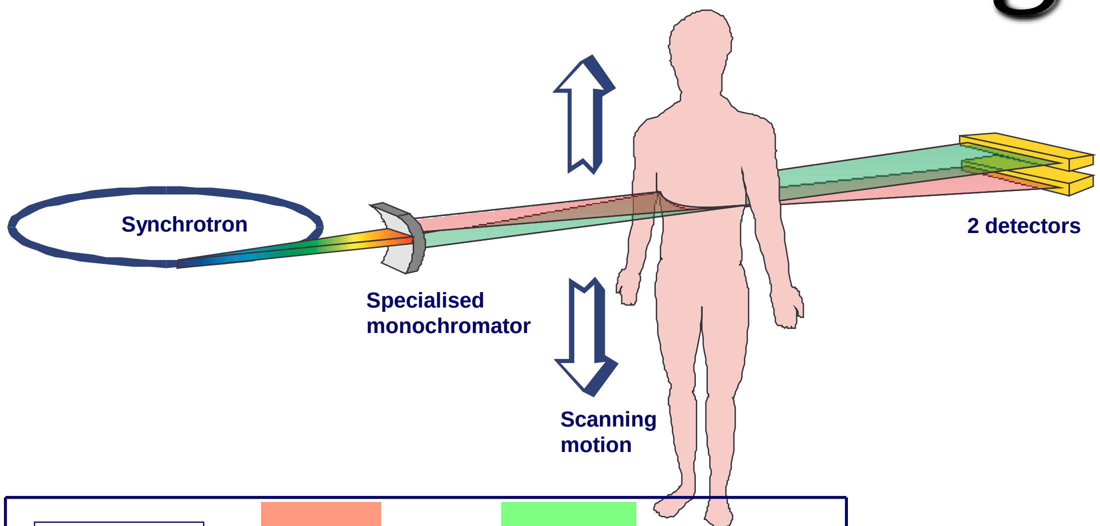
Ivan Williams et al European Journal of Radiology 68S (2008) S73–S77

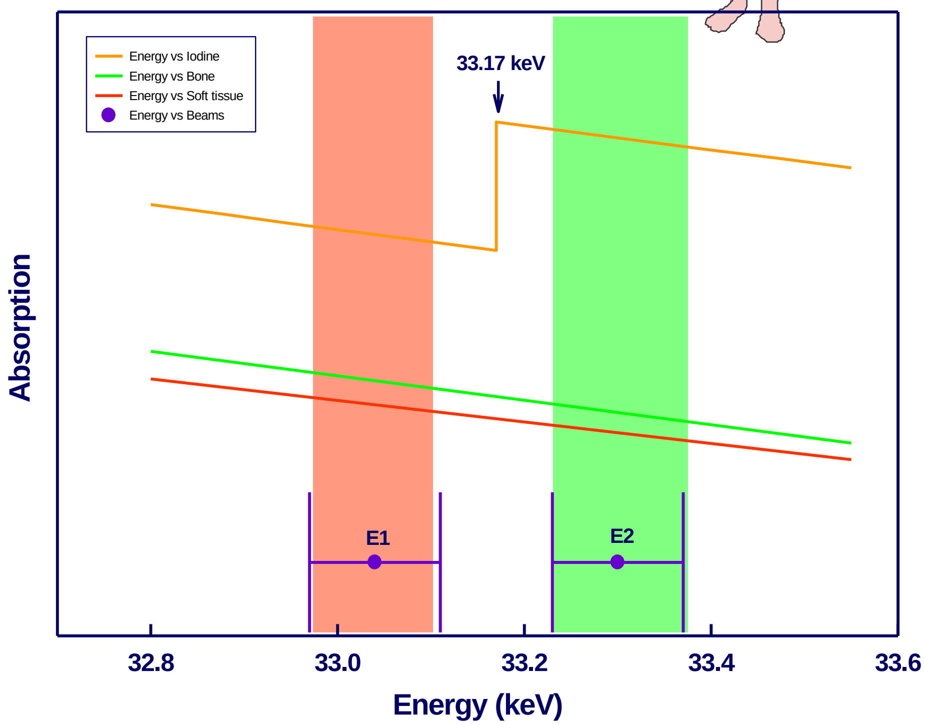
Imaging and Therapy Facility

Why a Long Beamline?

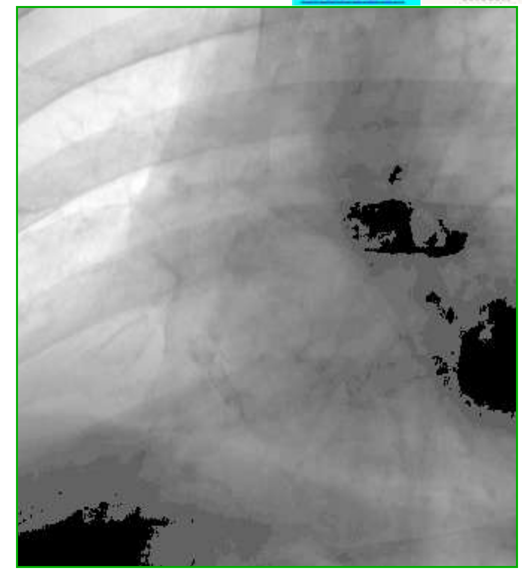


Subtraction Radiography

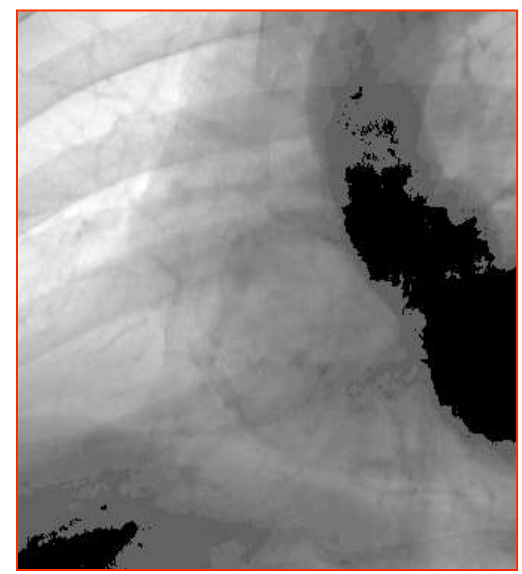




High



Low



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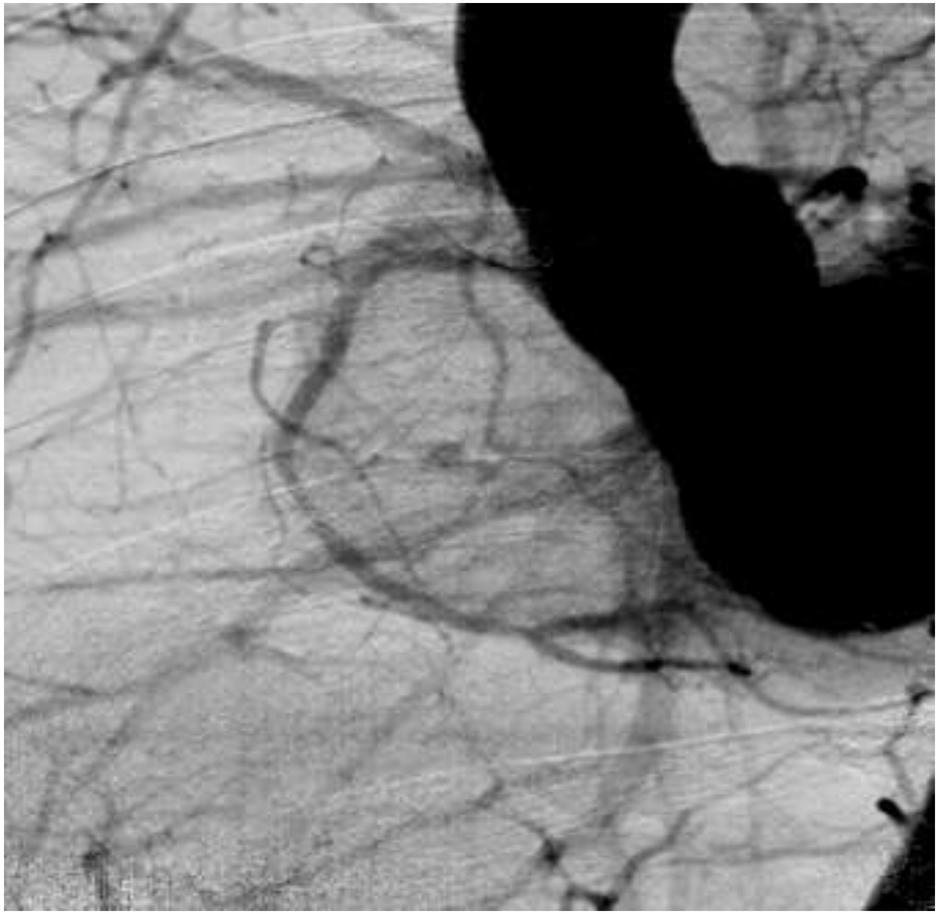
W. Thomlinson et al ESRF

Patient 1 - weight: 70 kg - iodine: 42ml



Synchrotron IV injection
n.b. 2 – LAO 40

Conventional angiography
Intra arterial injection

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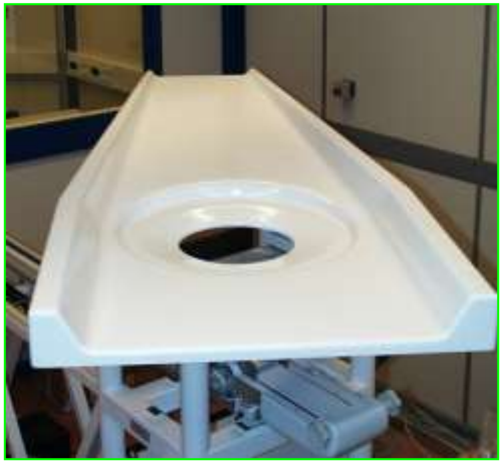
Synchrotron Clinical Studies

- Coronary Angiography
  - Several hundred patients in Hamburg and at ESRF
  - Synchrotron sensitivity allowed venous injection rather than arterial as is required in hospital
  - Not all coronary arteries always visualised well
- Mammography
  - Clinical program ongoing at Elettra
  - Preliminary results look encouraging



Synchrotron Medical Imaging

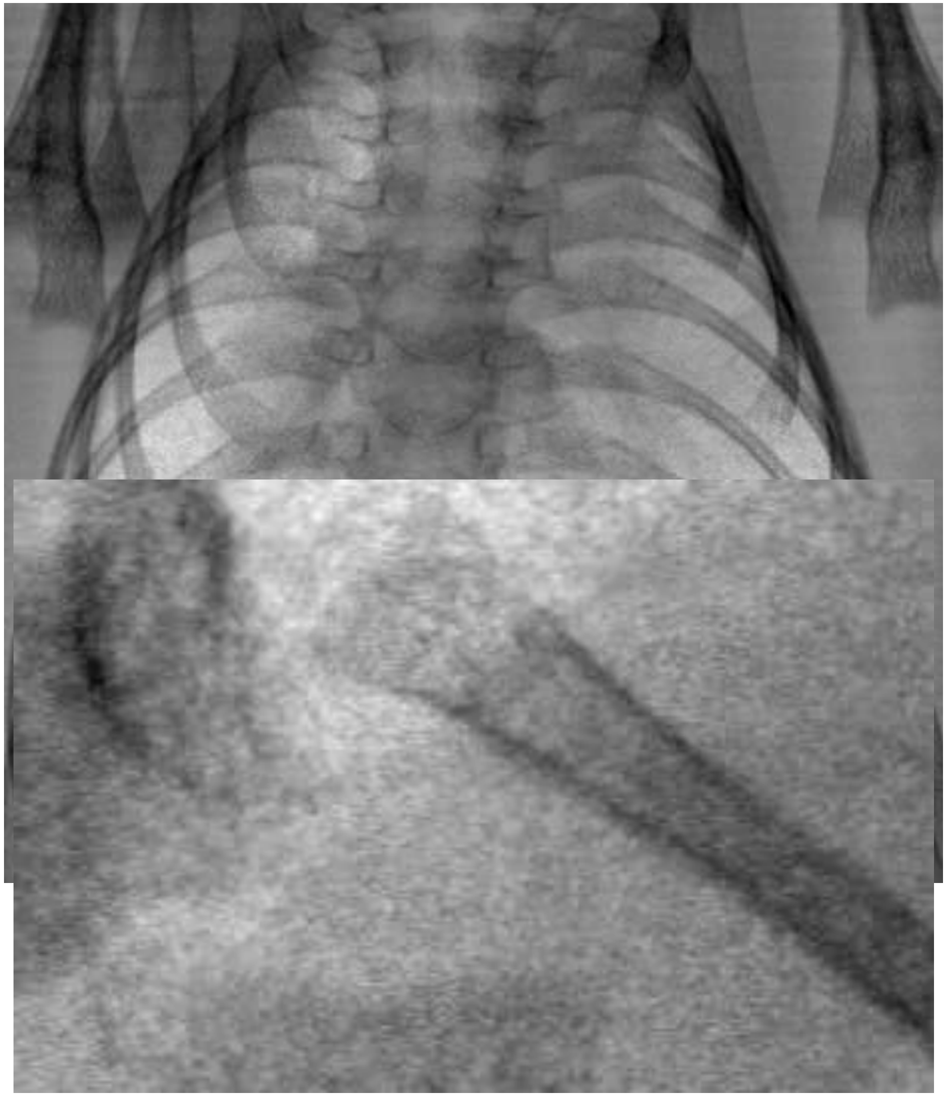
- Synchrotron Medical Imaging
  - ✓ Fantastic spatial resolution
  - ✓ Reasonable scan times
  - ✗ Uses ionising radiation
  - ✗ Very limited access
  - ✗ Extremely expensive
- Synchrotrons are not currently suitable for "routine" medical procedures

Case Study: Birth
One of the greatest Physiological challenges

- During fetal life the future airways of the lungs are liquid-filled
- At birth lungs must rapidly transform from being liquid to air filled
- How this happens is poorly understood but the process
  - Develops late in pregnancy
  - Is initiated by labour
- Preterm and caesarean section infants often develop problems
  - Incidence is increasing
  - Require weeks of assisted ventilation (>$2,000/day)
- We know that ventilating infants causes injury
  - ~30% develop chronic lung disease
  - Becomes apparent after 15 years

SPring-8 - Super Photon ring-8GeV

Rabbit Lung



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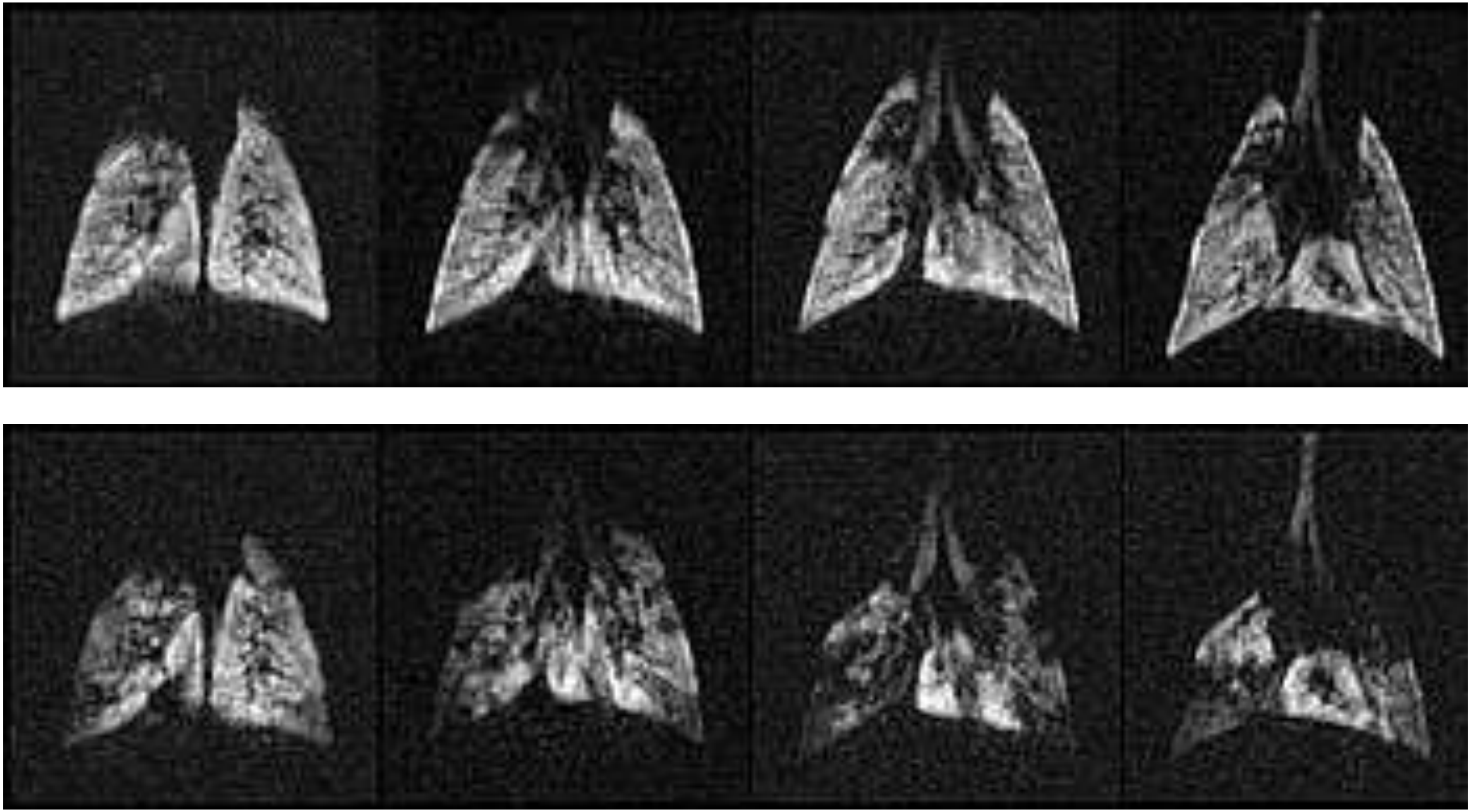
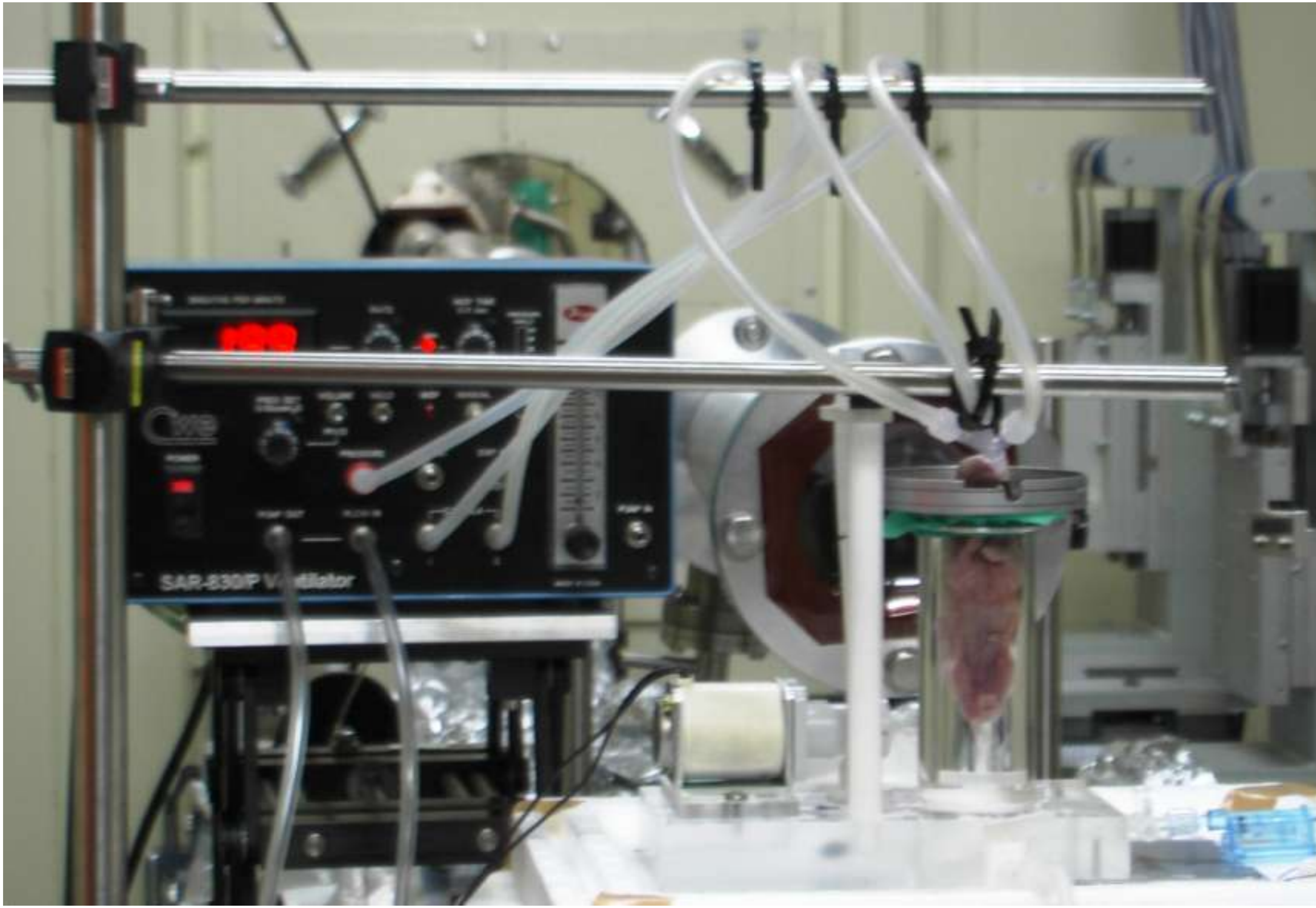
MRI State of the Art



