Application of computer models for advancement of X-ray breast imaging techniques

Grand Hotel Santa Lucia Napoli

Phase contrast mammography with synchrotron radiation

Alberto Bravin

European Synchrotron Radiation Facility (Grenoble, France)

HORIZON 2020
European Union funding
for Research & Innovation

The European Synchrotron | ESRF

THANKS

To MAXIMA organizers for their kind invitation

To all collaborators

A special thanks to:

- Prof. Paola COAN, LMU, Munich
- Dr. Alberto MITTONE, ESRF
- Prof. T. Peters, London, Canada

WHAT IS A SYNCHROTRON?

"A very large microscope to see deep inside matter"

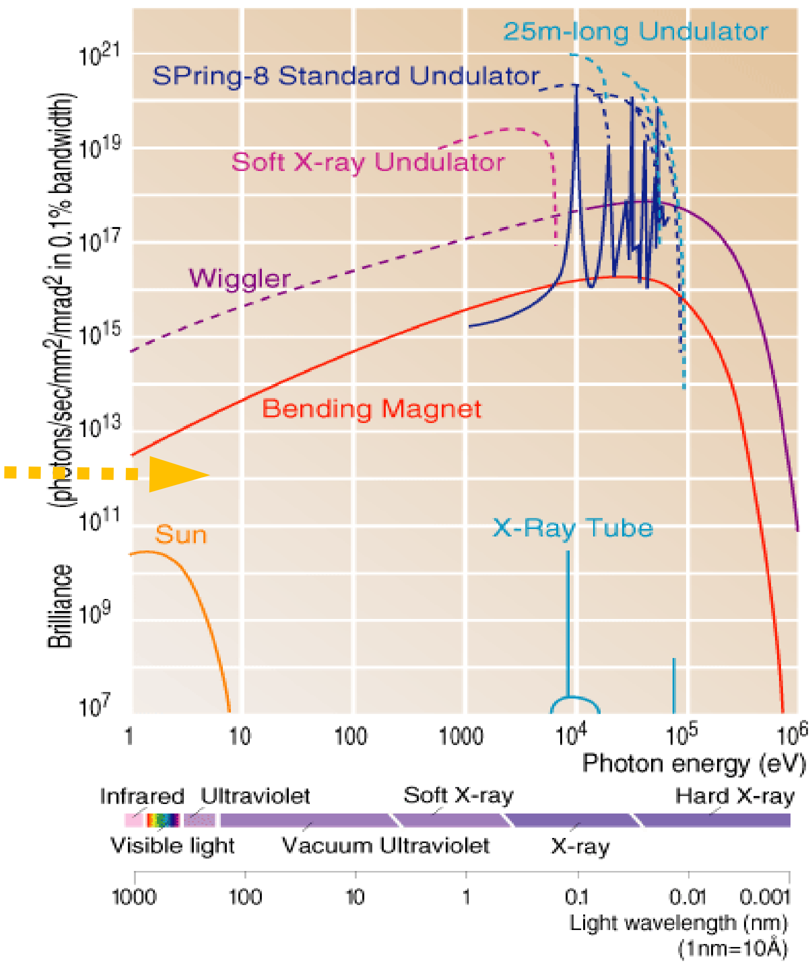
- **A source of X-rays produced by relativistic electrons of special characteristics:**

