Imaging and Radiotherapy with Synchrotron X-rays

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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)
Diagnostic Imaging in Australia

- Ultrasound: 34.4%
- Nuclear Medicine: 2.5%
- CT: 11.4%
- MRI: 2.8%
- Diagnostic Radiology: 48.9%

Uses Radiation: 62.8%
X-ray & CT: 60.3%
MRI-CT Comparison

- MRI not always best contrast

MRI

■ Fabulous Images but

■ Cost:
  ♦ **CT**: From $700 to $2,200
  ♦ **MRI**: From $1200 to $4000

■ Time taken for scan:
  ♦ **CT**: Usually completed within 5 minutes
  ♦ **MRI**: Typically 30-40 minutes

■ Narrow tunnel and noisy

■ Metal implants and pacemakers contraindicated
MRI Accidents
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!
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
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.)
Imaging Using Ionising Radiation

- Will be here for a long time because it;
- Can perform very fast scans
- Can tolerate implants
- Is relatively cheap
- So what is the risk from all this radiation?
Fluence and Dose: Head

All the red area stops in the head i.e. Dose!
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

- 11 March 2011, Tsunami hits Fukushima. Radiation ~210mSv/yr
- On 31 May, 2011 Fukushima prefecture dose rate was 13mSv/yr
  - 7.5 years to reach 100mSv

- It takes most radiation-induced cancers 10 to 20 years to develop in adults
- The average lifetime risk of developing cancer from all causes is 42%
- From early 1980s to 2006, 7× increase in population dose from medical procedures
Trends in Radiation Dose from Medical Imaging

Early 1980s

- Background (83 %)
- Medical (15 %)
- Occupational / industrial (0.3 %)
- Consumer (2 %)

Collective effective dose (person-Sv)
- Early 1980s: 835,000
- 2006: 1,870,000

Effective dose per individual in the U.S. population (mSv)
- Early 1980s: 3.6
- 2006: 6.2
3rd Generation CT Scanner

- Multiple detectors
- Translation-rotation
- Large fan beam
- Patient stationary for each 2-D slice acquisition; about 0.1 seconds per slice
- $kV = 120$, $mA = 500$
- Image then reconstructed in about 0.1 seconds
Volume CT image

Uses 3rd or 4th generation scanner.
Continuous patient motion.

Often with multi-slice detector arrays.
Affords “true” 3-D volume images.
Back Projection in Practice
Beam Hardening

![Graphs showing Beam Hardening](image-url)
Beam Harding Artefacts

uniform
Cone Beam Artefacts

Tube at 0°

Tube at 180°

z-axis

Inner detector row image

Outer detector row image
Exploit What Synchrotrons Are Good At

- So there is still work to do optimising imaging with ionising radiation
  - Eliminating artefacts
  - Reducing Dose

- 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
  - Synchrotron beams can be tuned
    - Select optimal energy

- We can do studies of better x-ray imaging and develop new methodologies
Subtraction Radiography

Synchrotron

Specialised monochromator

Scanning motion

2 detectors

High

Energy (keV)

32.8 33.0 33.2 33.4 33.6

Absorption

Energy vs Iodine

Energy vs Bone

Energy vs Soft tissue

Energy vs Beams

E1 E2

33.17 keV

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

Synchrotron IV injection
n.b. 2 – LAO 40

Conventional angiography
Intra arterial injection
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
Synchrotron Radiography

- Synchrotron
- Monochromator
- Scanning motion
- Scattered radiation
- Detector
Slot Scanning Image Scores

Dose decreases with energy!

Fit of the form \[ \text{Score} = A + \frac{B}{\sqrt{Dose}} \]
Refraction
Analyser Based Imaging

Sometimes called Diffraction Enhanced Imaging
Crystal Rocking Curve

Relative Intensity $I/I_0$

Low Angle Side

High Angle Side

Analyzer Angle ($\mu$radians)

$\delta z \sim 0.4 \mu$rad

$\Delta I \sim 0.1$
Rocking Curve

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

Analyzer Angle (μradians)

Relative Intensity /Io

Energy = 25keV
 ABI Mathematics

- $I_L$ & $I_H$ = Intensities on low and high angle sides of rocking curve
- $\text{Grad}_L$ & $\text{Grad}_H$ = Gradients of low and high angle sides of rocking curve
- $I_R$ is intensity
- $\Delta \theta_Z$ = refraction angle

Given

$$I_L = I_R \cdot (R_L + \text{Grad}_L \cdot \Delta \theta Z)$$
$$I_H = I_R \cdot (R_H + \text{Grad}_H \cdot \Delta \theta Z)$$