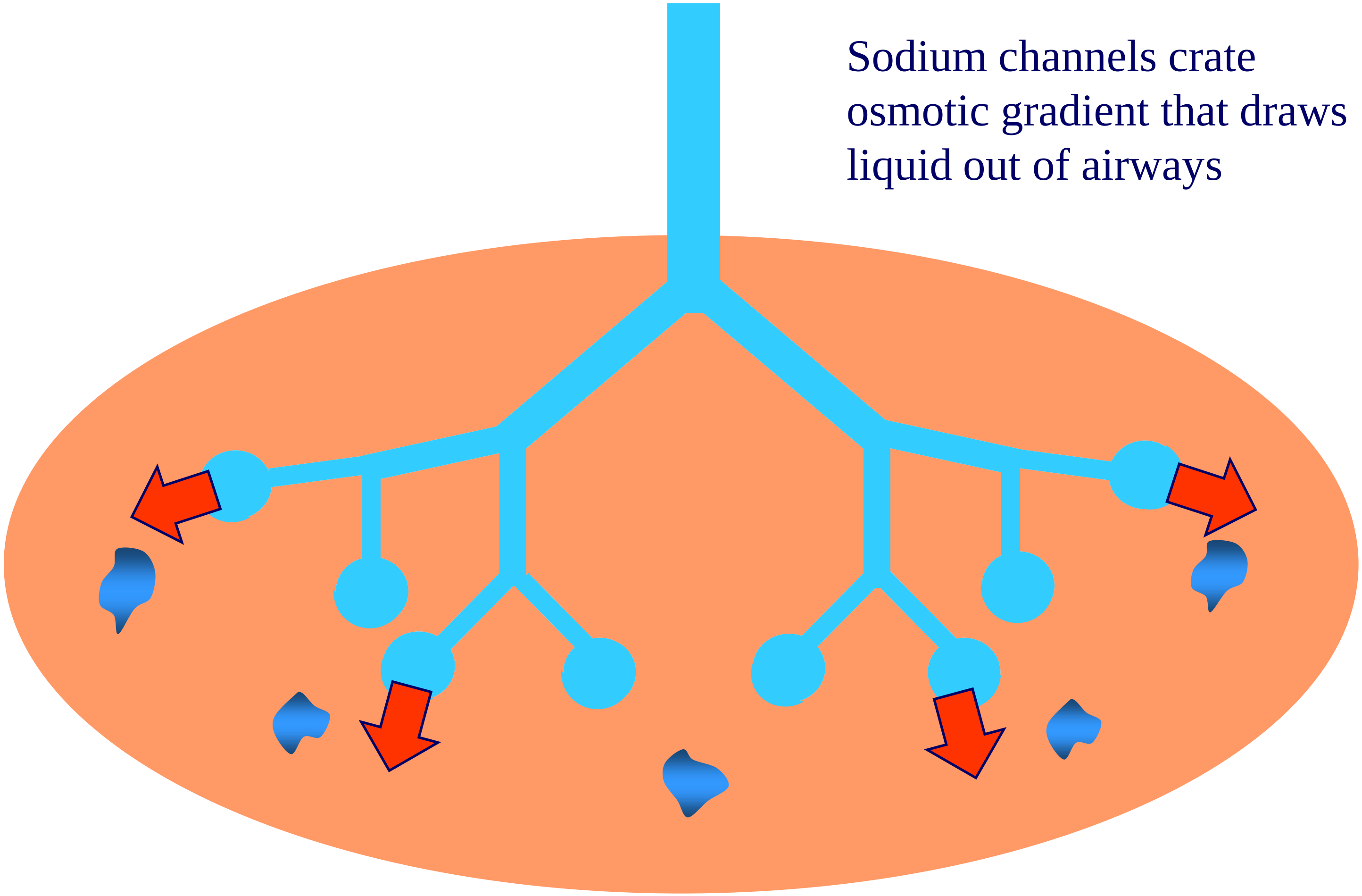
Bronchoconstriction induced by metacholine

Rabbit Pup Lung Imaging - Delivery

Artificial Ventilation

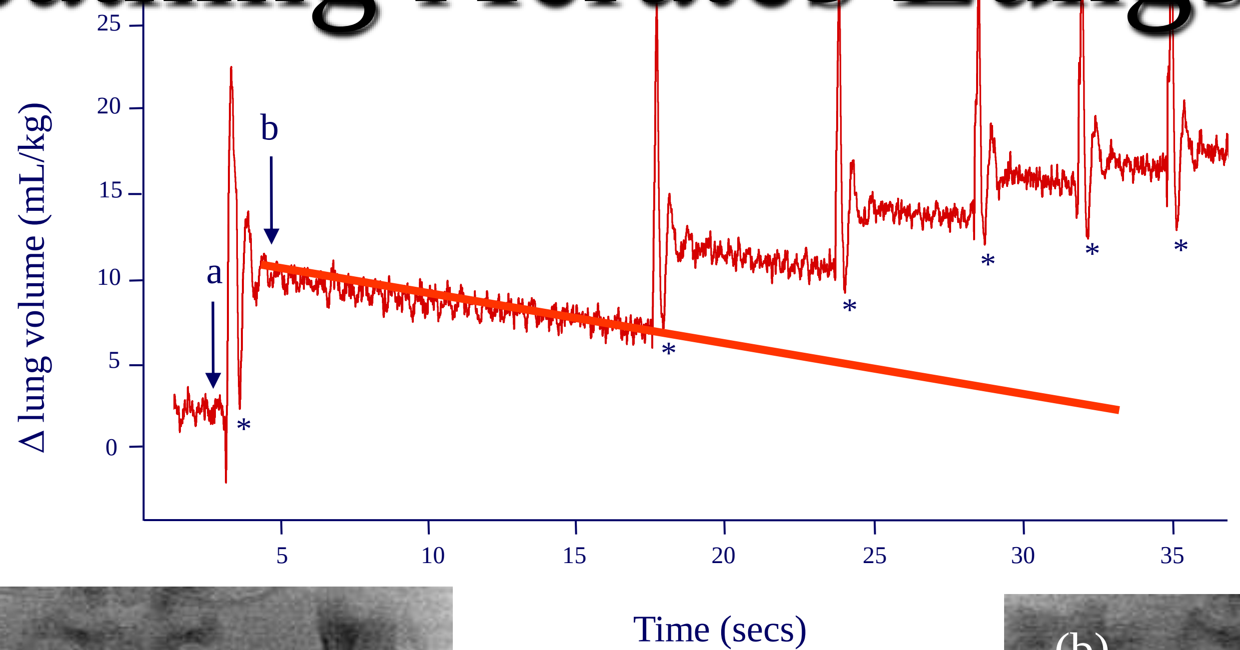


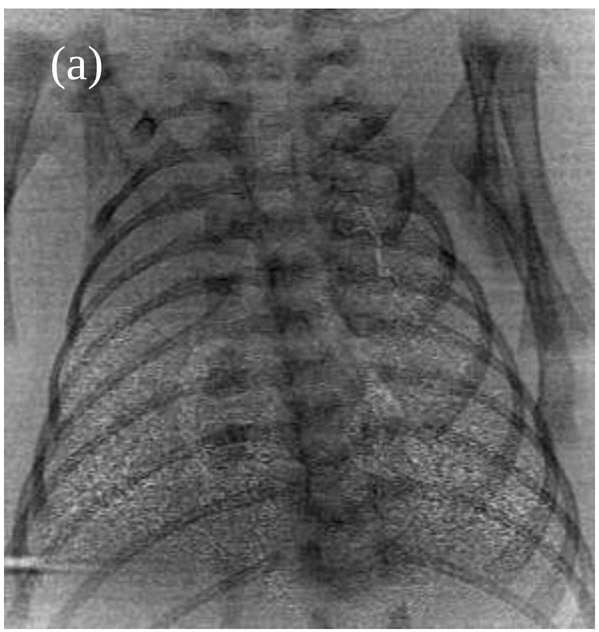
Lung aeration: Airway liquid clearance

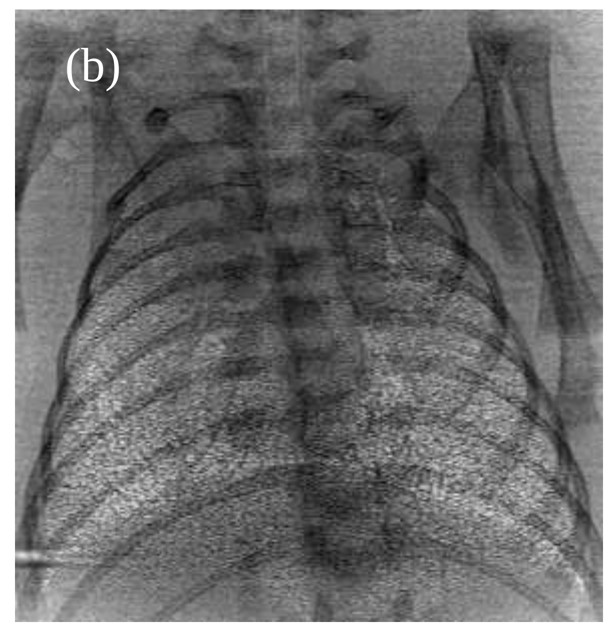


Sodium channels crate osmotic gradient that draws liquid out of airways

Breathing Aerates Lungs

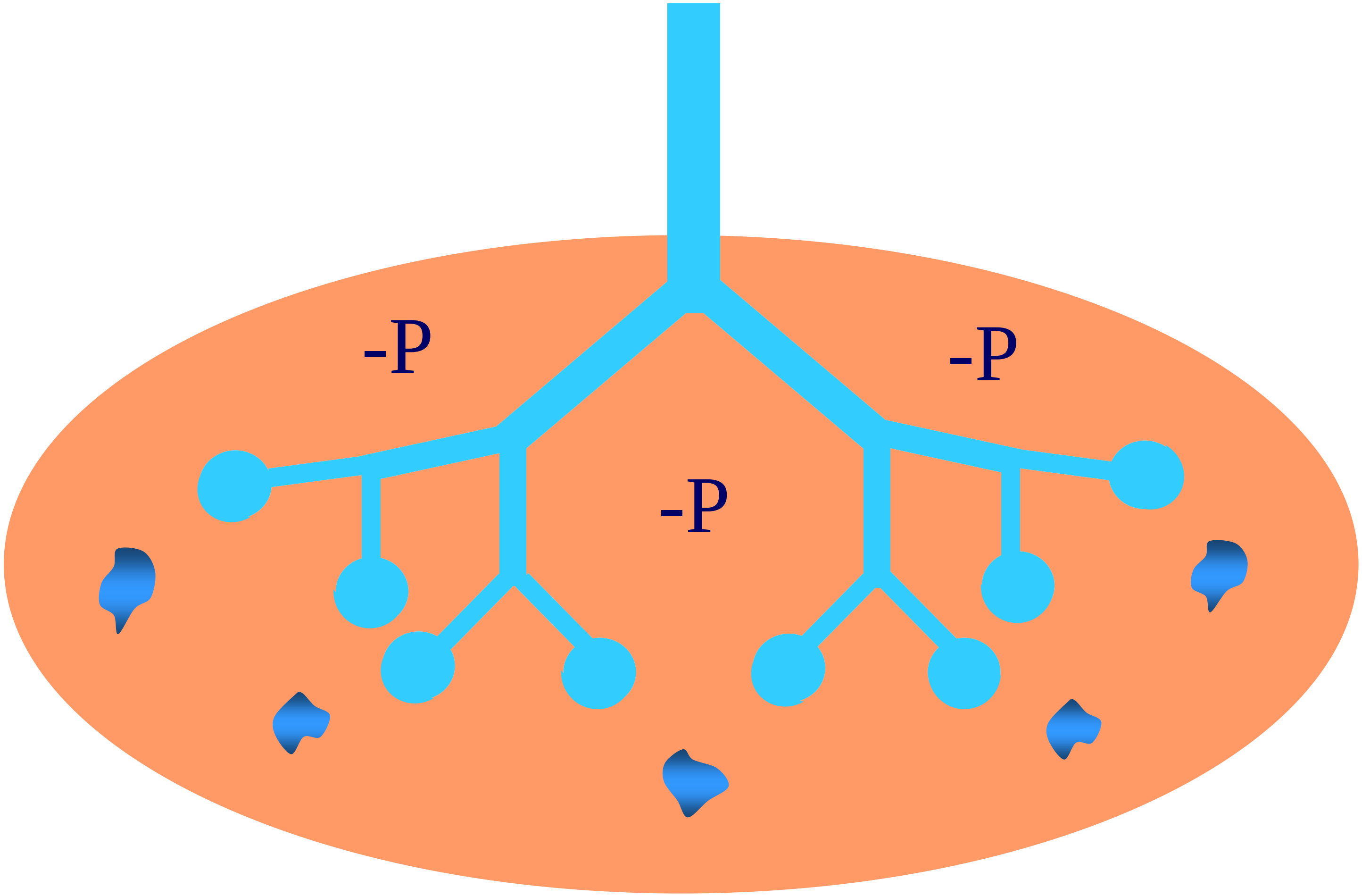




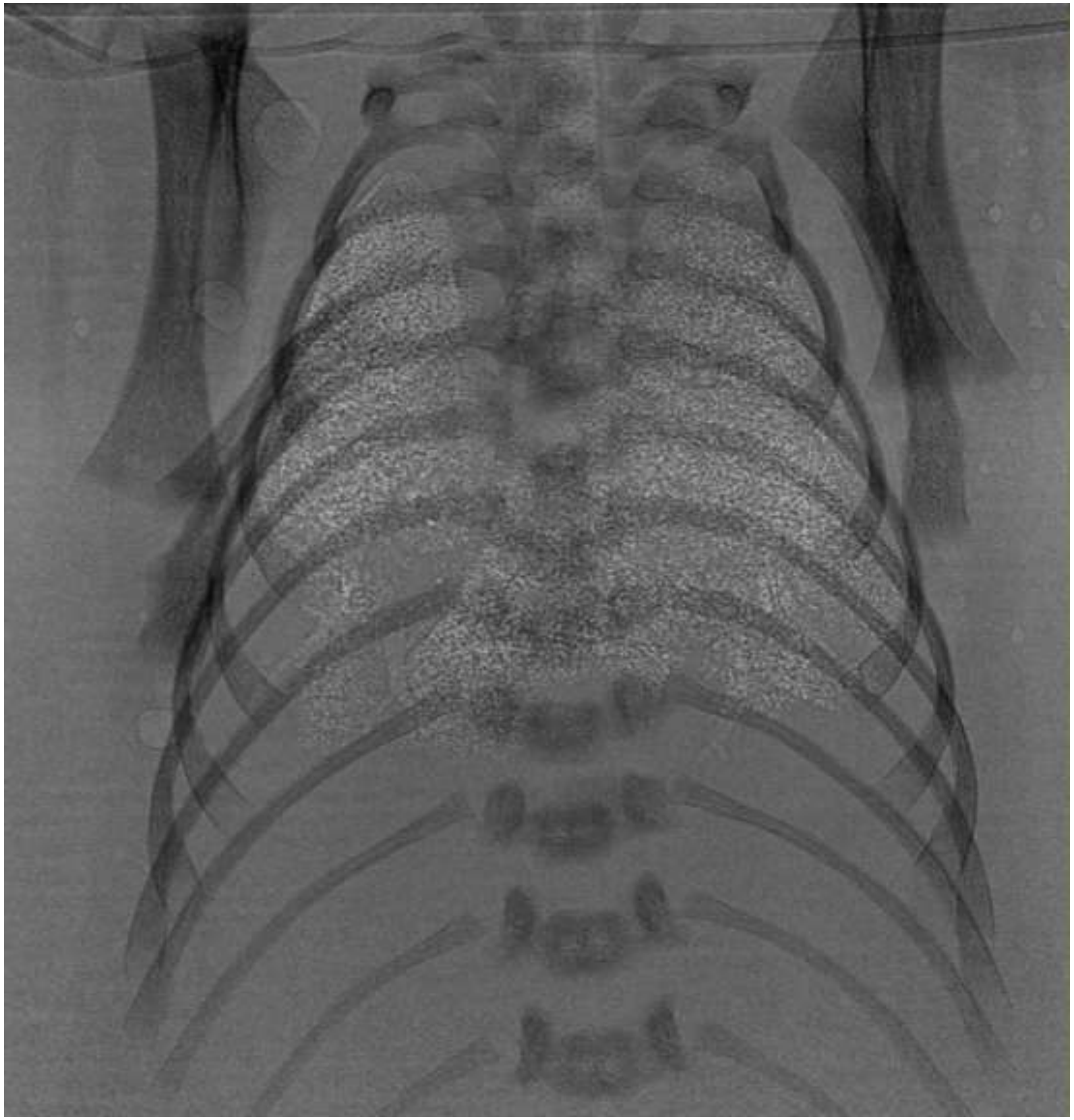


Lung aeration: Airway liquid clearance

Inspiration forces liquid out of airways



Post Mortem Artificial Ventilation



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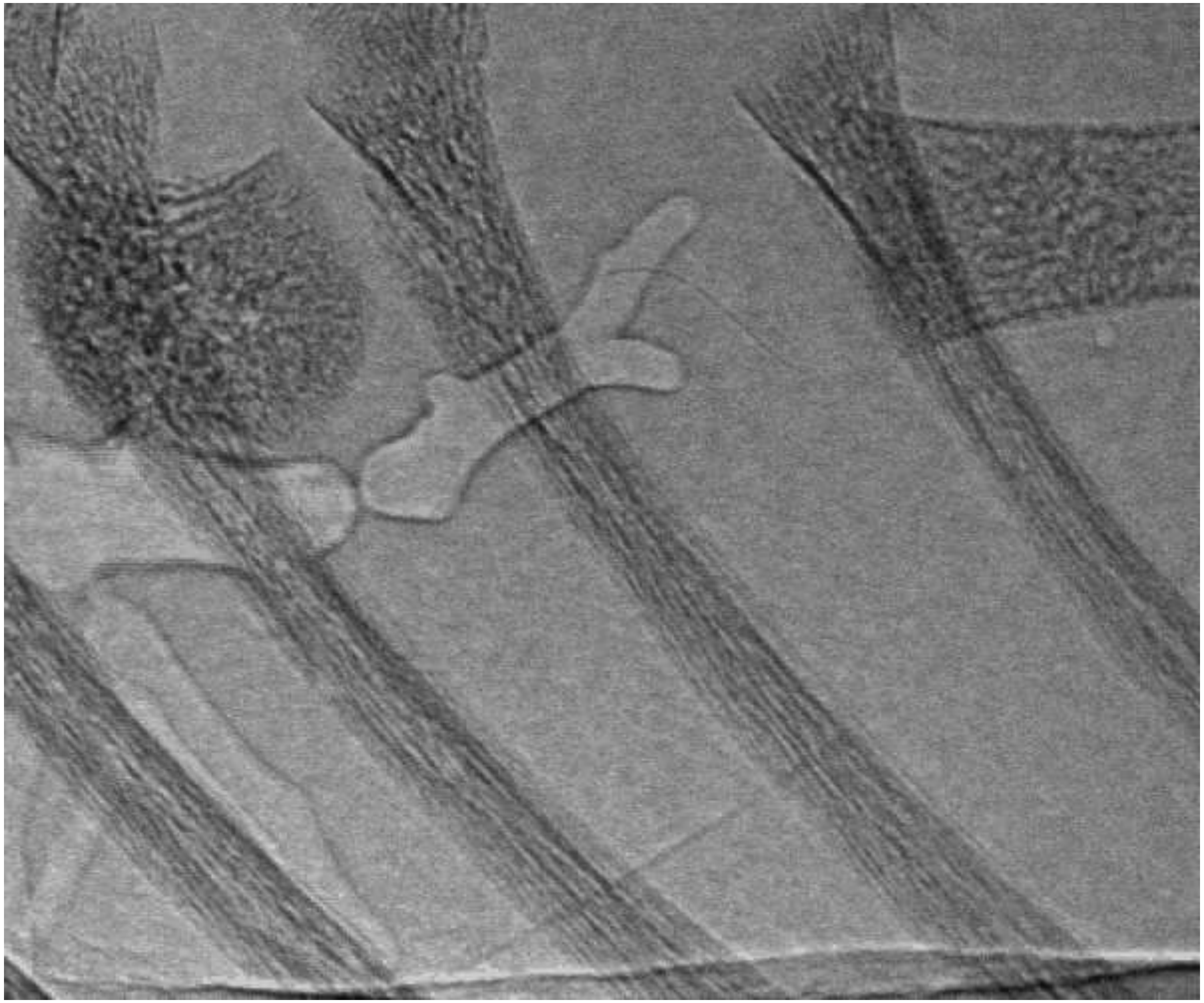
RA Lewis et al Phys. Med. Biol. **50,** 5031
S. Hooper et al FASEB **21**, 3330 (2007)