- **Extremely intense: the most intense on earth**

- **Highly collimated**

- **Brilliant**

- **Tunable in energy**



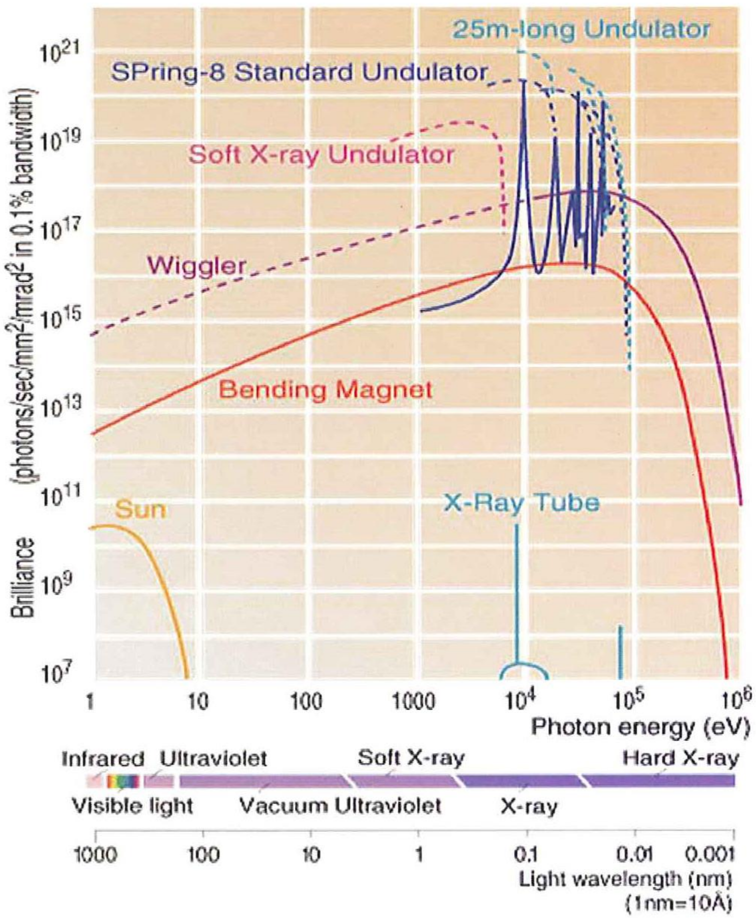
Why is SR interesting for imaging and therapy?

- ~$10^6/10^8$ more intense than medical X-ray generators or LINACS
- tunable monochromatic energy
- parallel beam
- (sub)micrometric spatial resolution

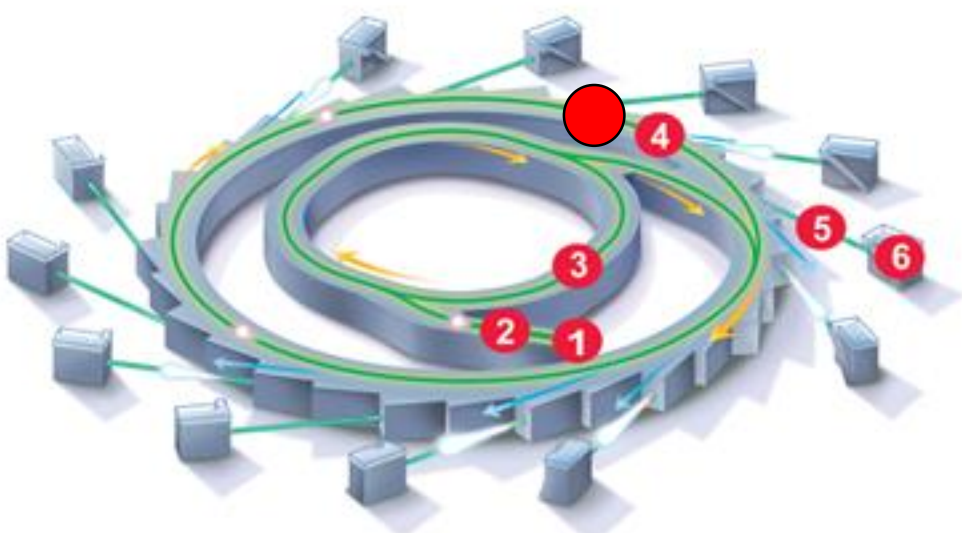
HOW IS A SYNCHROTRON MADE?