Find $I_R, \Delta \theta Z$ →

$$\left( \frac{\text{Grad}_H \cdot I_L - \text{Grad}_L \cdot I_H}{\text{Grad}_H \cdot R_L - \text{Grad}_L \cdot R_H} \right)$$
$$\left( \frac{I_H \cdot R_L - I_L \cdot R_H}{\text{Grad}_H \cdot I_L - \text{Grad}_L \cdot I_H} \right)$$
TOR Mam Conventional

Simulated breast tissue

Spectrum = Mo:Mo 28kVp
TORMAM Peak

Energy = 20keV
TORMAM Refraction

Energy = 20keV
Advantages of synchrotron micro-CT

SkyScan 1072 (Desktop) 7 μm

Spring8 (Synchrotron) 12 μm

12 hrs

0.5 hrs

David Cooper, UofS; David Thomas, Melbourne
Mouse CT

David Parsons and Karen Siu
Mouse Cochlea
Mouse Fly Through

Kaye Morgan, Karen Siu, David Parsons
Phase Contrast

- **Contact:** $N_F \gg 1$  **Geometric approximation**
  - The intensity distribution is a pure absorption image.
- **Near field:** $N_F \gg 1$  **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.

$$N_F = \frac{d^2}{\lambda z}$$
Propagation Based Imaging
Phase Contrast CT

Lungs of newborn rabbit
Propagation distance = 1m
Energy = 24 keV

Phase Contrast CT

- SNR increased 10x, enabling high quality visualization

Brain undetectable in projection image (a), and faintly visible with 5m propagation distance (b) in CT reconstruction. Energy = 24 keV.

Phase retrieval renders structures of the brain highly visible against the noise. Improvement in SNR of 200x!
Phase Contrast: Mouse Embryo

Absorption CT

Phase CT
Phase Contrast: Mouse Embryo

6 days

6 & 9 days: 4.9µm/pixel
10-15 days: 23.5µm/pixel

9 days
10 days
11 days
13 days
15 days

Hoshino M et al Biology Open 1, 269–274
Phase Contrast: Mouse Embryo
Synchrotron Brain Imaging

3600 projections
3m propagation distance
1s/image

K Uesugi & M Hoshino JASRI Spring-8
Phase Contrast: Brain
Synchrotrons allow fantastic spatial resolution but…….

\[ Dose_{\text{skin}} = \frac{2e^{\mu L} SNR^2_{\text{out}}}{DQE(f) \mu^2 \text{size}_{\text{obj}}^4 \text{Contrast}^2_{\mu}} E_{\gamma}(\frac{\mu}{\rho}) \]
Phase Contrast Dose Advantage

Image Score

Mean Glandular Dose (mGy)

Synchrotron AB phase contrast

Synchrotron Slot scanning

60%

50×

Conventional

Complex Refractive Index

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

\[
\eta = 1 - \delta - i\beta
\]

Where \(\beta = \text{absorption}\)
\(\delta = \text{phase shift}\)

\text{Nb.}
\delta \sim 1000 \beta \\
\delta \sim E^{-2} \\
\beta \sim E^{-4}
Aim of the study: to prospectively evaluate on a limited number of selected patients the diagnostic contribution of SR Phase Contrast mammography in patients with doubtful or suspicious breast lesions identified at the conventional mammography in the Hospital Clinical Mammography at ELETTRA (Trieste, Italy)

Examination room for SR mammography

Phase 1: March 2006 - December 2009 (71 patients) screen-film system, first protocol for recruitment

Phase 2: in 2012- Image Plate detector, Fuji FCR Capsula XL II

Phase 3: from 2013- digital detector, new recruitment protocol

THE COLLABORATION
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Clinical Mammography at ELETTRA (Trieste, Italy)

RESULTS
Evaluation of lesions and structure visibility: comparing mammography with SR and conventional (hospital) mammography

MSR allows a better visualization, both for the lesions and for the glandular tissue

Hospital mammography identified:
21/40 patients with final benign diagnosis
23/29 pt with final malignant diagnosis

MSR identified:
38/40 patient with final benign diagnosis
25/29 patient with final malignancy diagnosis

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.
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
Phase Contrast in the Clinic