Lower Lung



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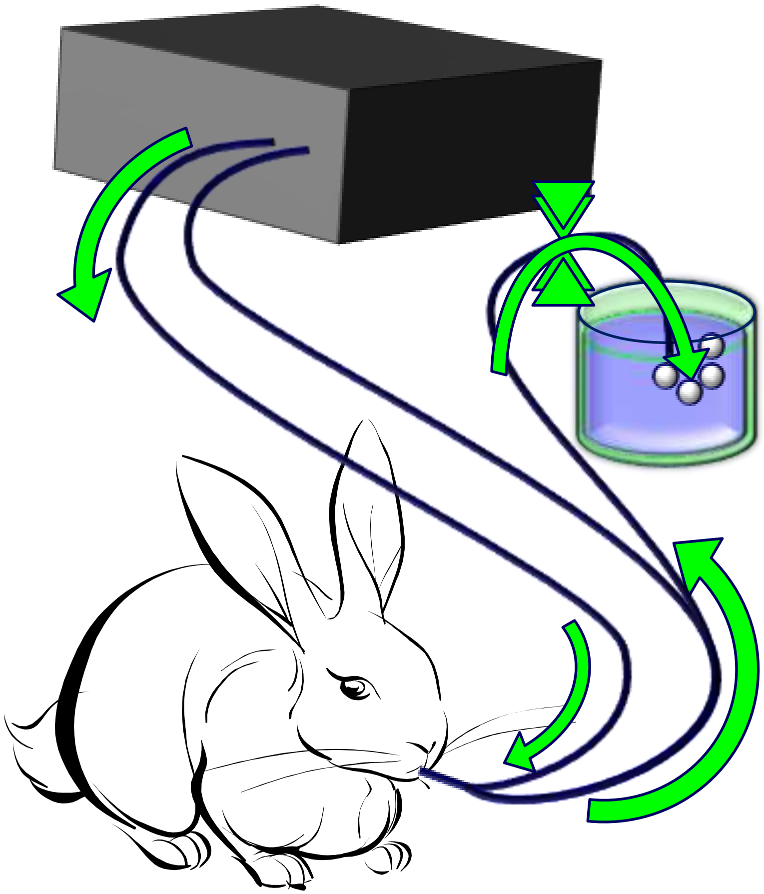
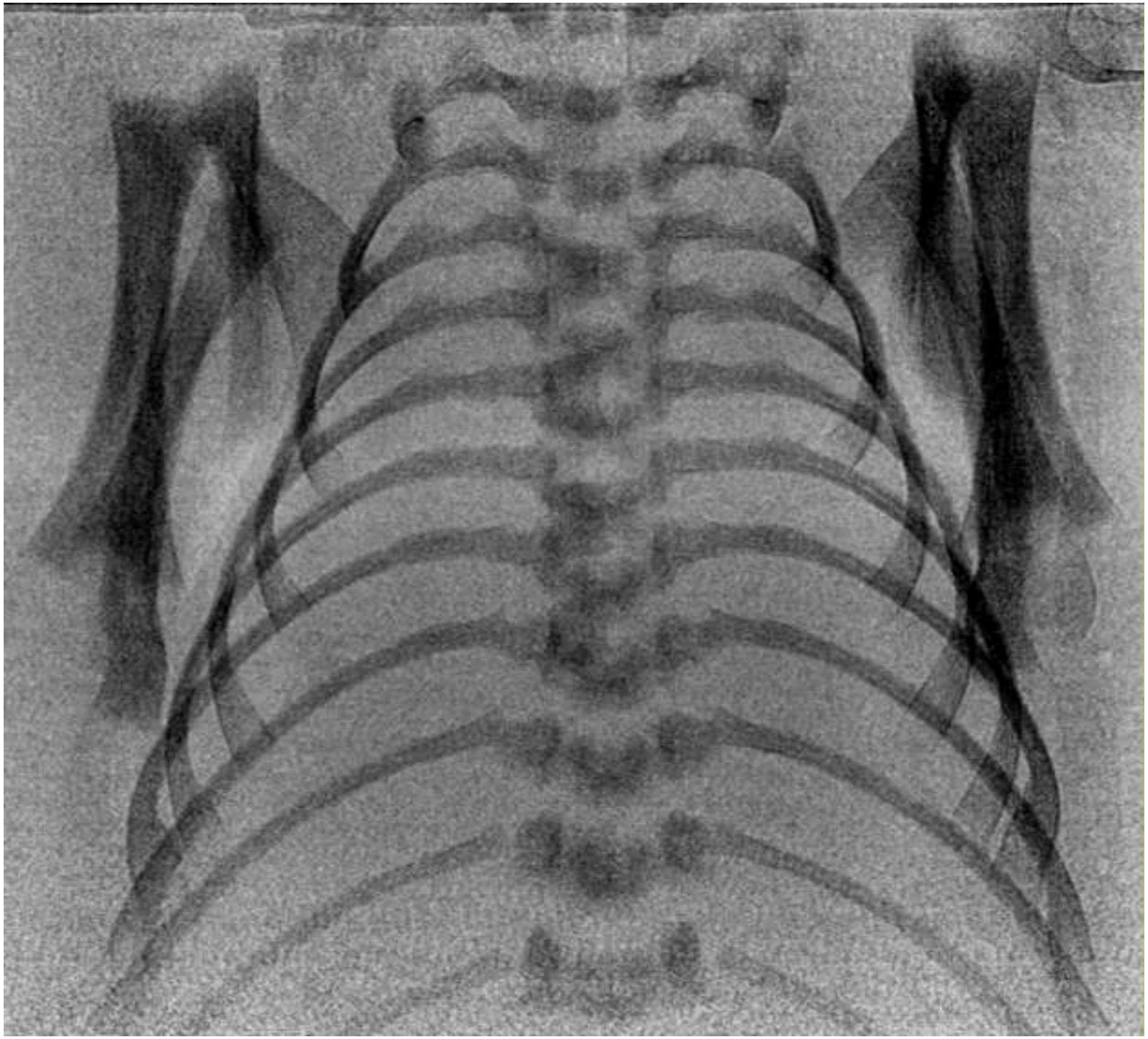
Medical Relevance

- Respiratory Ventilation
- Positive End Expiratory Pressure (PEEP) is used in some hospitals as it is thought to help
- It is currently excluded from international resuscitation guidelines for ventilating infants due to lack of evidence



Rabbit Pup: No PEEP



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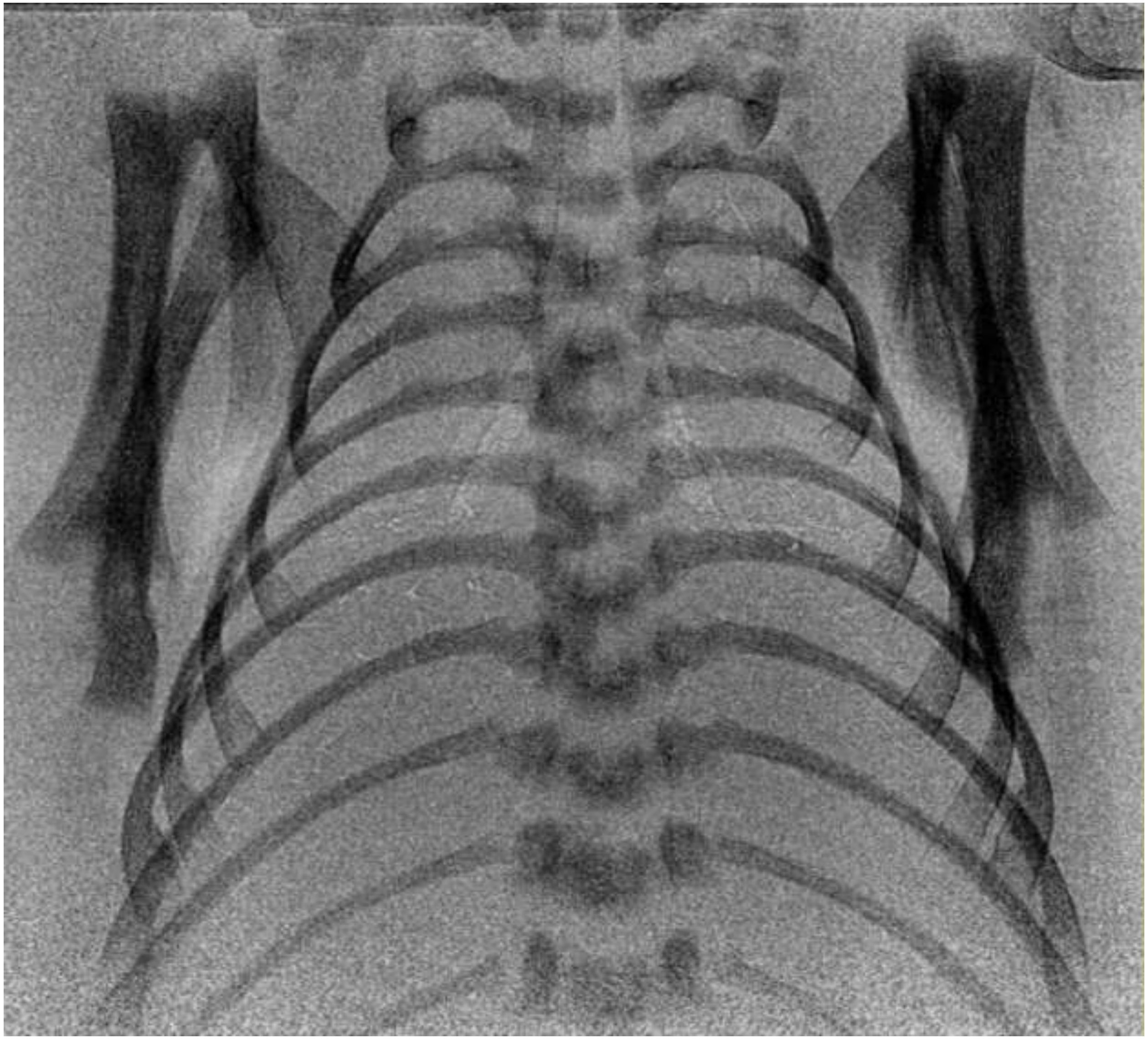
RA Lewis et al Phys. Med. Biol. **50,** 5031
S. Hooper et al FASEB **21**, 3330 (2007)

Rabbit Pup: With PEEP



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Te Pas et al Pediatric Research **65**(5), 537-541 2009
S. Hooper et al FASEB **21**, 3330 (2007)

Phase Retrieval: Single Image

- Approximate 'contact' intensity from Beer's Law

$$I(\mathbf{r}_\perp, z=0) = I_O \exp(-\mu T(\mathbf{r}_\perp))$$

- Approximate 'contact' phase by

$$\phi(\mathbf{r}_\perp, z=0) = -\frac{2\pi}{\lambda}\delta T(\mathbf{r}_\perp)$$

- Use Transport-of-Intensity Equation (TIE)

$$\nabla_\perp \cdot (I(\mathbf{r}_\perp, z)\nabla_\perp \phi(\mathbf{r}_\perp, z)) = -\frac{2\pi}{\lambda}\frac{\partial}{\partial z} I(\mathbf{r}_\perp, z)$$

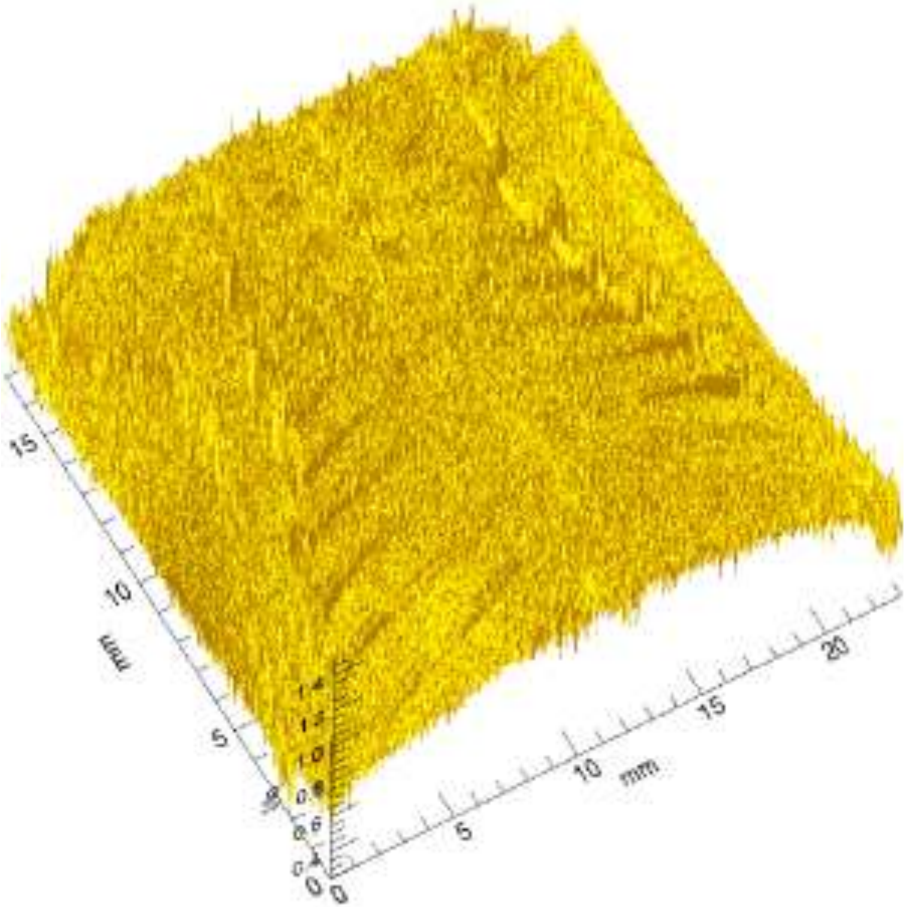
- Solve for object's projected thickness using Fourier Derivative Theorem

$$T(\mathbf{r}_\perp) = -\frac{1}{\mu}\ln\left(\mathbf{F}^{-1}\left\{\mu\frac{\mathbf{F}\left\{M^2 I(M\mathbf{r}_\perp, z=R_2)\right\}/I_O}{MR_2\delta|\mathbf{k}_\perp|^2+\mu}\right\}\right)$$

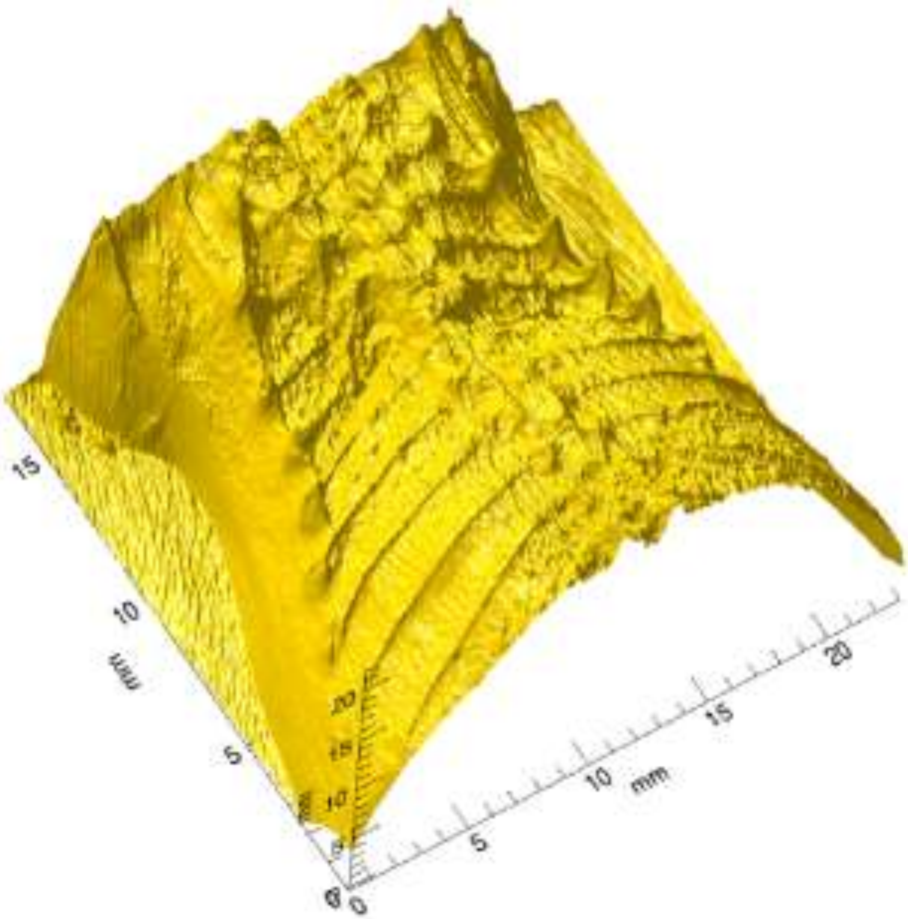
Paganin, D et al., Journal of Microscopy, Vol. 206 Pt 1 April 2002, pp. 33-40