SR is a very intense source of radiation from Infra Red to hard X-rays

SR is produced by electrons with relativistic energies circulating in a ring



Synchrotron machine scheme

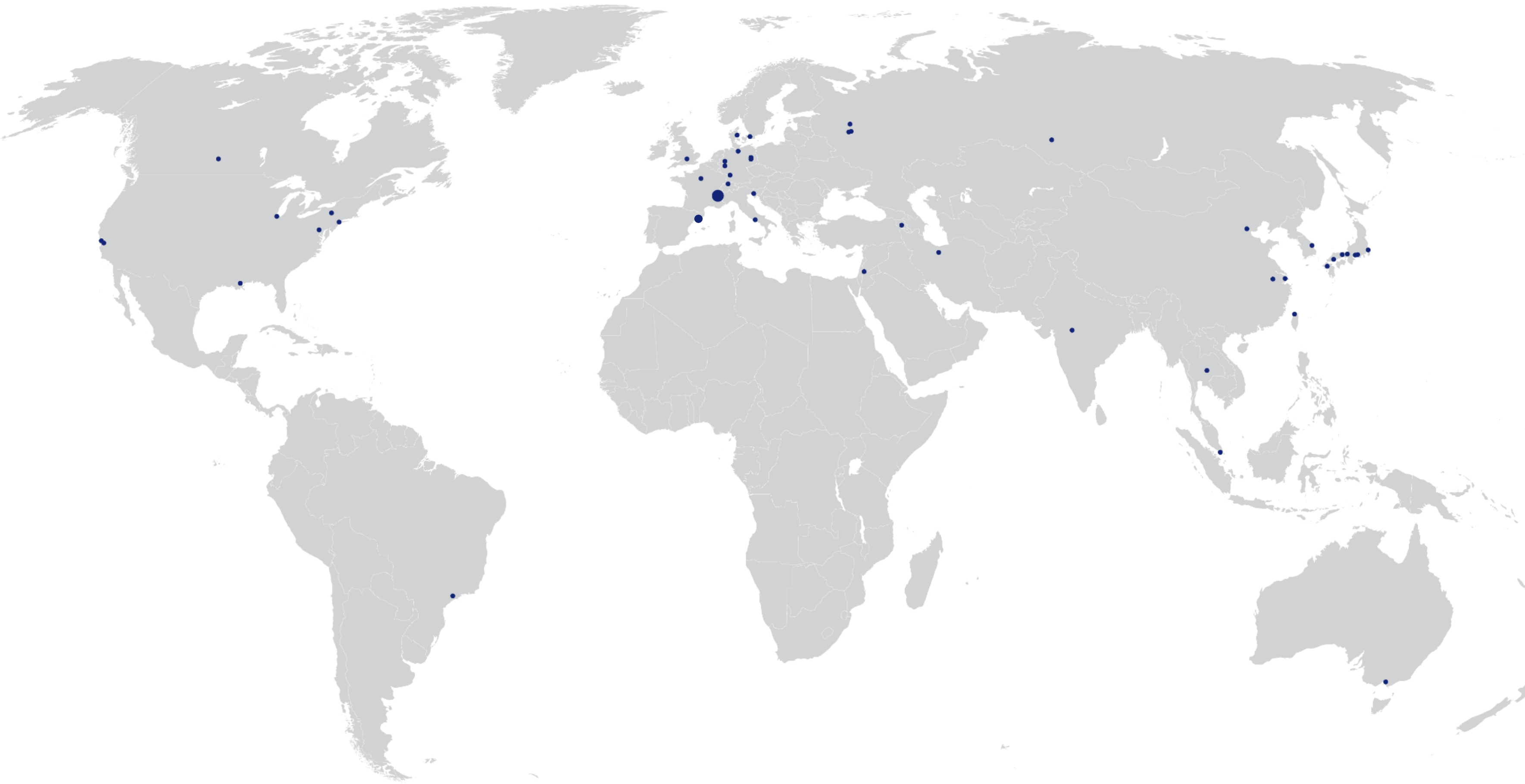


1 injector 2 transfer line 3 booster
4 storage ring 5 beamline 6 exp. station

SYNCHROTRONS IN THE WORLD

3 larger facilities

5 with dedicated medical beamlines



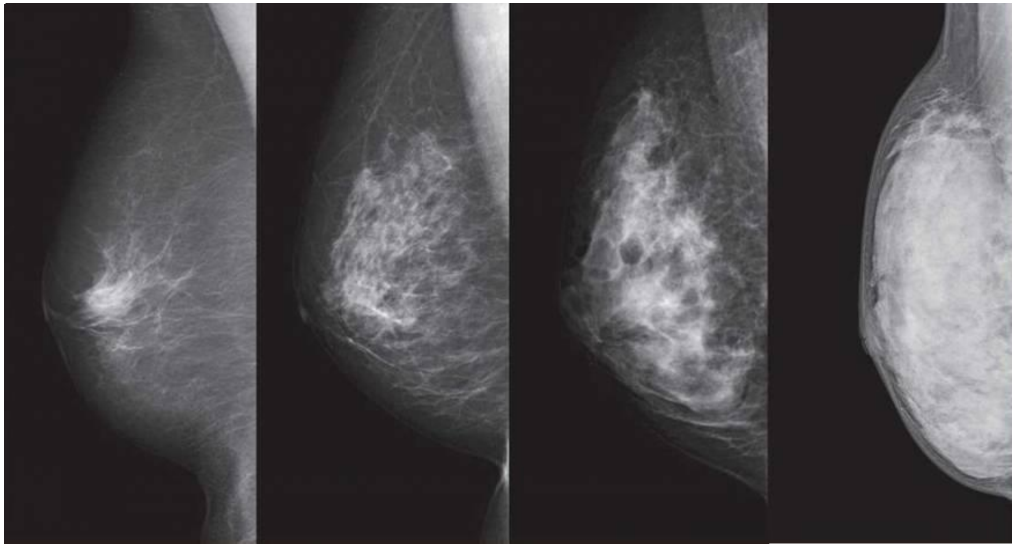
LIMITS OF CONVENTIONAL X-RAY RADIOGRAPHY IN BREAST IMAGING

Breast cancer: First mortality cause for women in western countries

Diagnosis is simple in a fatty breast (radiotransparent)

Fat - Glandular tissues

90%/10% → 10%/90%



Tumors in dense breasts are masked by tissues

Challenges in mammography

" ~10% of palpable malignant tumours are not visible in mammography (dense breast, infiltrating tumors etc)"

- High radiosensitive organ
  --> Possible radio-induced tumors -- > Risk benefit evaluation
- Small difference in contrast between tumor and normal tissues
  -- > need more images, higher doses
- Need of resolutions better/= 40 microns (microcalcifications)