Konica Minolta REGIUS PureView

Phase Contrast
Contact
Development of standing type machine

Measurement: 32 sec
X-ray exposure: 19 sec
Skin dose: 5 mGy

Enhanced spiculations visibility

Conventional mammography

Phase contrast mammography

Z. Wang, XNPIG2012
Birth: An amazing event

- In utero lungs are full of liquid
- At birth lungs fill with air
- The transition is poorly understood
- Preterm and caesarean section infants can have major problems and often need to be ventilated
- We don’t know how to best ventilate and sometimes ventilation injures the lung
SPring-8 - Super Photon ring-8GeV
Why a Long Beamline?
Bronchoconstriction induced by metacholine
Rabbit Pup Lung Imaging - Delivery
Artificial Ventilation
Post Mortem Artificial Ventilation

RA Lewis et al Phys. Med. Biol. 50, 5031
S. Hooper et al FASEB 21, 3330 (2007)
Phase Retrieval: Single Image

- Approximate ‘contact’ intensity from Beer’s Law
  \[ I(r_\perp, z = 0) = I_o \exp(-\mu T(r_\perp)) \]

- Approximate ‘contact’ phase by
  \[ \phi(r_\perp, z = 0) = -\frac{2\pi}{\lambda} \delta T(r_\perp) \]

- Use Transport-of-Intensity Equation (TIE)
  \[ \nabla_\perp \cdot (I(r_\perp, z)\nabla_\perp \phi(r_\perp, z)) = -\frac{2\pi}{\lambda} \frac{\partial}{\partial z} I(r_\perp, z) \]

- Solve for object’s projected thickness using Fourier Derivative Theorem
  \[ T(r_\perp) = -\frac{1}{\mu} \ln \left( F^{-1} \left\{ \mu \frac{M^2 I(Mr_\perp, z = R_2)}{MR_2 \delta |k_\perp|^2 + \mu} \right\} / I_o \right) \]
Phase to Projected Thickness

**Phase image** $R_2=4.26\text{m}, E=33\text{keV}$

**Projected thickness**

Marcus Kitchen, Monash
Lung aeration: Airway liquid clearance

Sodium channels create an osmotic gradient that draws liquid out of airways
Breathing Aerates Lungs

(a) Breathing

(b) Time (secs)

[Graph showing changes in lung volume (mL/kg) with time (secs)]

Δ lung volume (mL/kg)

-1.5
-1.0
-0.5
0.0
0.5

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77245 77250 77255 77260 77265 77270 77275 77280 77285 77290

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(a) Breathing

(b) Time (secs)
Lung aeration: Airway liquid clearance

Inspiration forces liquid out of airways

-P

-P

-P

-P
Medical Relevance

- Respiratory Ventilation
- Positive End Expiratory Pressure (PEEP) used to be excluded from international resuscitation guidelines for ventilating infants due to lack of evidence
- It is now recommended as a direct consequence of this work
Rabbit Pup: No PEEP

RA Lewis et al Phys. Med. Biol. 50, 5031
S. Hooper et al FASEB 21, 3330 (2007)
Rabbit Pup: With PEEP

Te Pas et al Pediatric Research 65(5), 537-541 2009
S. Hooper et al FASEB 21, 3330 (2007)
Effect of PEEP in Ventilated Preterm Rabbits

Tidal volume (mL/kg)

5 cmH$_2$O PEEP

0 cmH$_2$O PEEP
Measuring Lung Motion

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

A. Fouras, et al
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

A. Fouras, S Dubsky et al
Whole Breath Lung Morphology

S Dubsky, A Fouras et al
4D Flow
Simultaneous Phase Imaging and Angiography
Major Problem: Technical

- Static beam greatly limits 4D imaging (x, y, z, t)
Setup for X-ray triscopic imaging

Schematic drawing of X-ray triscopic imaging system (top view)

Beam stopper + attenuator

Si crystal 1

Si crystal 2

Sample

Detector for absorption imaging

Detectors for refraction contrast imaging

X-ray beam

100mm

Picture taken from above of crystals and a sample

Raw three-beam image without sample

Masato Hoshino et al  JSR Volume: 18  Pages: 569-574
X-ray triscopic images of mouse chest

Absorption contrast image measured by single detector

Refraction contrast image measured by three detectors
Synchrotron Pros ‘n Cons

Pros

♦ Tunable Wavelength
  ✓ Contrast specificity
  ✓ Target elements

♦ High Intensity
  ✓ Short exposure times and hence movies
  ✓ MRT

♦ Scatter Reduction
  ✓ Reduced dose, improved contrast

♦ Phase Contrast
  ✓ Reduced dose, improved contrast

Cons

♦ Fixed beam
  ● Rapid CT very difficult

♦ Limited availability

♦ High Price
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

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.
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

- 200 Gy
- 400 Gy
- 800 Gy
Survival Fractions EMT 6.5

Weakly metastatic

Days Post Inoculation

Cum Survival

1120Gy

560Gy
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

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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