Phase to Projected Thickness

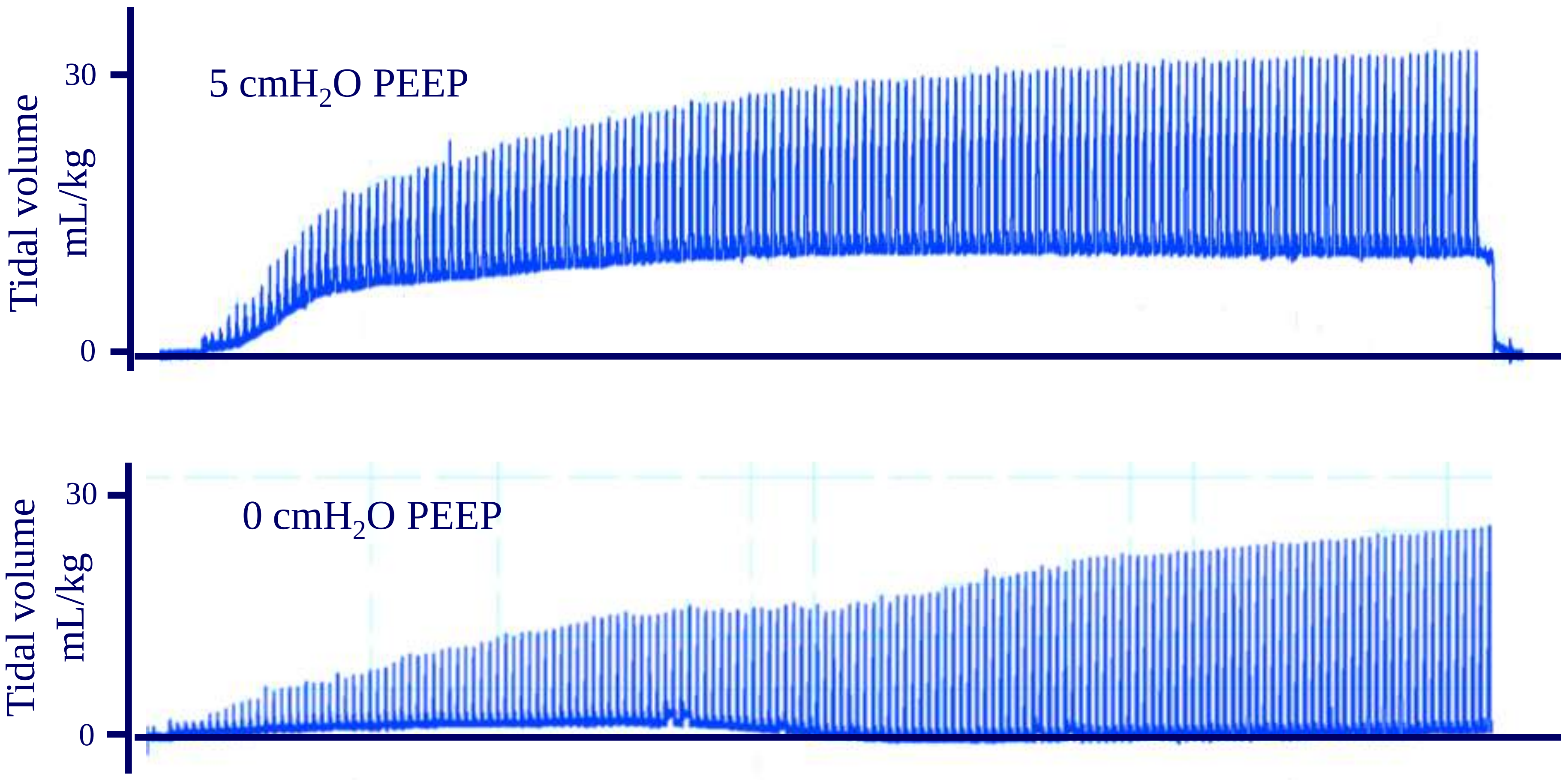
Phase image R_2=4.26m, E=33keV



Projected thickness



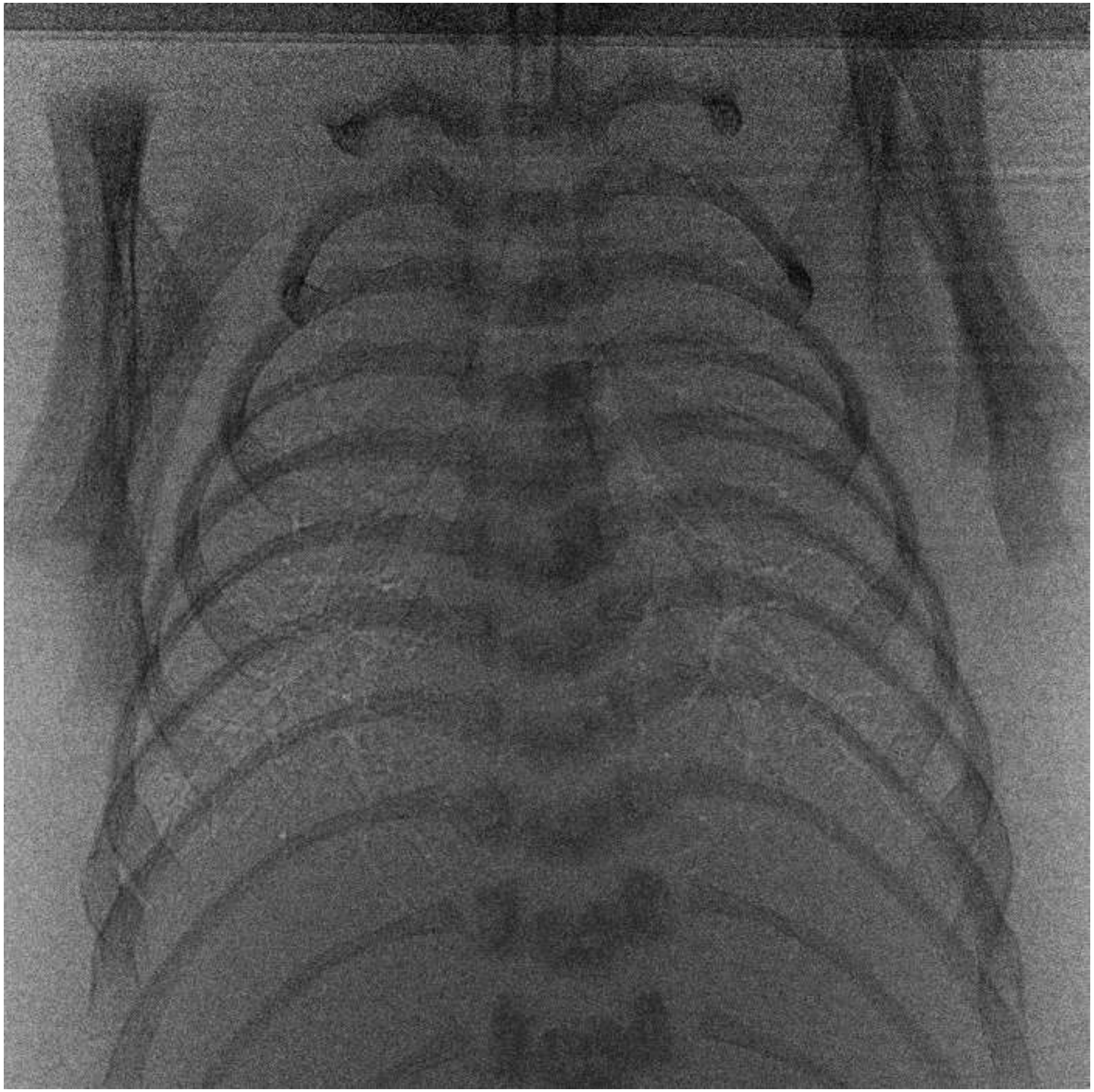
Effect of PEEP in Ventilated Preterm Rabbits



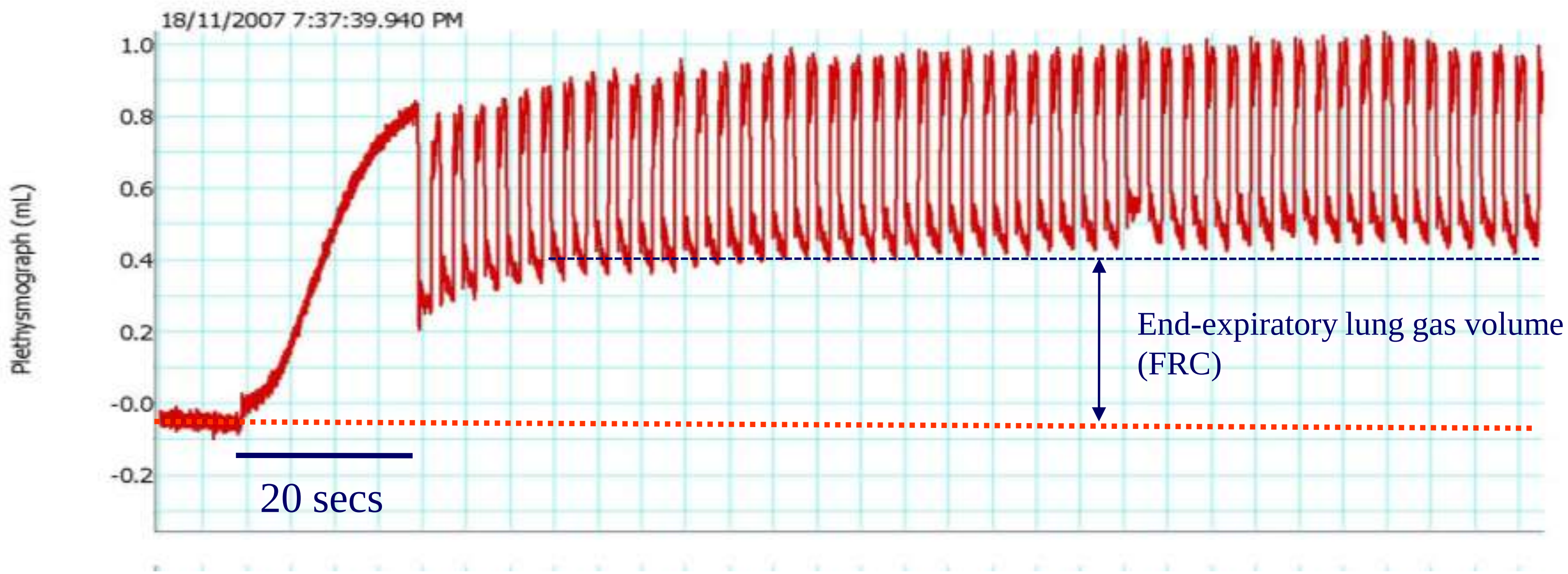
Result of this research:

- The following recommendation is now likely to be added to the international resuscitation guidelines (ILCOR) in 2010
- An end-expiratory pressure should be applied to the airways during resuscitation of newborn infants at birth
- Is this all?