  -- > doses increase with the 1/pixel^2
- Need of better identification of the lesion (2.5D – 3D imaging)
  --> higher doses

SOLUTION STRATEGIES

- **Improve contrast formation**: from absorption to phase contrast imaging
  -- >use improved source or setup (Olivo, Longo, Bravin, Paterno…)

- **Move from 2D to 2.5 and 3D:** vision in depth
  -- > tomosynthesis or CT (K. Bliznakova)

- **Improve detectors** -- > higher efficiency of used dose
  -- > single photon counting (Kalender, Boone, Esposito..)

- **Improve image reconstruction** technique to use fewer X-rays and reduce dose
  -- > use improved reconstruction algorithms (This talk)

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

A software platform for phase contrast x-ray breast imaging research

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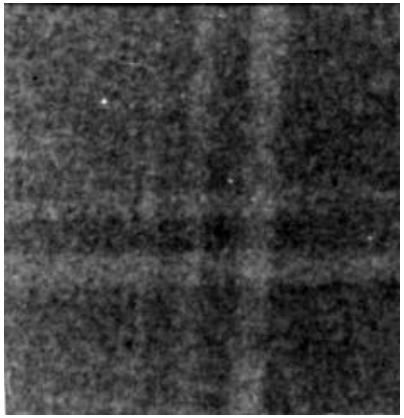
In-line phase-contrast breast tomosynthesis: a phantom feasibility study at a synchrotron radiation facility

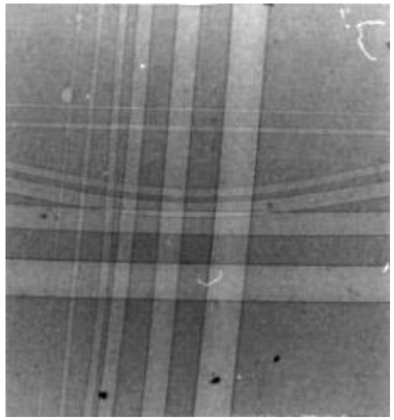
K Bliznakova[1], P Russo[2], Z Kamarianakis[4], G Mettivier[2], H Requardt[3], A Bravin[3] and I Buliev[1]

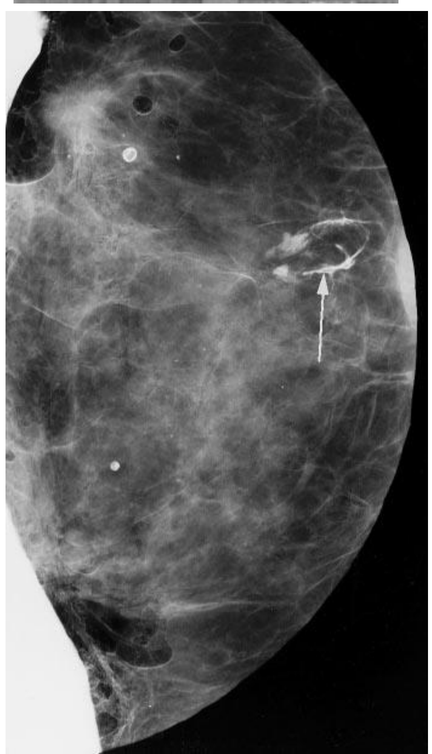
Phys. Med. Biol. 61 (2016) 6243–6263

PHC IN THE 90IES: FROM NYLON WIRES TO FIRST MAMMOGRAPHIES

Conventional radiography | **Phase contrast**







Elettra synchrotron
1997-1998

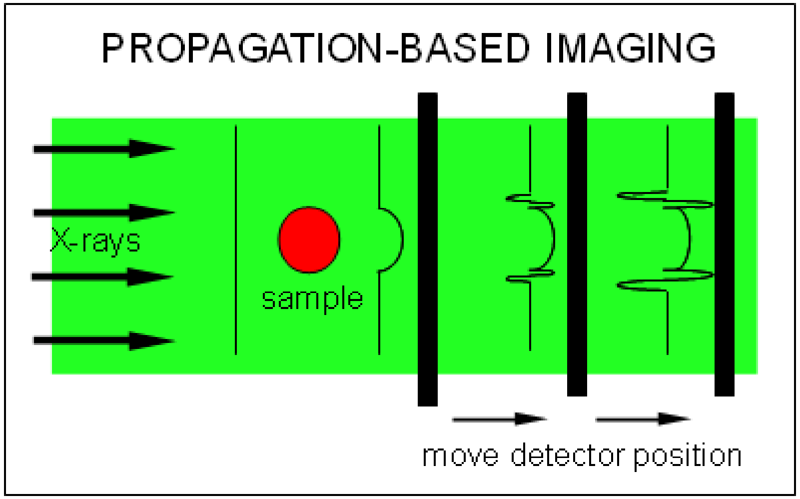
F. Arfelli, A. Bravin et al,
Physics in Medicine and Biology 43, 1998

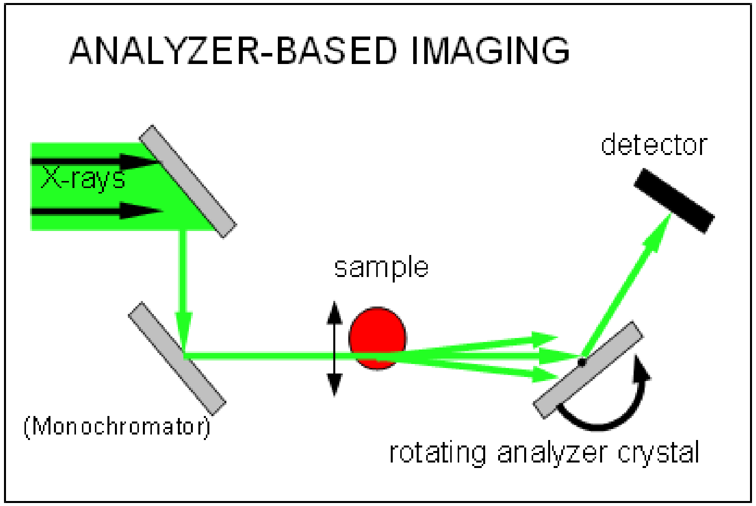
"Yes, but it can work only in simple objects"

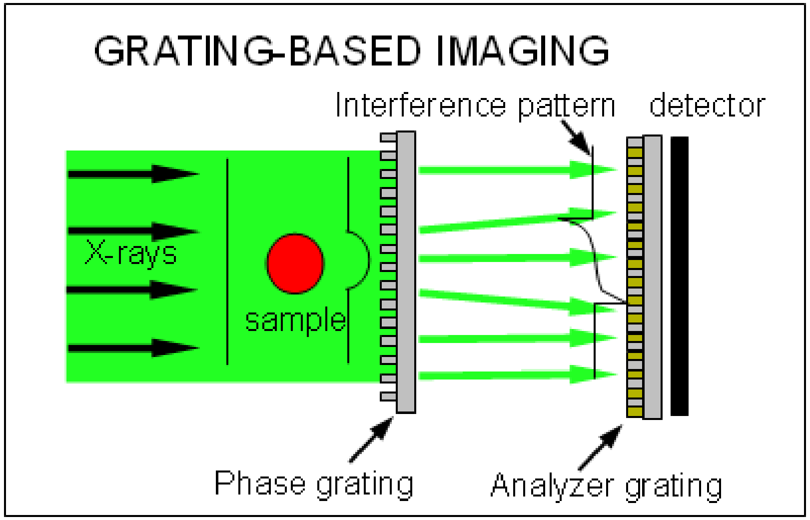
First demonstration of phase contast imaging in a full human organ