20sec First Inspiration



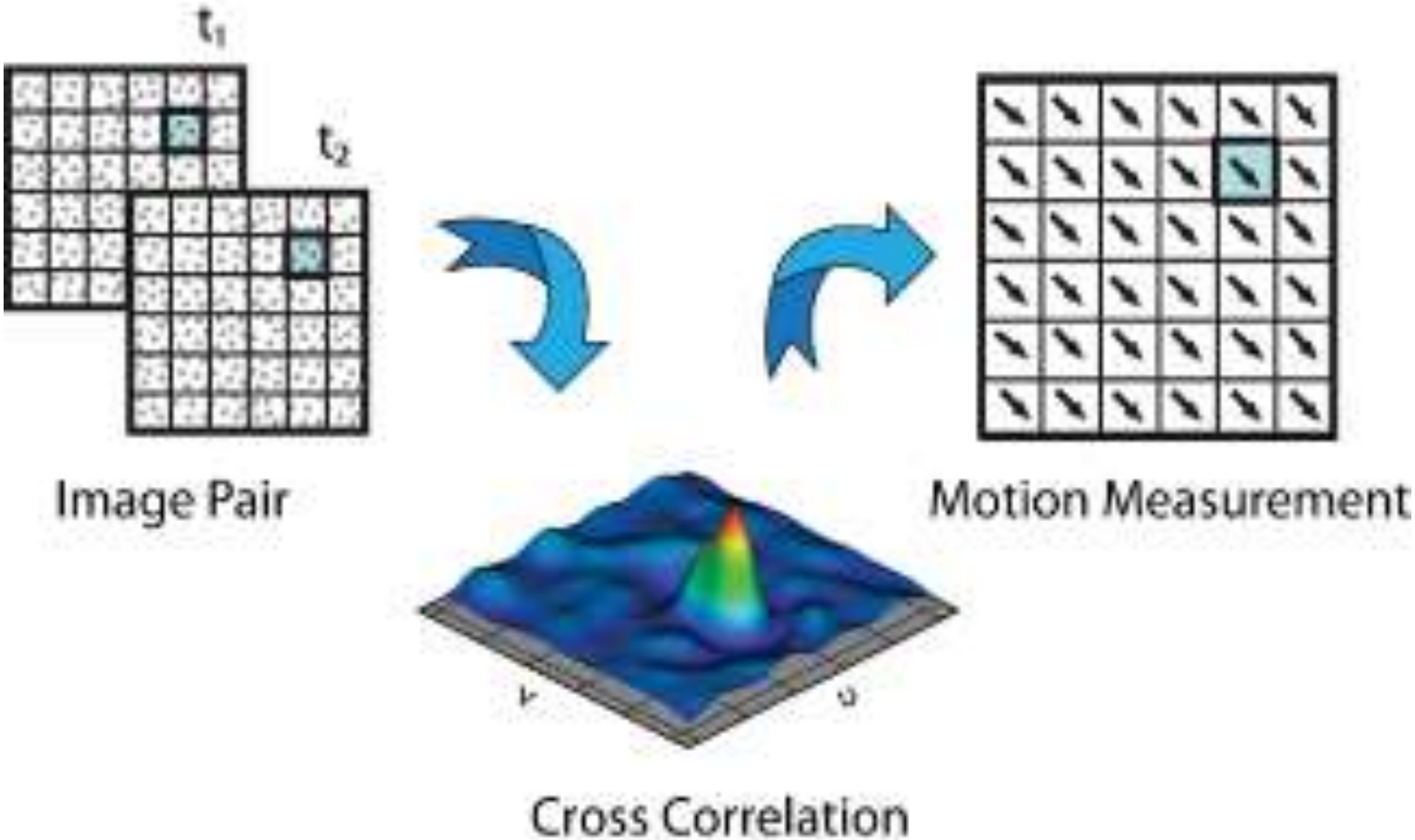
Long First Inspiration



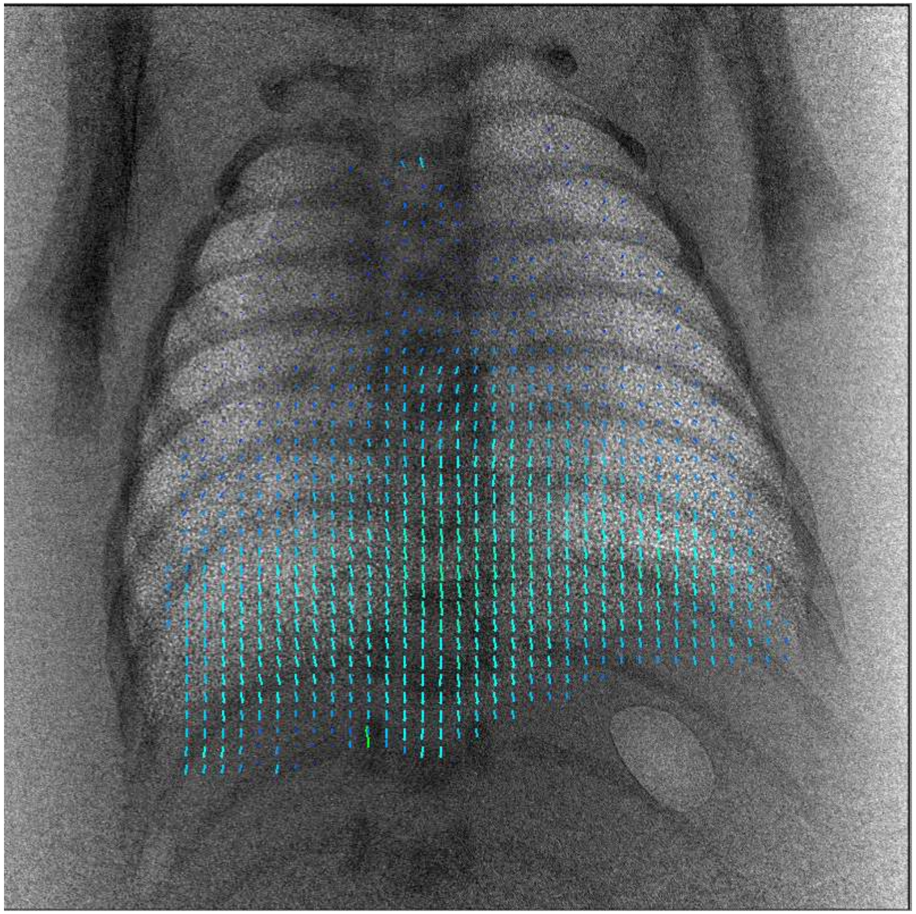
20 sec long inspiration
5 cmH_2O PEEP

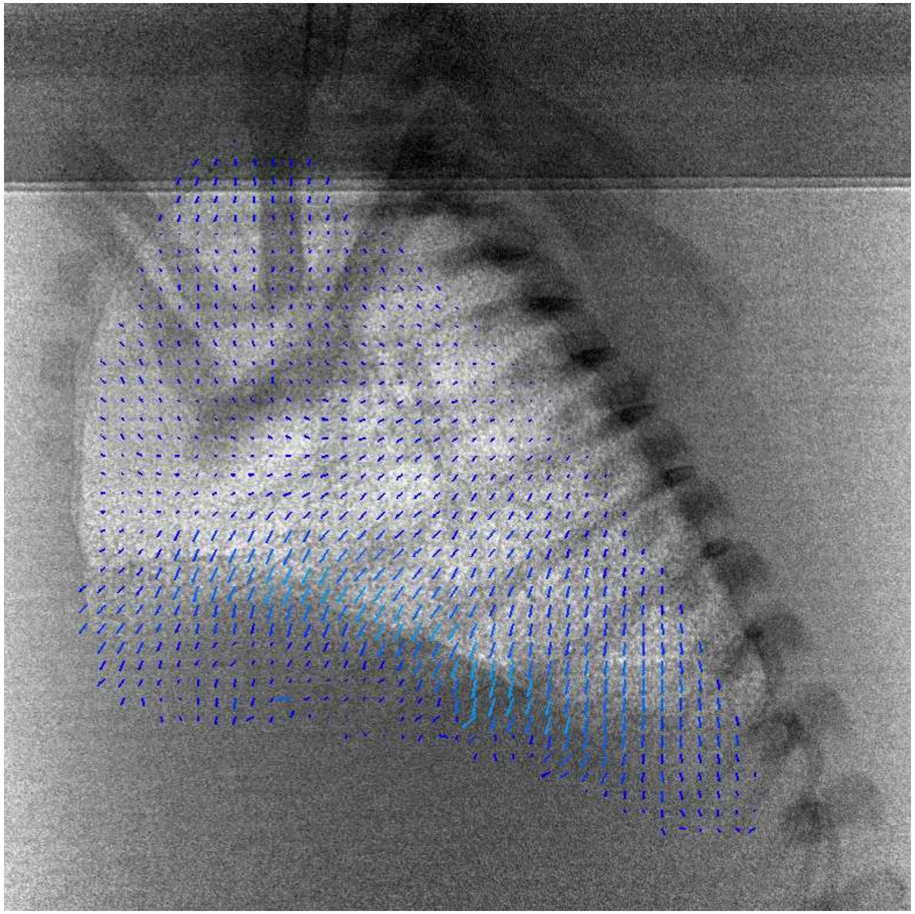
Measuring Lung Motion

- Particle Image Velocimetry detects speed & direction of particle (lung) motion



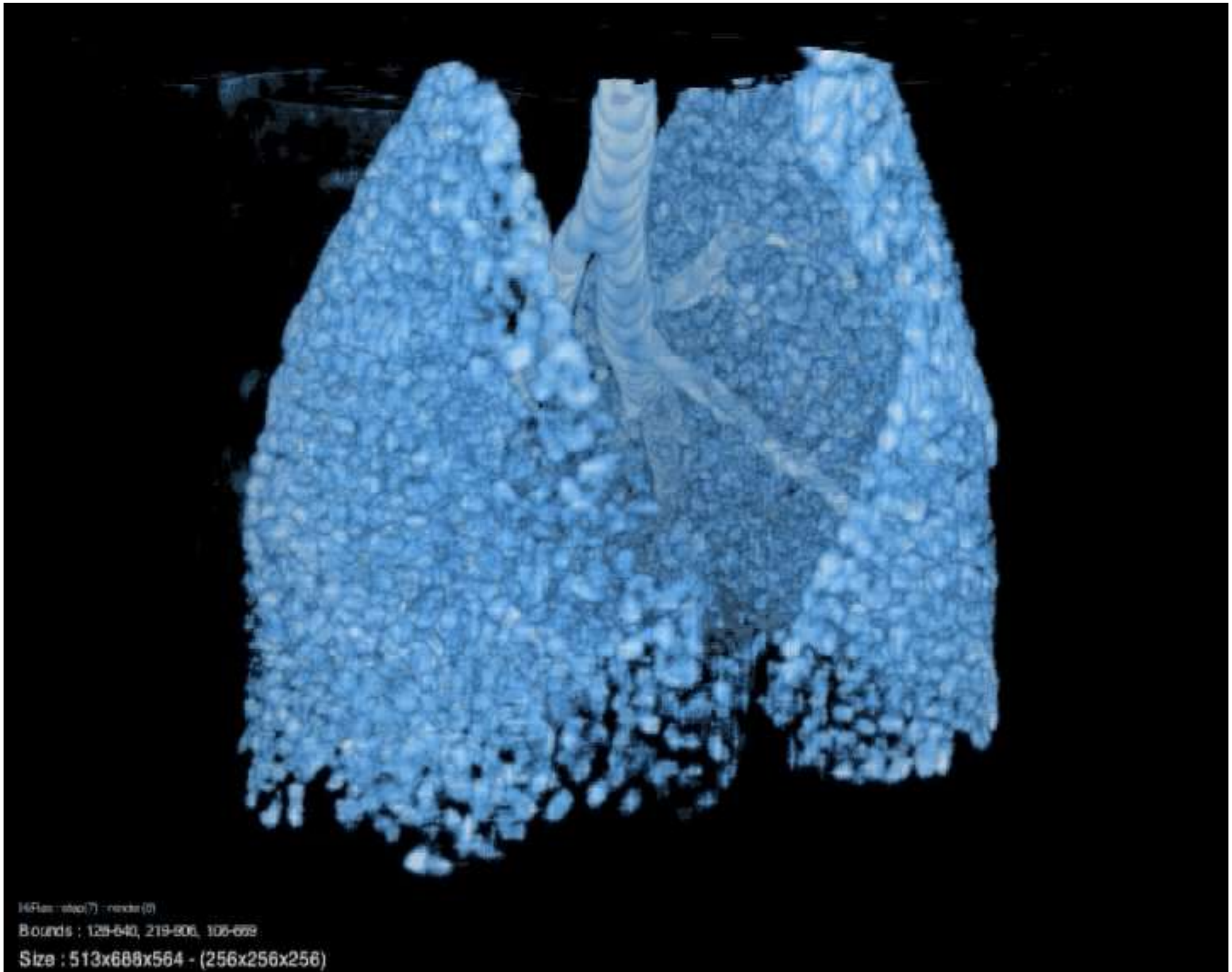
Particle Image Velocimetry





A. Fouras, et al

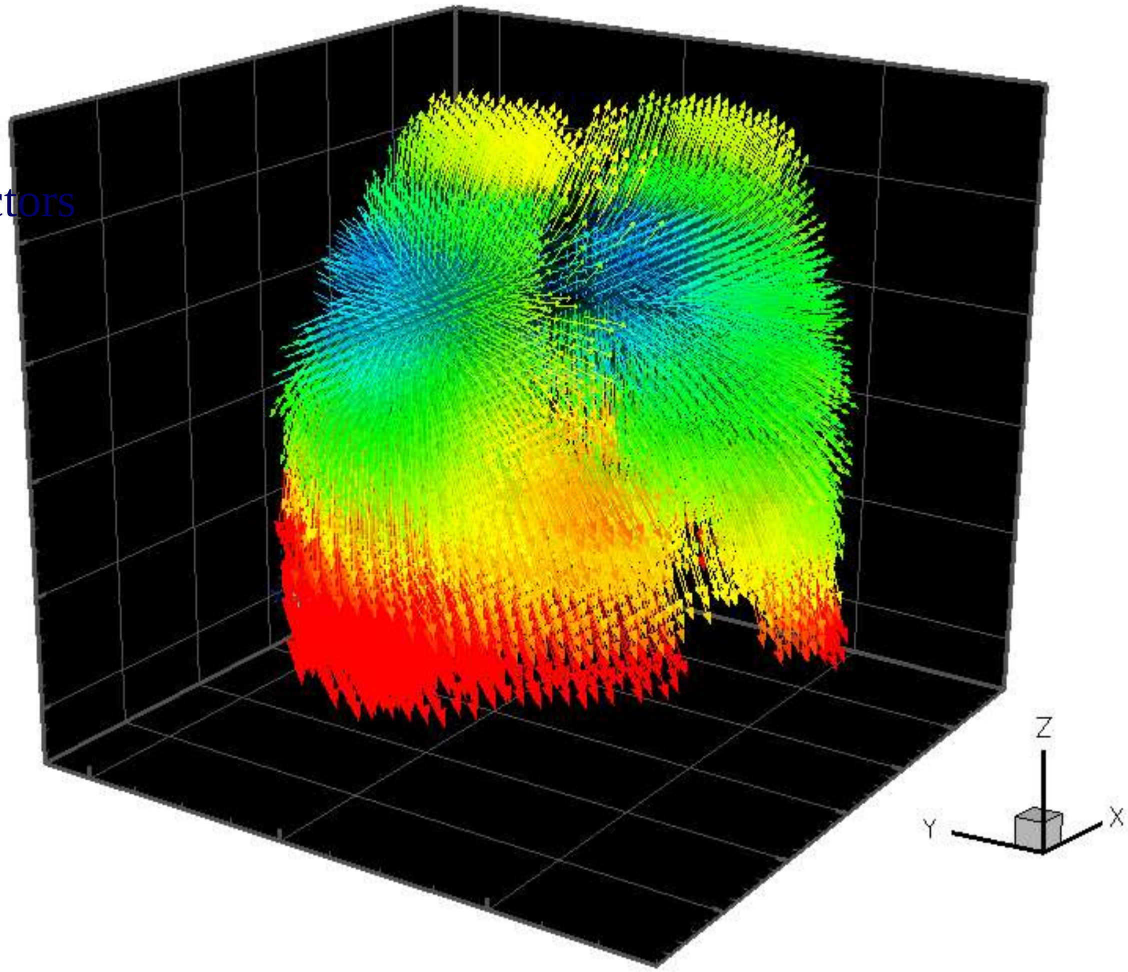
Whole Breath Lung Morphology



S Dubsky, A Fouras et al

Whole Breath Vectors

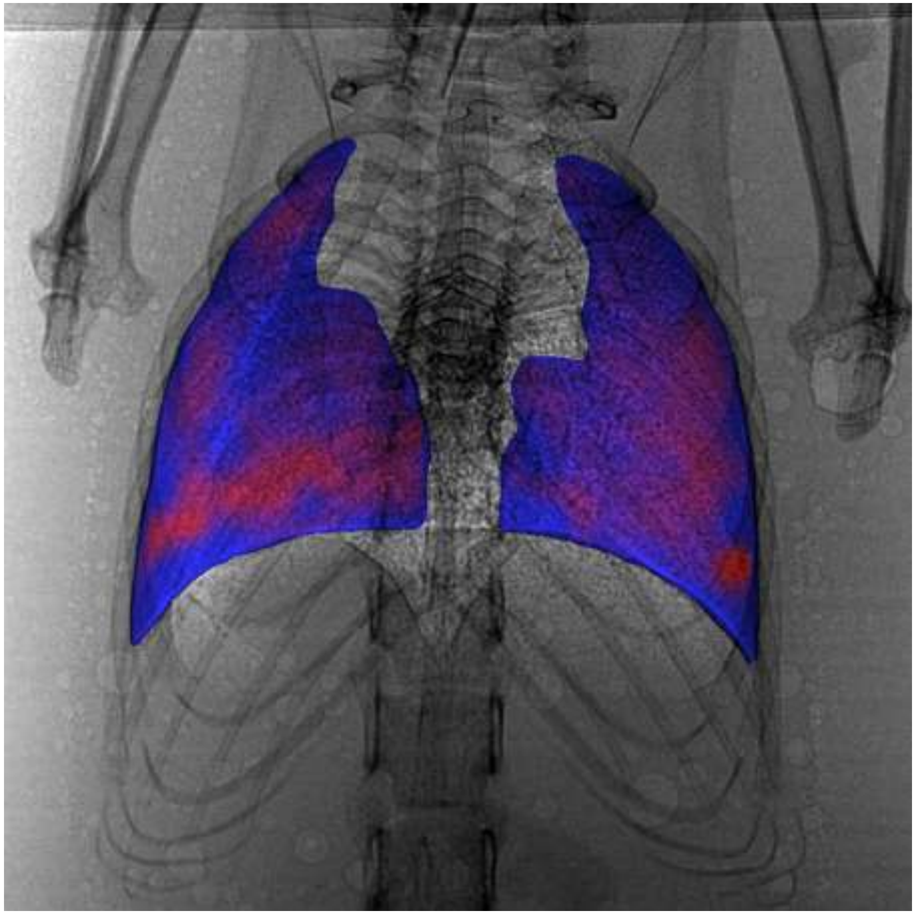
128 × 128 × 64 vectors



Disease Detection

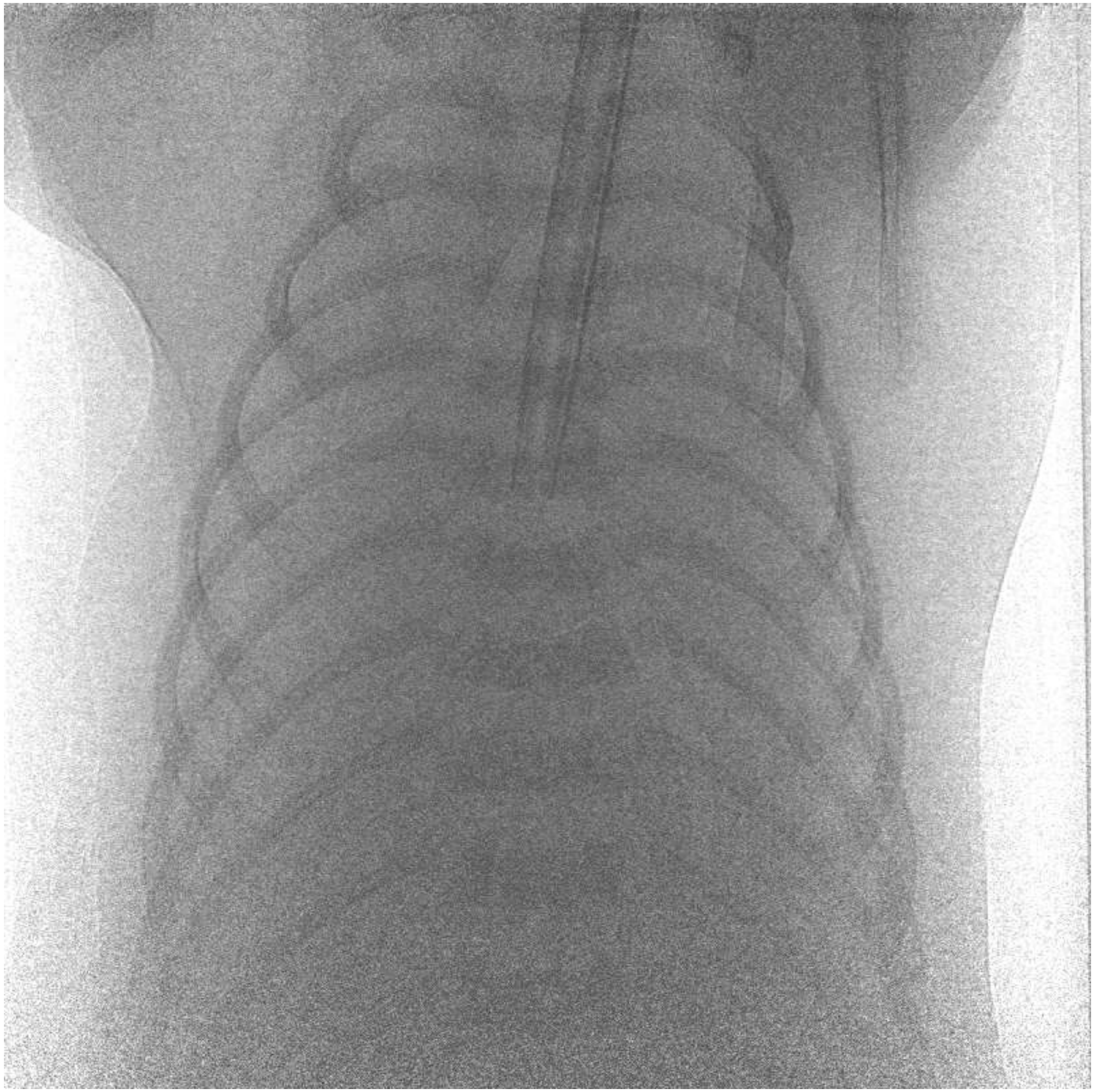
Plots of regional compliance, calculated from motion maps in mouse lungs

Healthy Lung, showing uniform compliance

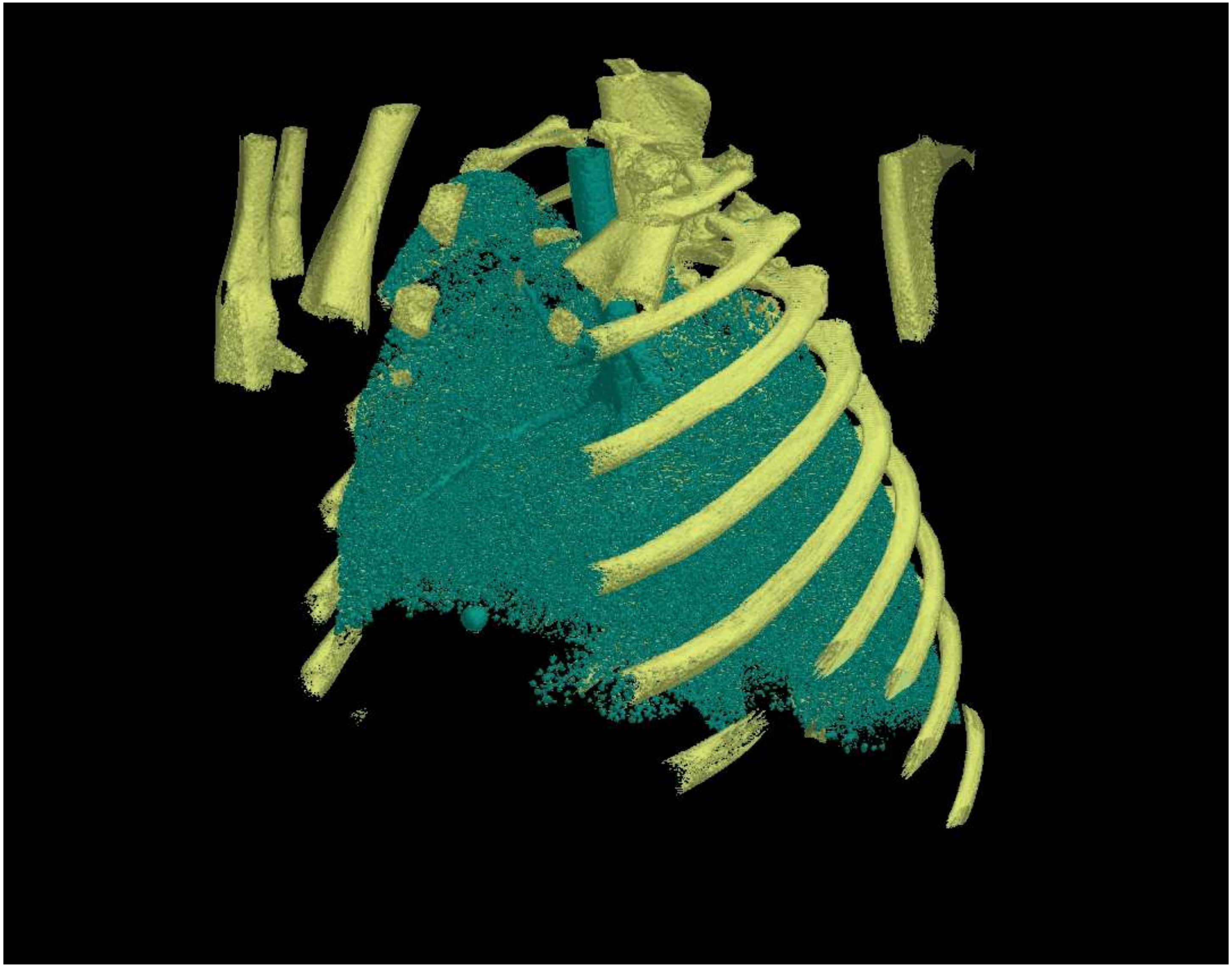


Fibrotic lung, showing regional differentiation of compliance

Simultaneous Phase Imaging and Angiography



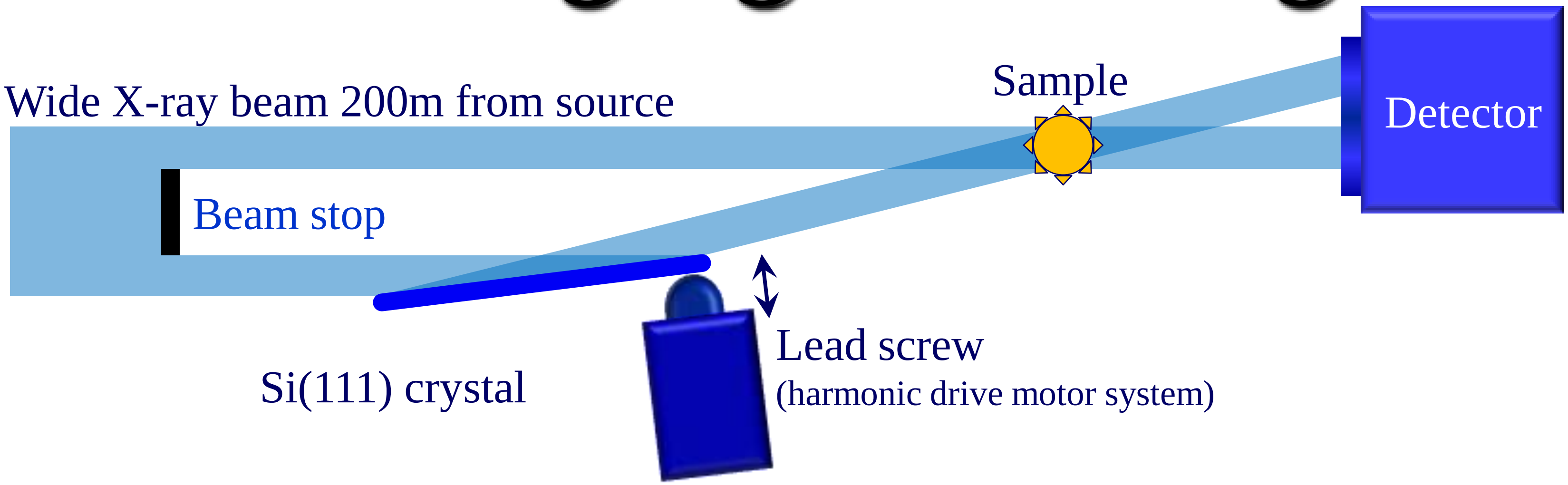
Rabbit Pup CT

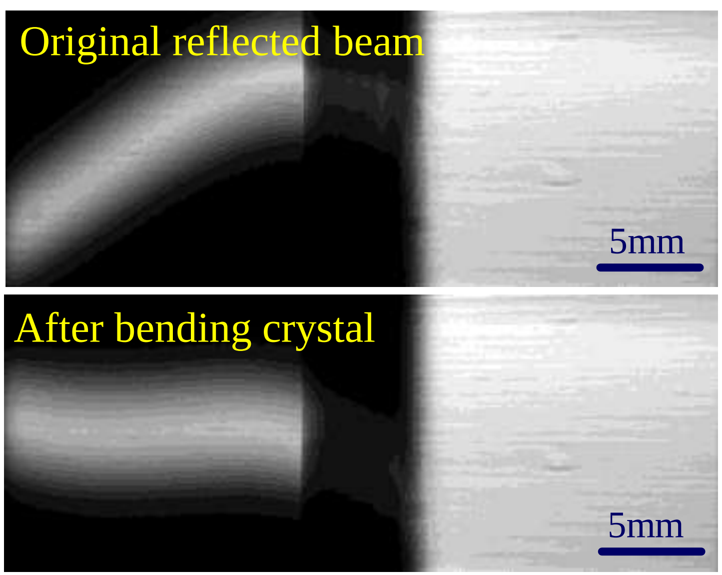


Major Issues: Technical

- Static beam greatly limits 4D imaging (x, y, z, t)

Stereo imaging at SPring-8



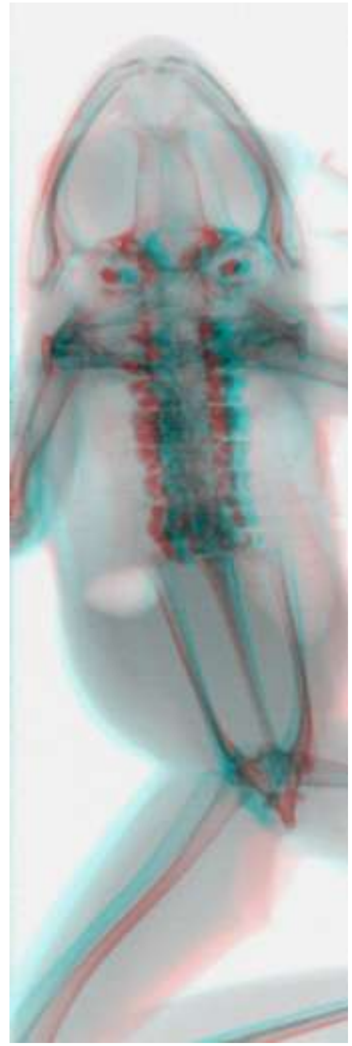


- Distorted reflected beam a result of…
  - Vertical energy dispersion of monochromator
  - Vertical and horizontal spread of X-ray beam.
  - Deformation of first crystal in monochromator by heat load
- Corrected by
  - Bending silicon crystal by pushing one end with screw while keeping the other end fixed (see figure)

X-ray Stereo Imaging

X-ray stereo image

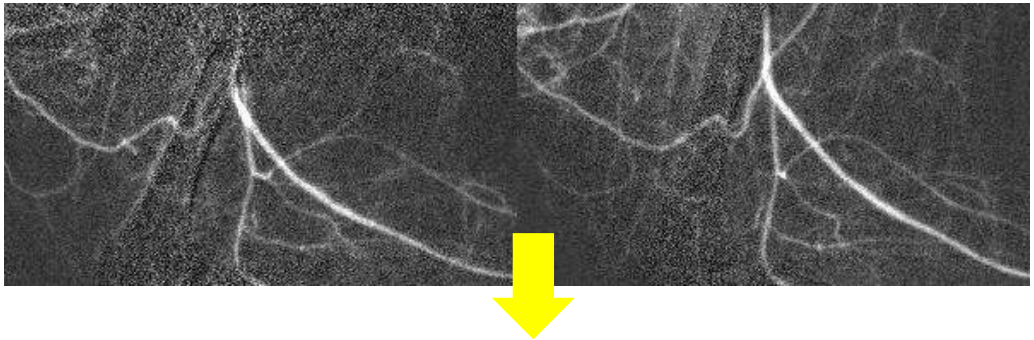
5mm



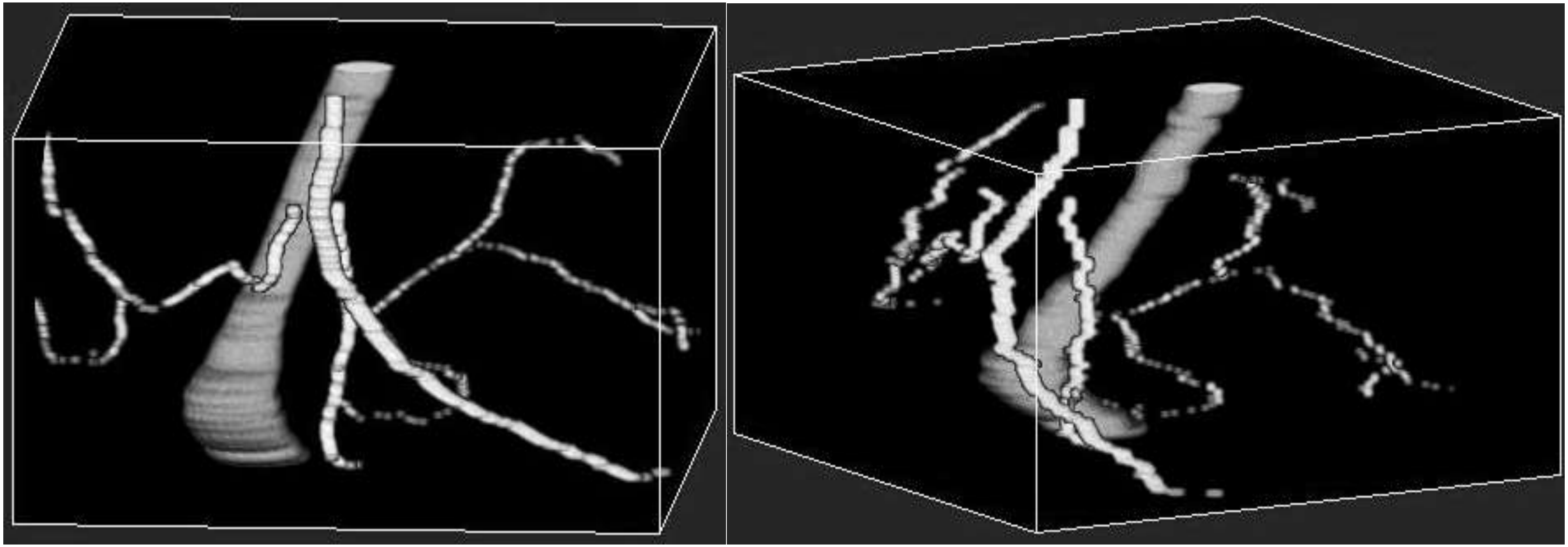
Anaglyph

- Live Frog (*Rana japonica*)
- CCD Frame rate: 20Hz
- X-ray energy: 15keV
- Sequential images were acquired whilst vertically translating sample
- The images were combined digitally

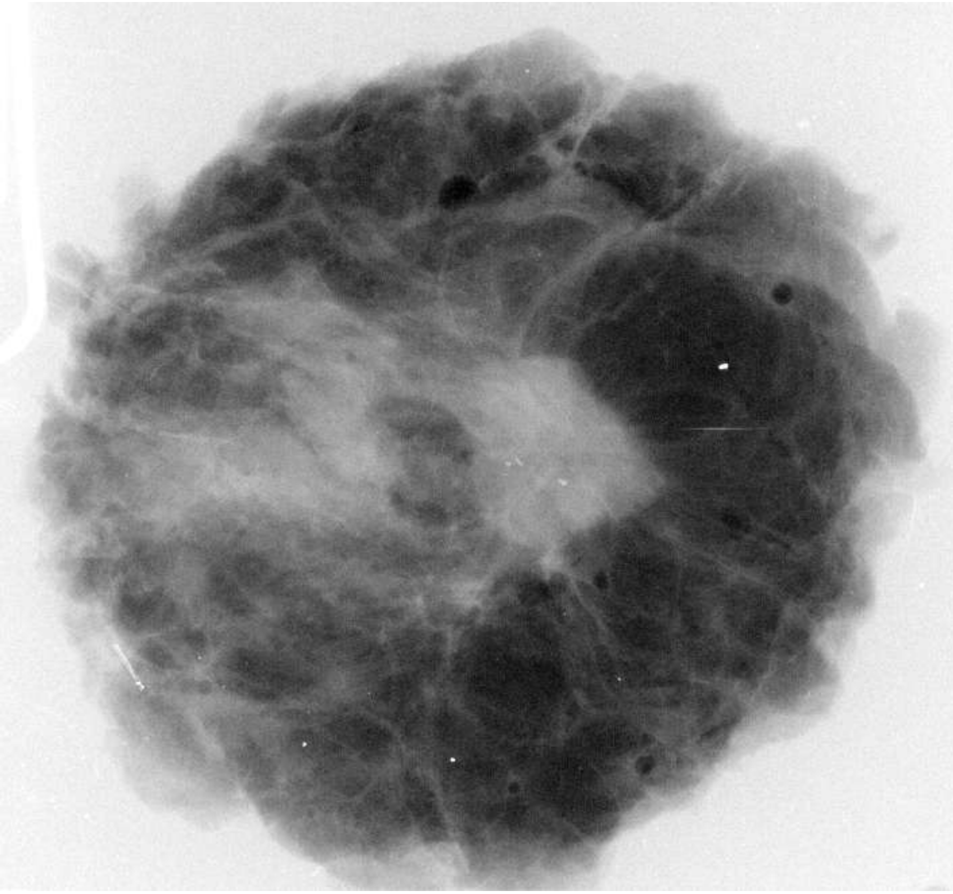
Time-Resolved 3D Imaging



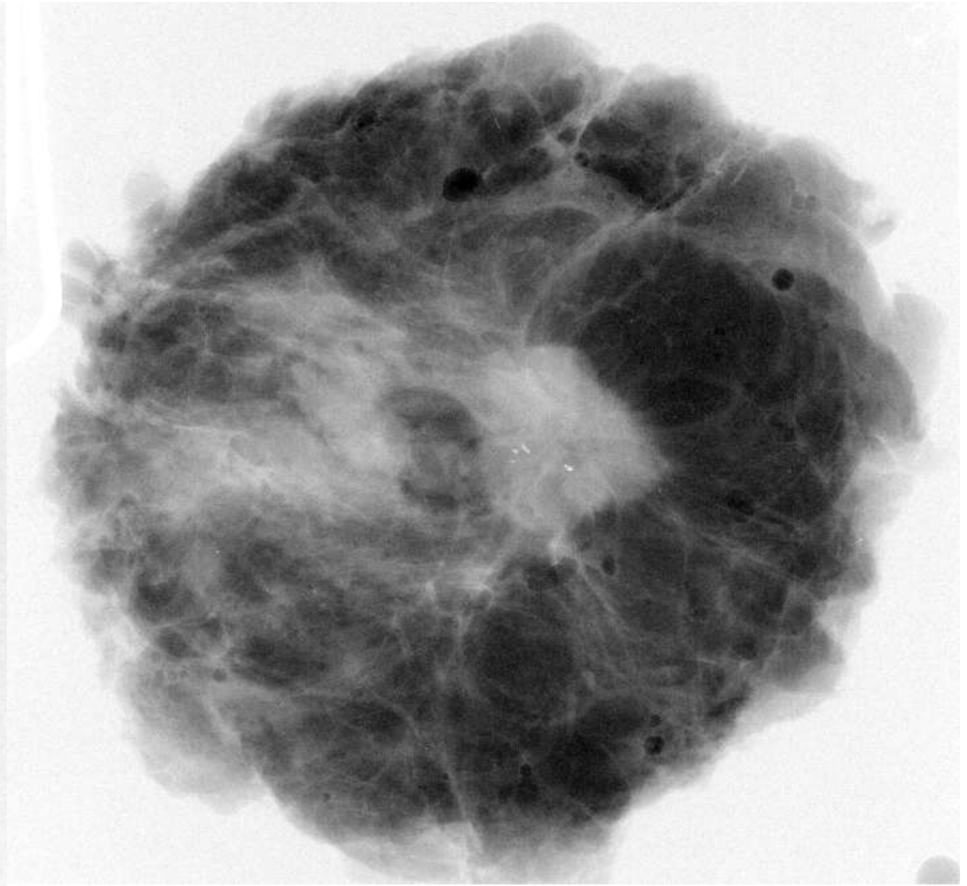
The three-dimensional arrangement of femur and blood vessels was estimated from X-ray stereo angiography.
The 3D quality is far from X-ray CT but sub-second time resolution possible



Phase Contrast in the Clinic



Conventional Image



Phase Contrast (Monash Geometry)

Ivan Williams et al European Journal of Radiology 68S (2008) S73–S77

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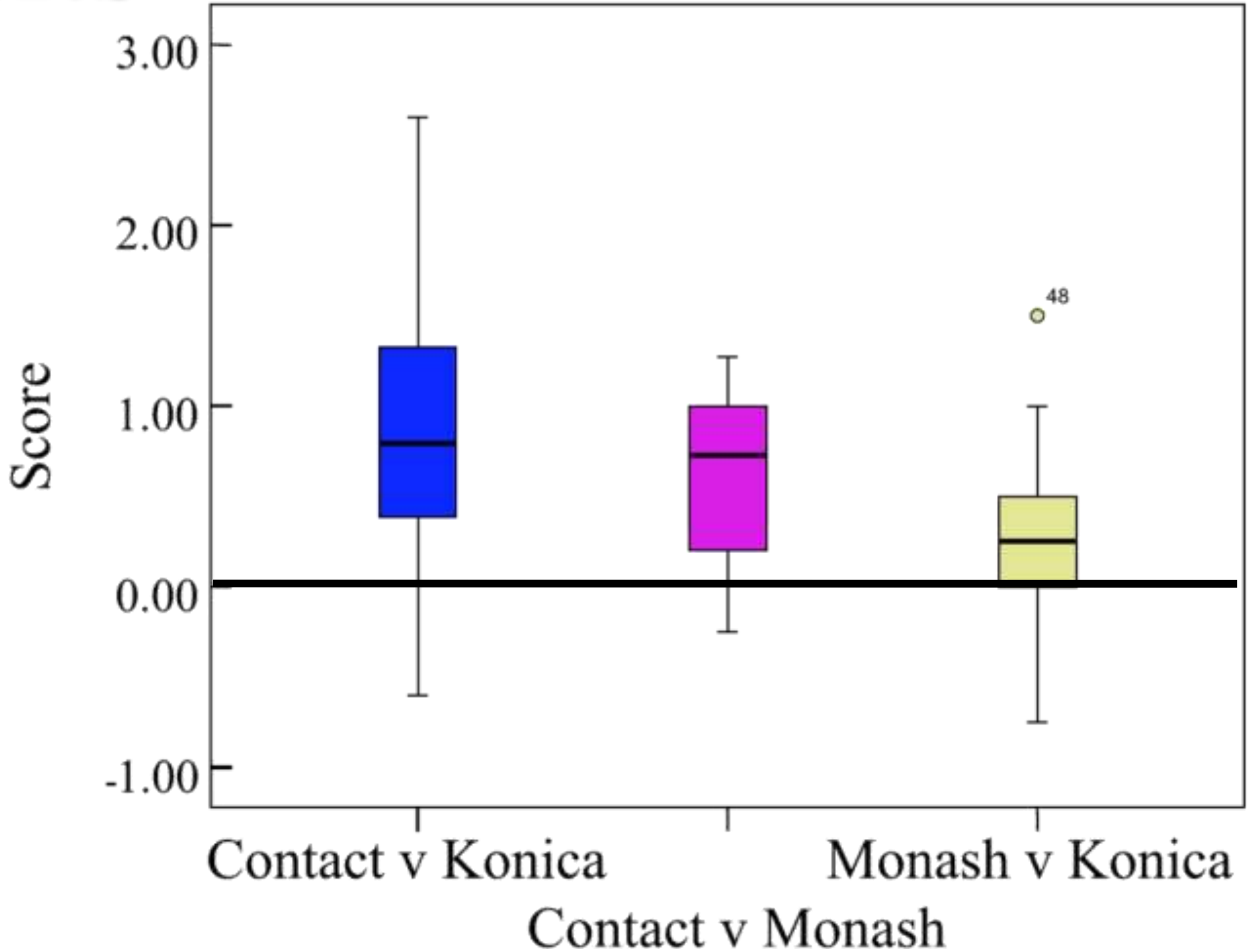
Results



Box-and-whiskers plot of the raw data averaged for each scorer for each of the three scoring comparisons, a positive score indicates that the second of the two geometries involved in the comparison was scored to advantage. The horizontal line within each box denotes median, box covers 25th percentile, whiskers denote the greater of 3.5 times 25th percentile and outer most point.

The two left-most show that two PCI geometries scored better than the Contact. The bar on the right shows that the Konica geometry was scored better than the Optimised. The single data point at 1.4 in the Optimised vs Konica comparison is an extreme outlier more than three standard deviations from the median.

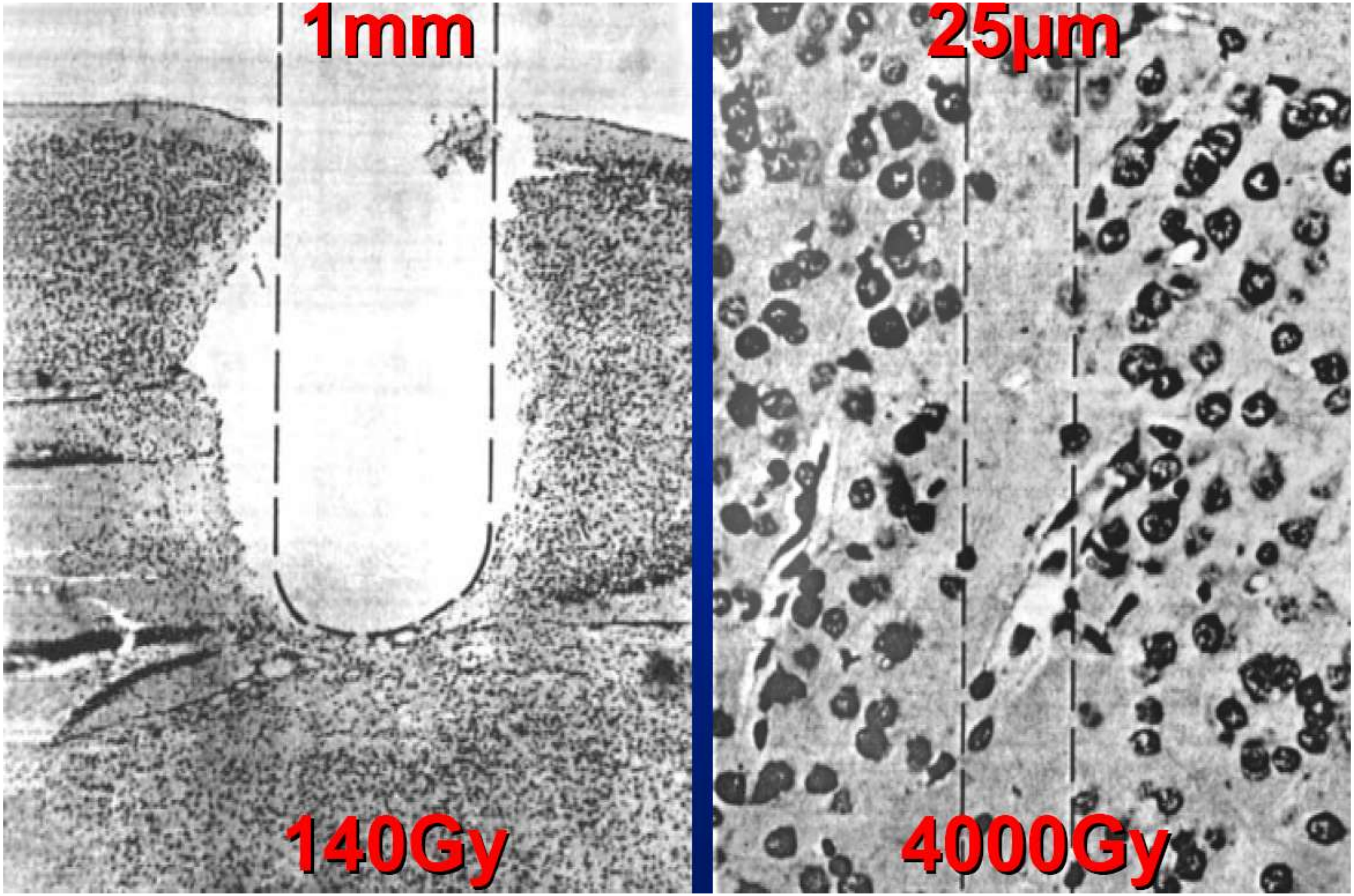
Radiotherapy

- The tumour can always be destroyed……
- …If we give it enough dose
- The question is…..
- ...Can we keep the patient alive and healthy whilst we do it?
- The radiation dose we can give to the tumour is limited by…..
- ..How much dose healthy tissue can tolerate whilst we try to zap the tumour