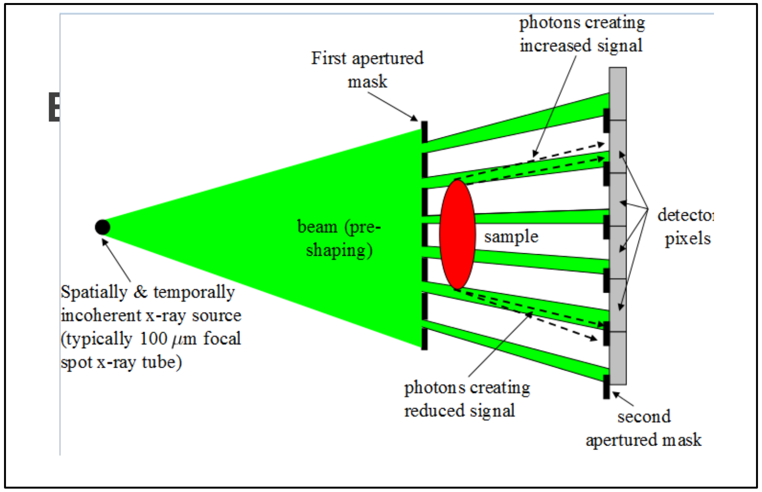
F. Arfelli, A. Bravin et al,
Radiology 215, 2000

TECHNIQUES AVAILABLE FOR PHASE CONTRAST IMAGING



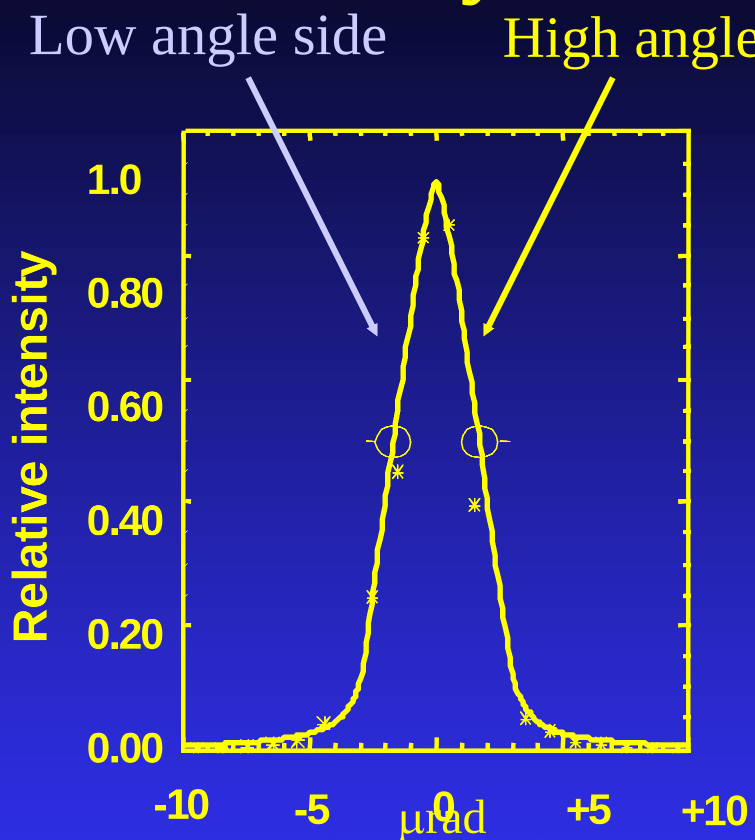






Optimal radiation is monochromatic collimated, and coherent X-rays, presently available only at synchrotron radiation sources

Analyzer-Based Imaging (ABI)