Radiotherapy

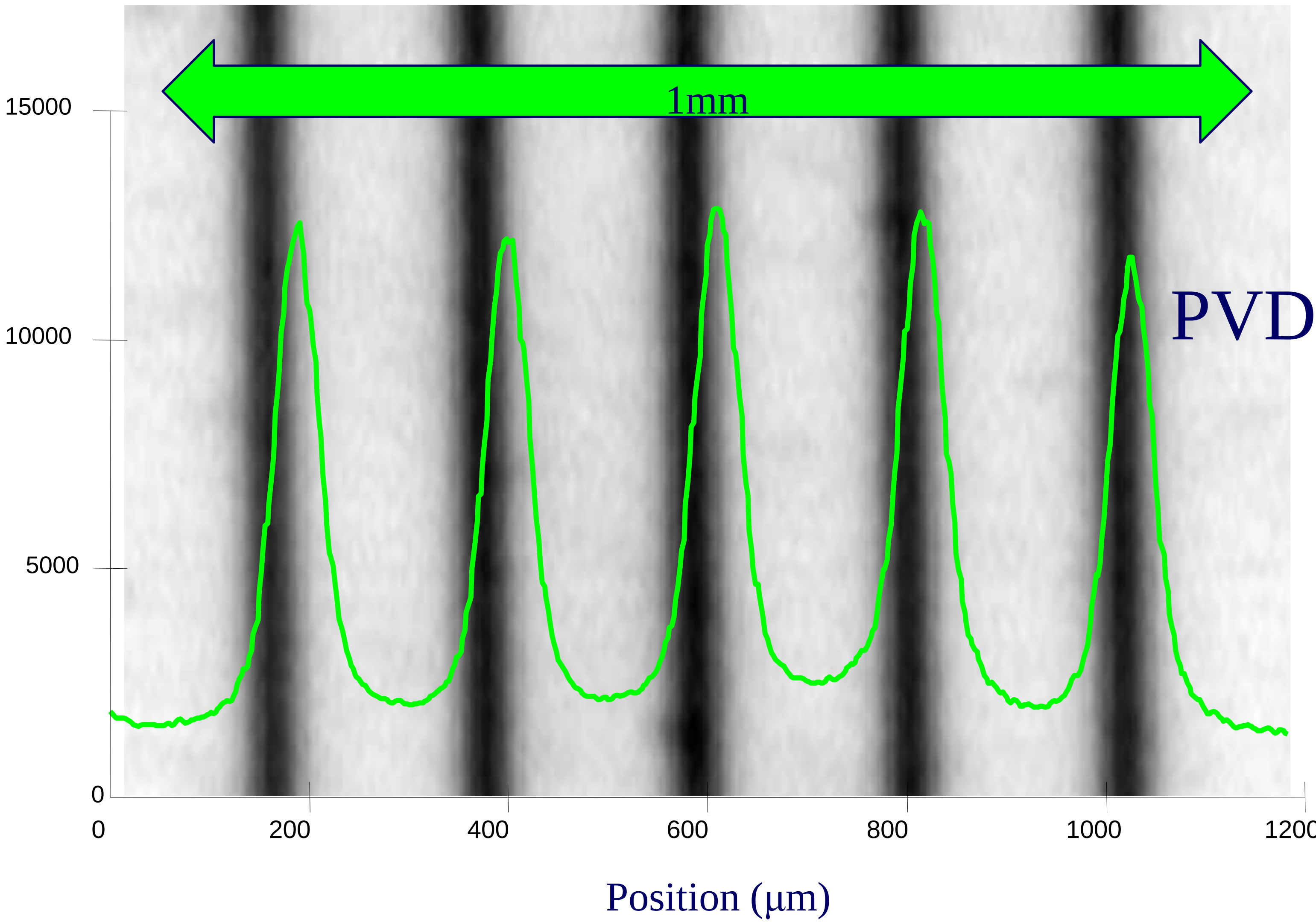
- The radiation dose that can be delivered to the tumour is limited by…..
- ..The tolerance of the surrounding healthy tissue
- Conventional Therapy
  - Uses a LINAC (high energy X-rays several MeV)
  - Uniformly irradiates tumour

Deuteron Beam: Mouse Visual Cortex



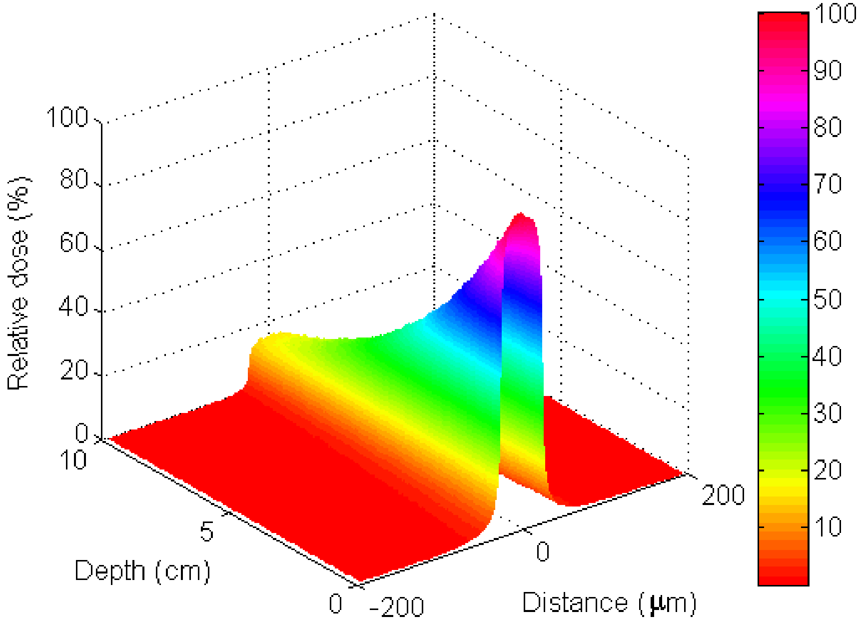
Zeman et al, Radiat Res 15 (1961) 496

Peak to Valley Ratios



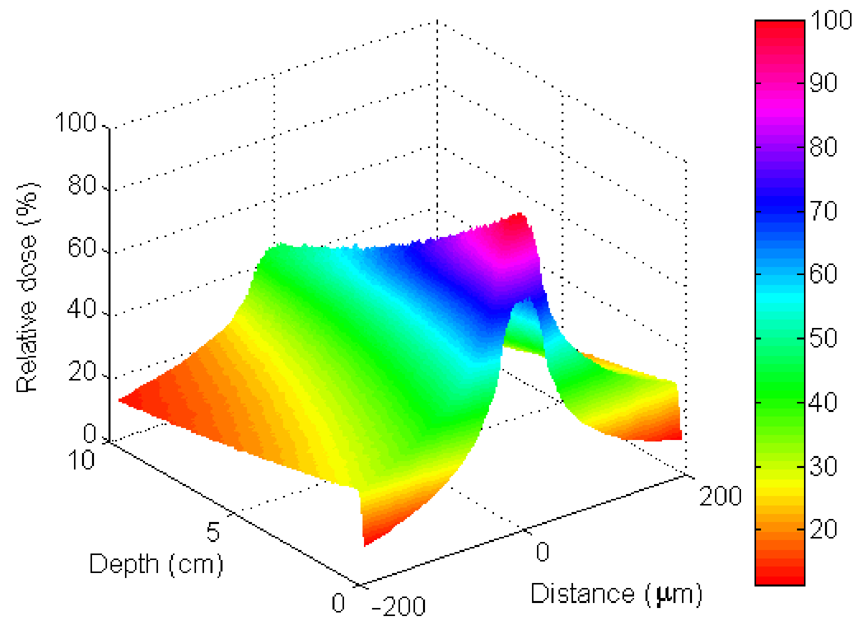
PVDR ~ 50

Dose Depth Curves



Synchrotron Spectrum (~100keV)

1 MeV



Loss of Pattern with Depth

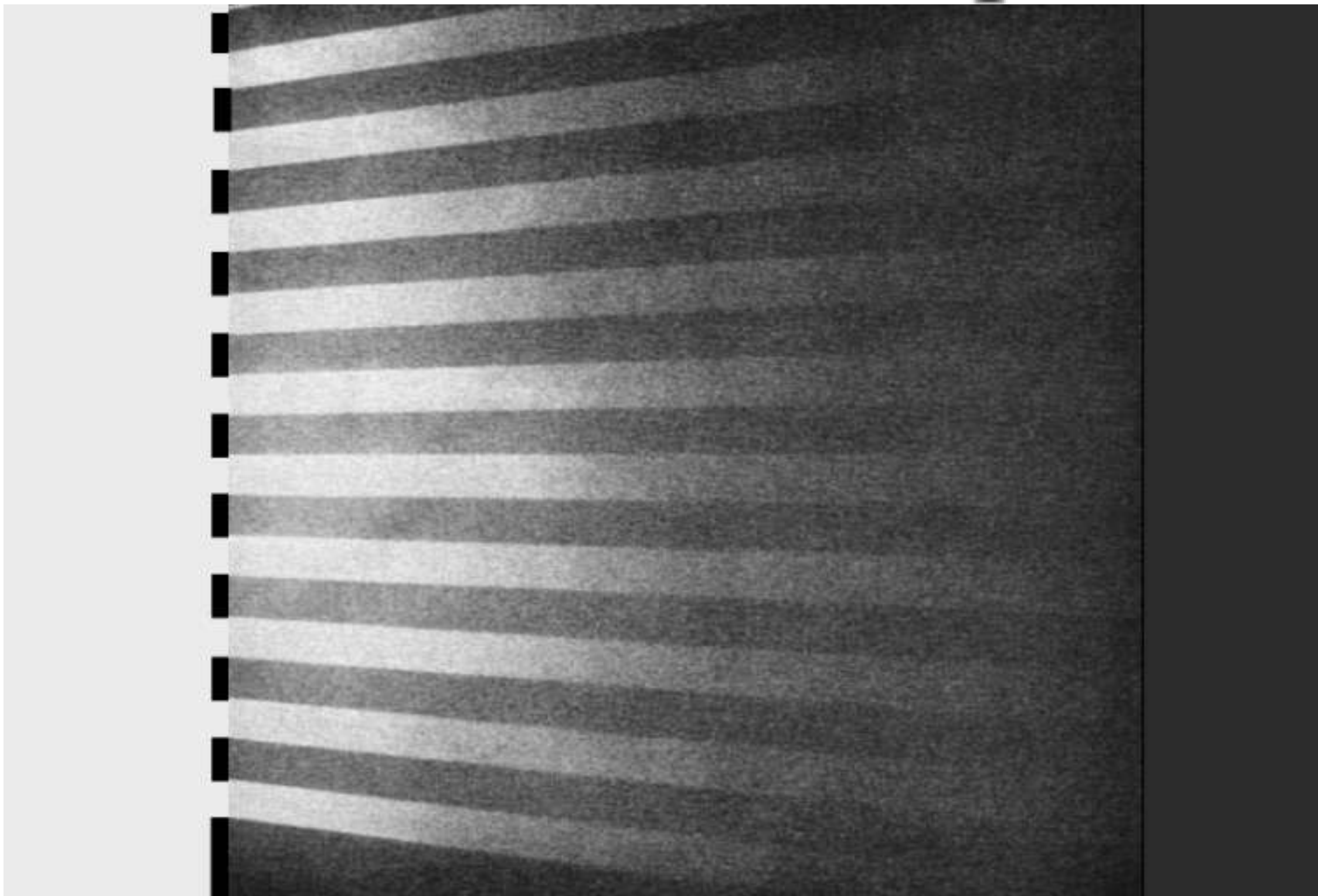
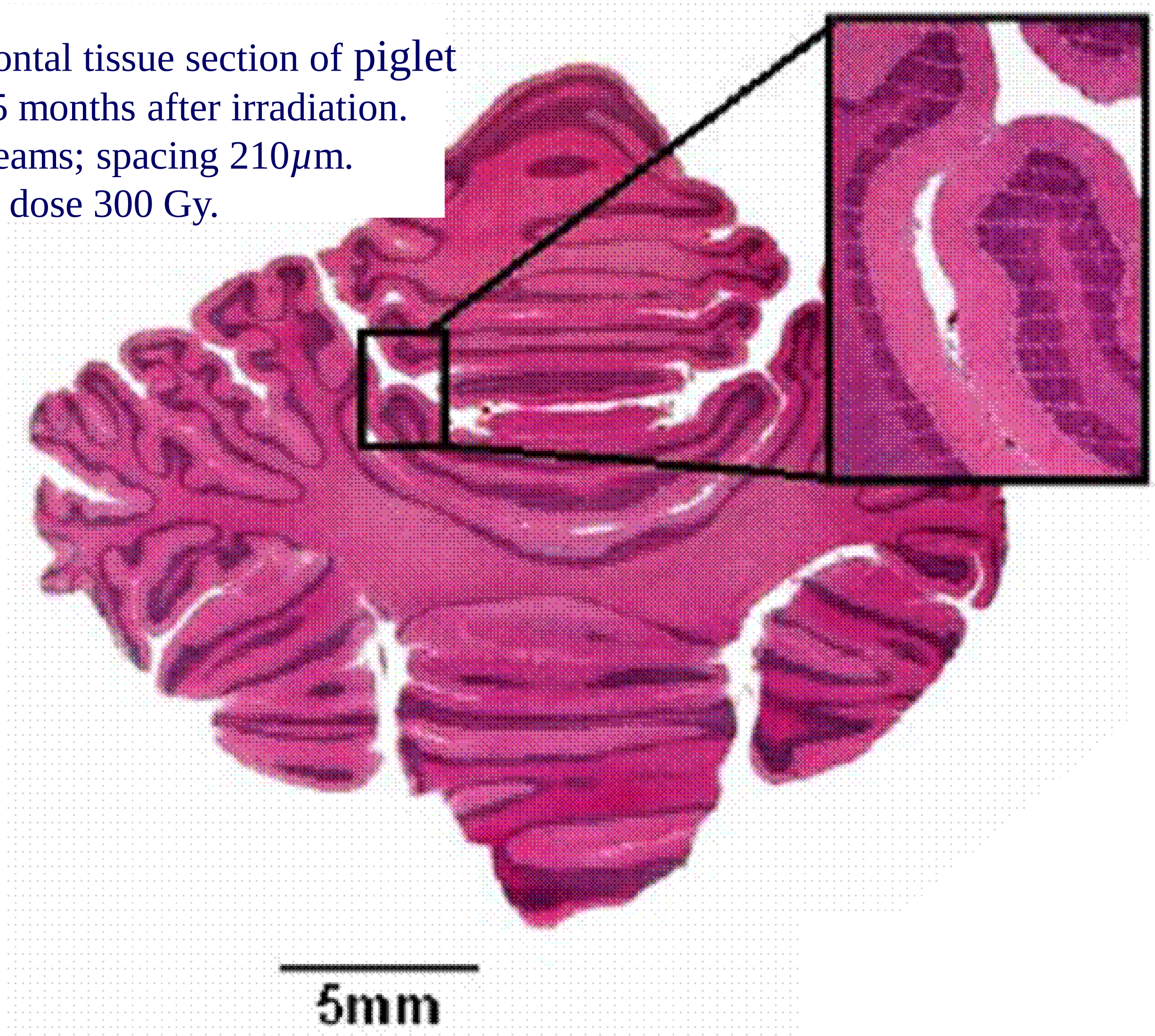


Fig. 43. Shafts of radiation through sieve fields showing divergence and obliteration of sieve pattern in depth

Jolles, 1953

Piglets

Stained horizontal tissue section of piglet cerebellum 15 months after irradiation. 25μm wide beams; spacing 210μm. Skin entrance dose 300 Gy.

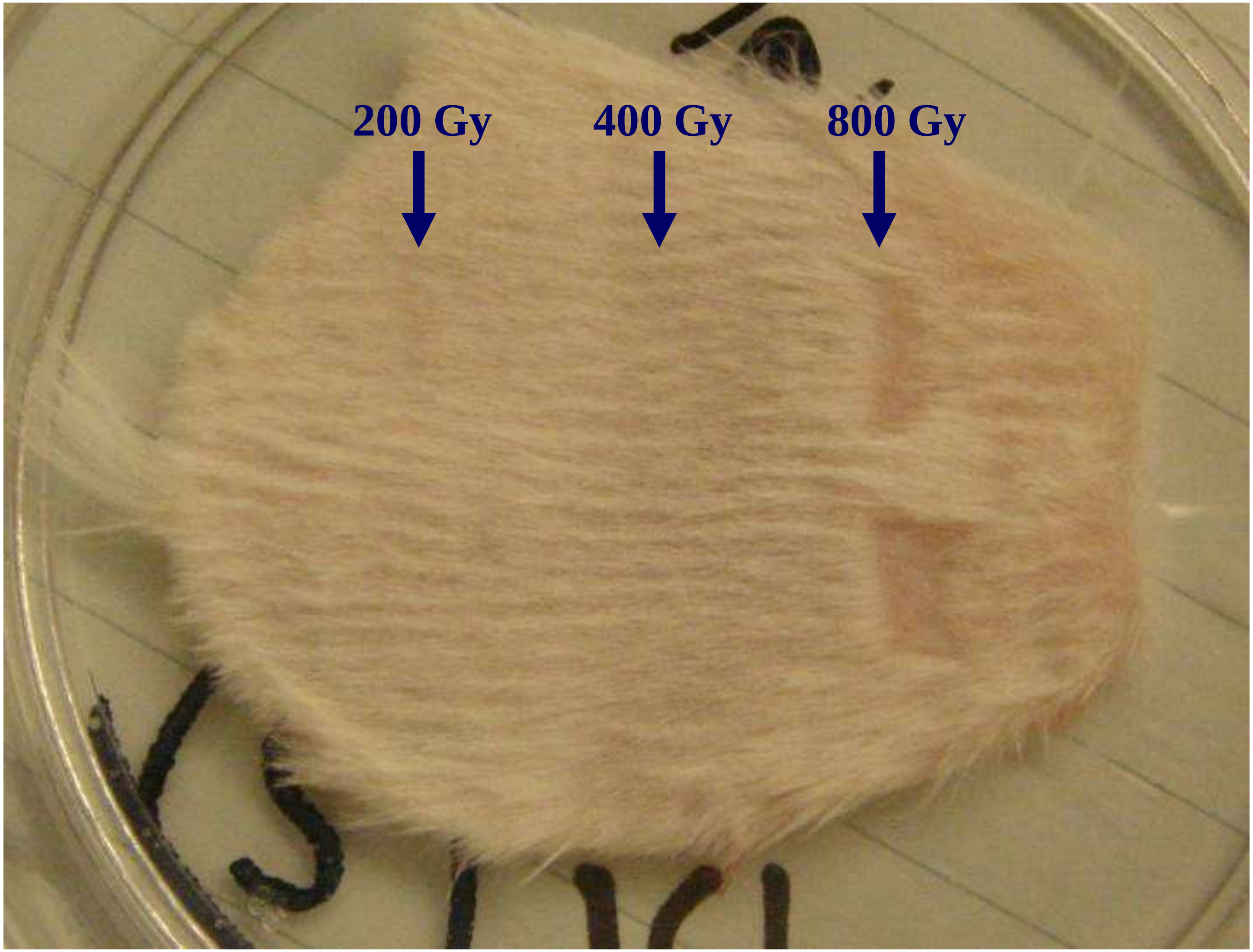


Laissue J A *et al* 2001 *Proc. SPIE* **4508** 65–73

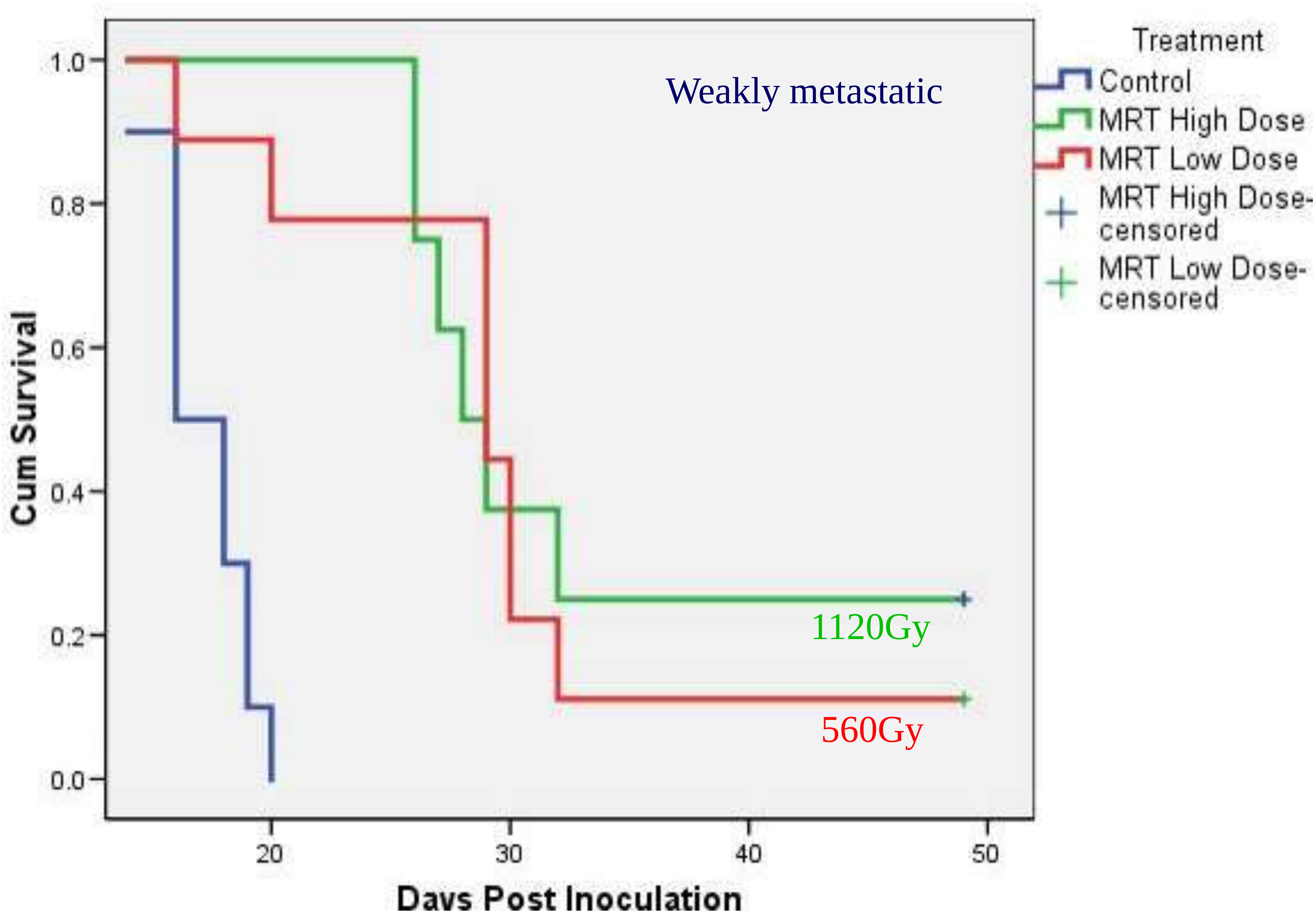
MRT on Mice

- Radiobiology of MRT is not well understood
- An understanding of the radiobiology is crucial for the optimisation of MRT and for any clinical implementation
- Understanding MRT will also inform conventional radiotherapy
- Mice are by far the best characterised mammal
  - Many GM mouse models already available
  - Many assays have been developed

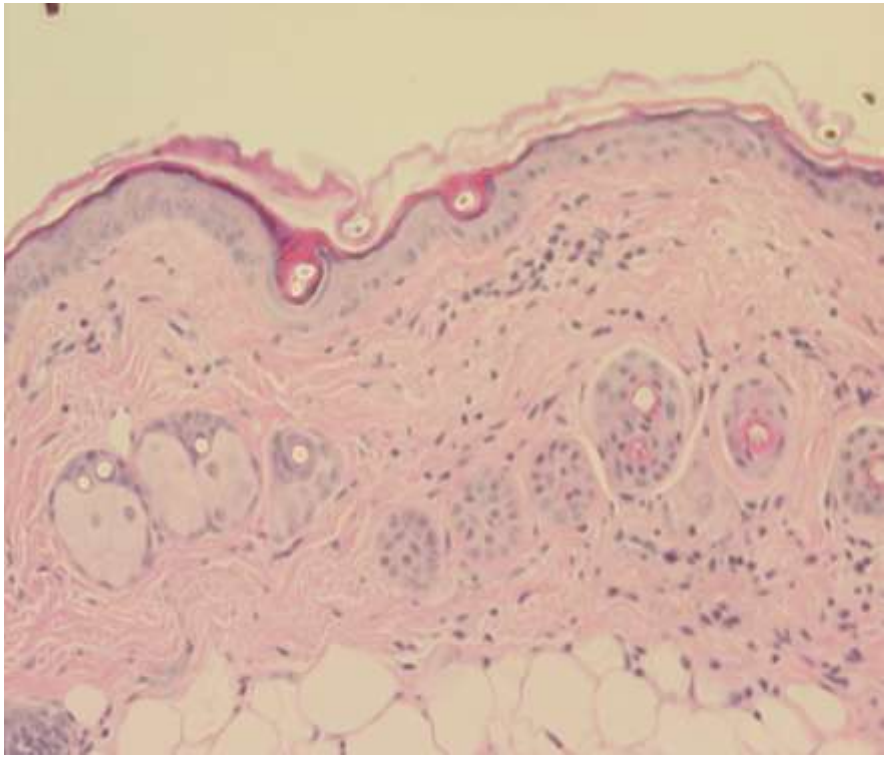
Exfoliation

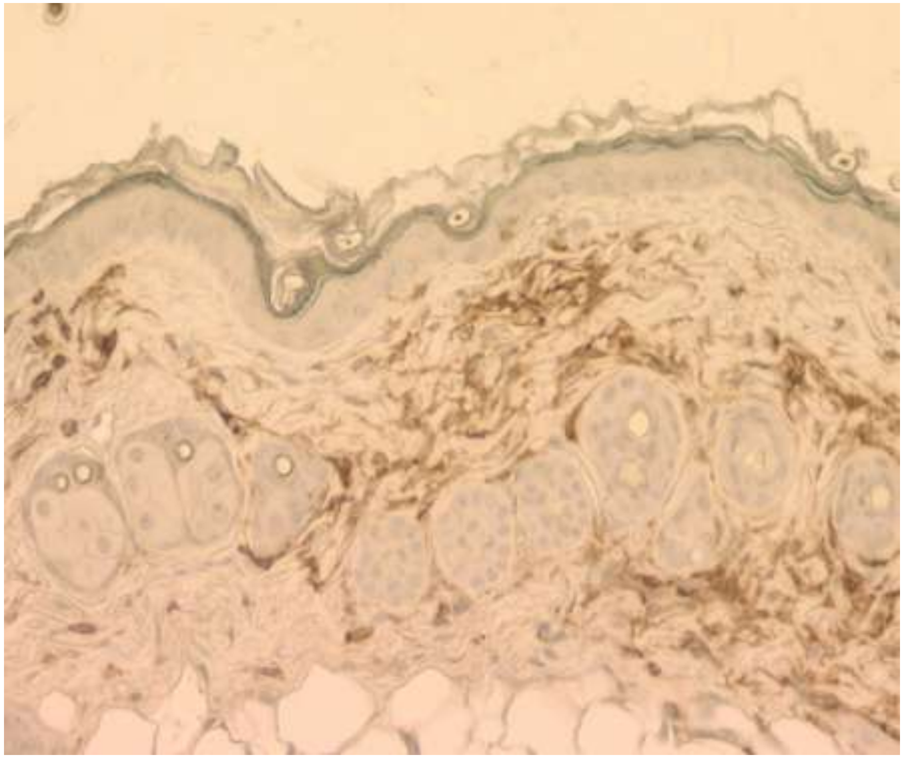


Survival Fractions EMT 6.5



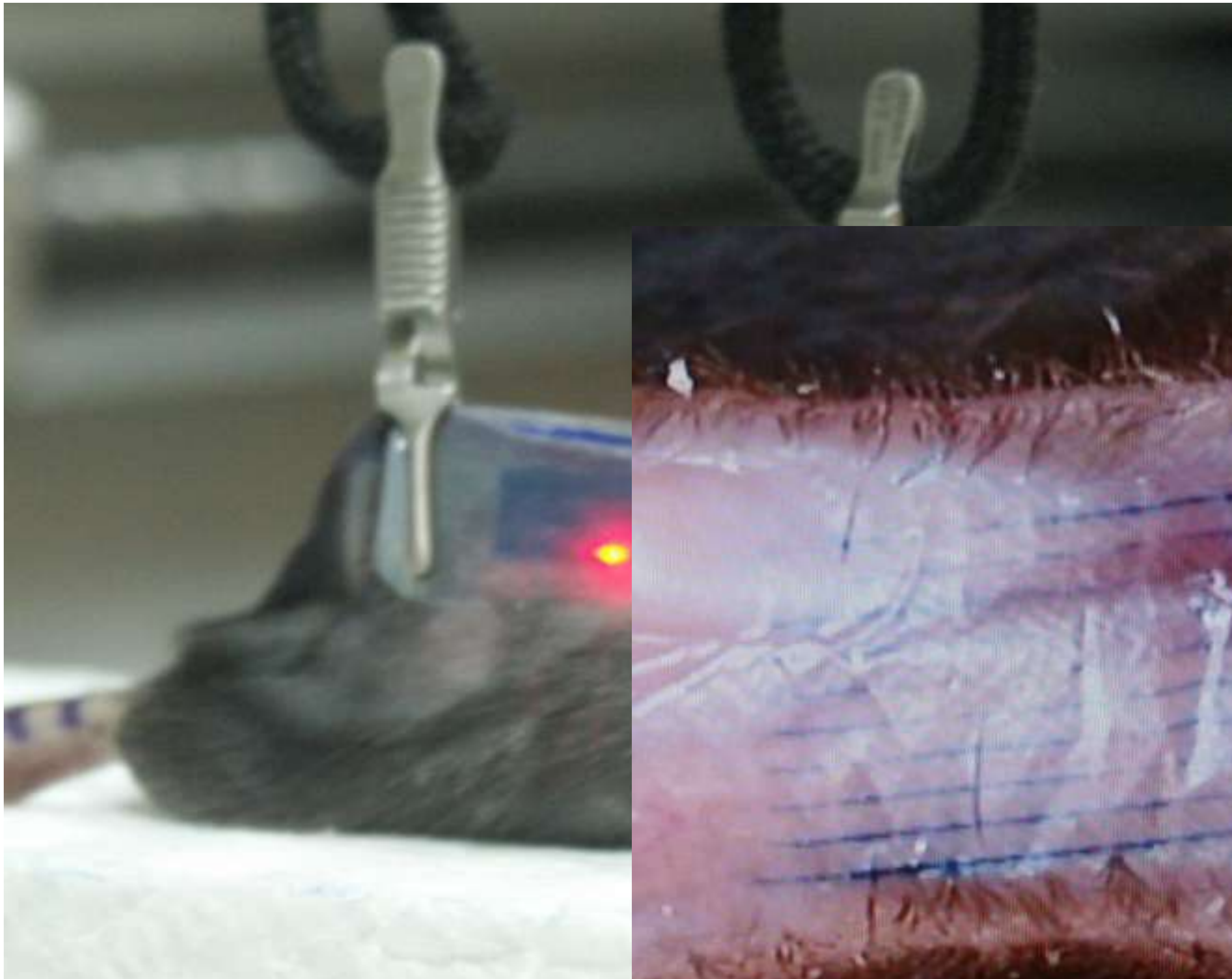
Results - Immunohistochemistry





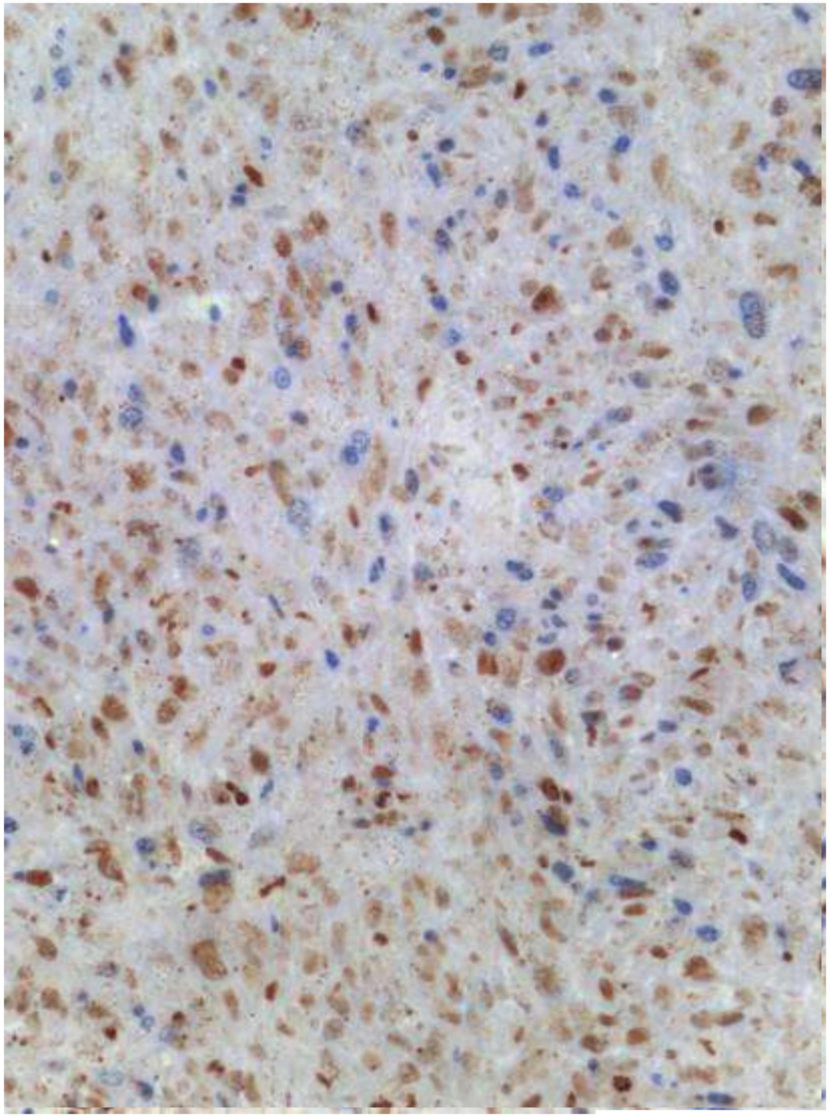
- H&E and CD45 Leukocyte Common Antigen (LCA) Staining of MRT-irradiated Mouse skin 5.5 days PI   (x 100)
- Intact hair follicles & sebaceous glands

Using Radiochromic Film to Locate Microbeams

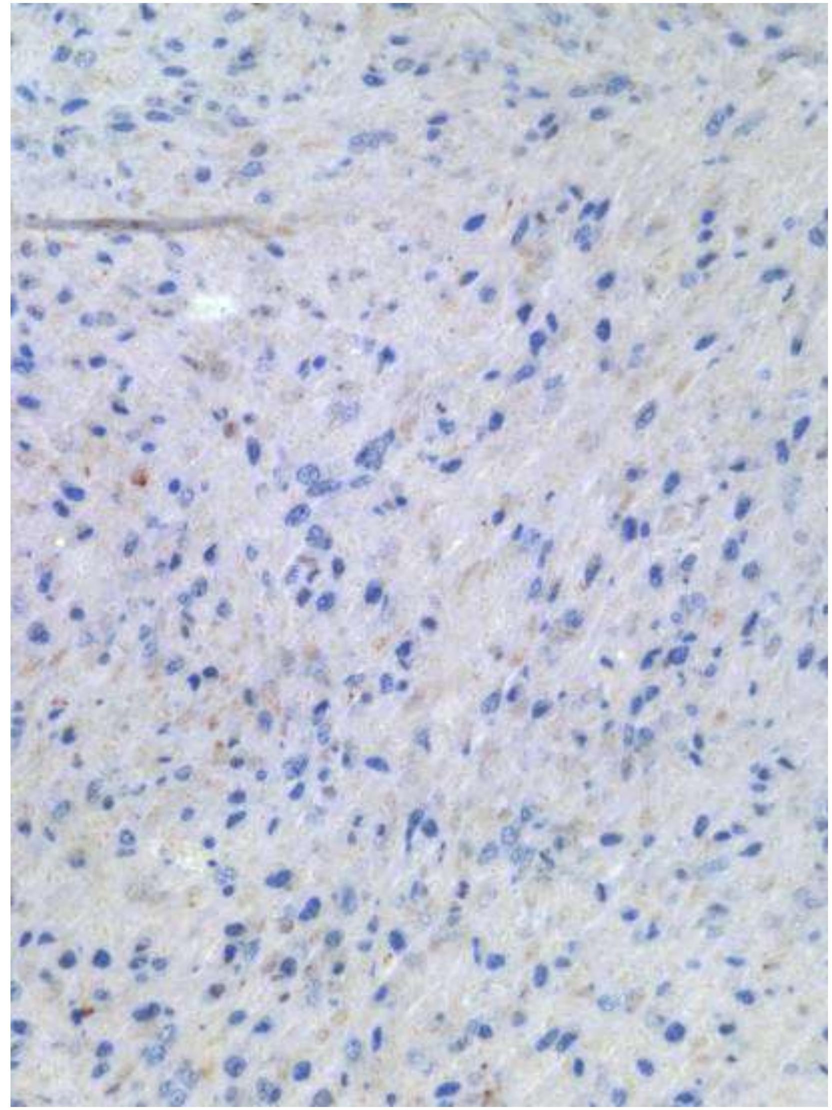


γH2AX/BrdU IHC post 560 Gy

MRT treated



Control



48 hours after irradiation

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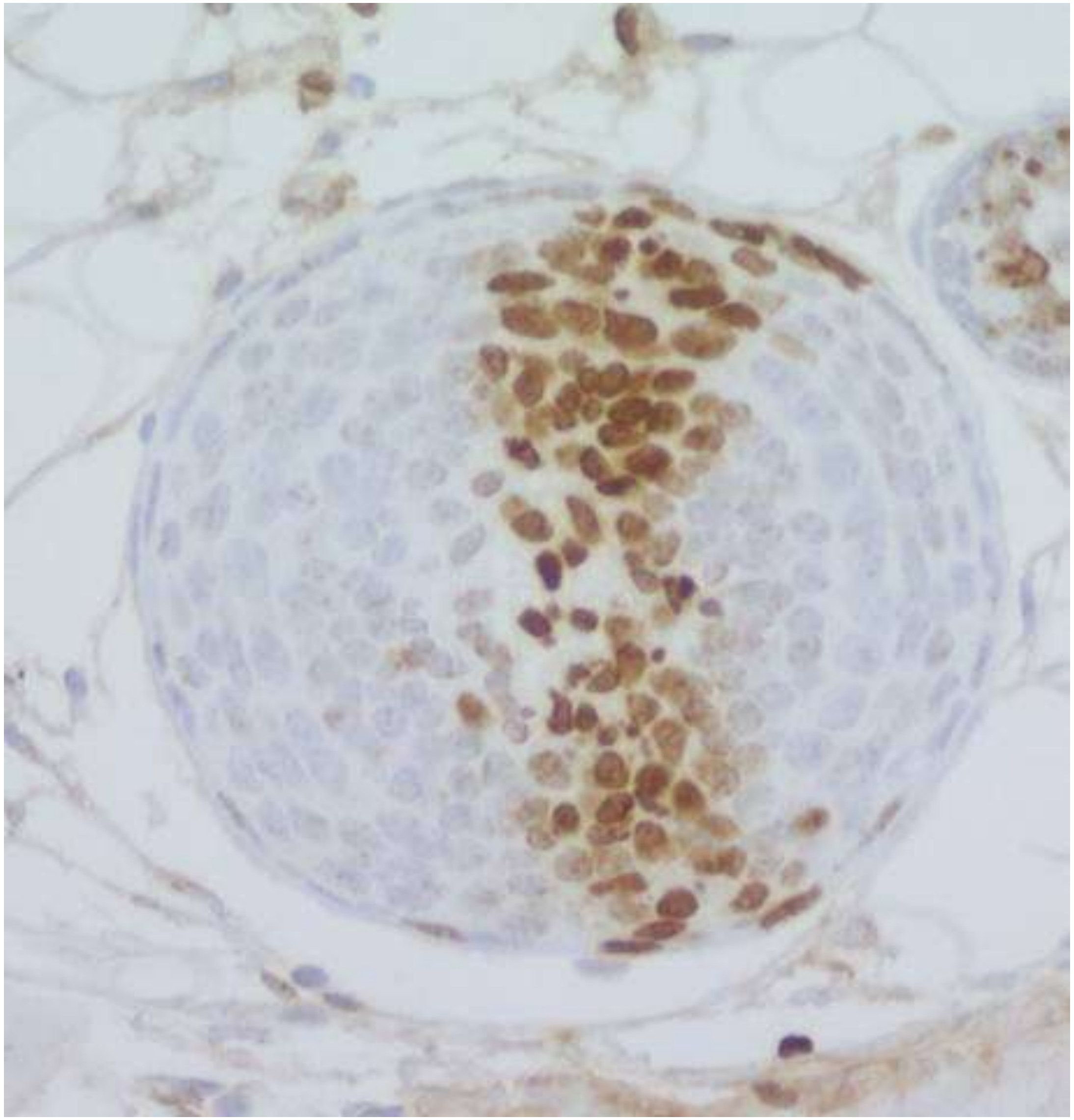
Jeff Crosbie, Peter Rogers, Robyn Anderson, Rob Lewis

Splitting Hairs!



Conclusions

- X-rays are here for a while
- Synchrotrons have an important role in developing new x-ray methods in medicine
- In order to translate the research into the clinic, some human studies are necessary
- Much can be achieved with animal studies

The Team

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- Beth Allison
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- Arjan te Pas
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- David Parsons
- Peter Rogers
- Jeff Crosbie