Analyzer:
acts as a perfect and extremely narrow slit

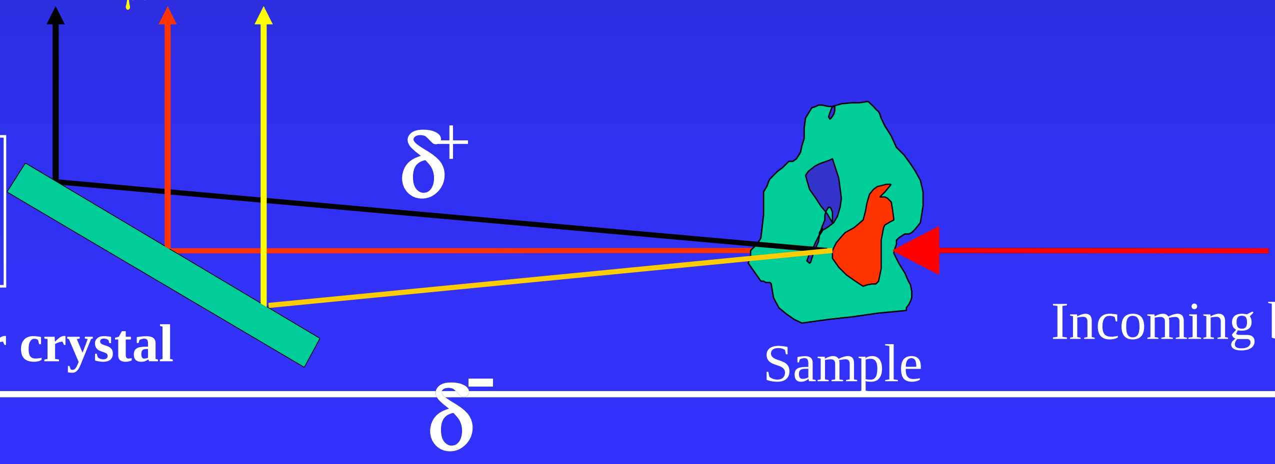
Rocking curve width Si (333)

~ 3.0 µrad at 25 keV

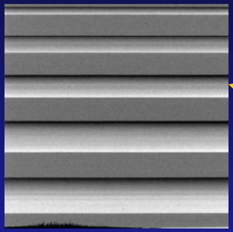
~ 1.3 µrad at 50 keV

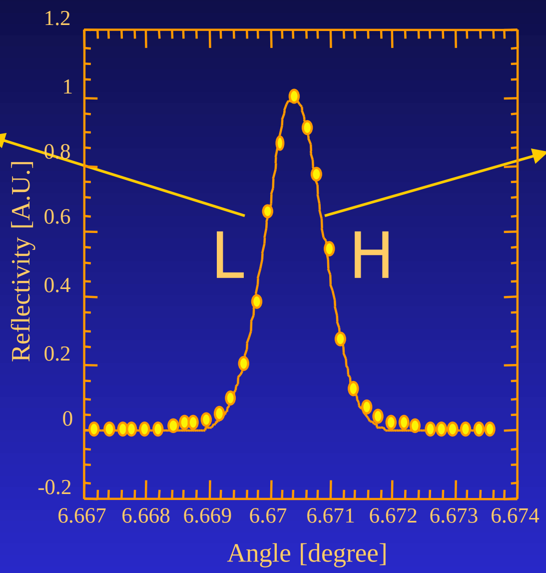
~ 0.9 µrad at 60 keV

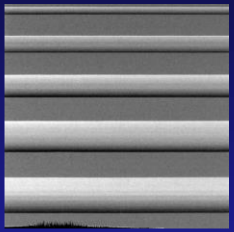
Bragg's law:
2dsinθ=nλ



Diffraction Enhanced Imaging: an algorithm for ABI







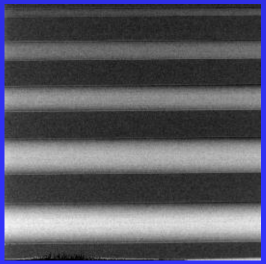
$$I_L = I_R\left(R(\Theta_L) + \frac{\partial R}{\partial \Theta}(\Theta_L)\Delta\Theta_z\right)$$

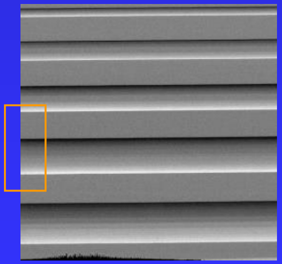
$$I_H = I_R\left(R(\Theta_H) + \frac{\partial R}{\partial \Theta}(\Theta_H)\Delta\Theta_z\right)$$

I_R = apparent absorption image

$\Delta\Theta_Z$ = refraction image in the plane of the object

$$I_R = \frac{I_L \cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_H} - I_H \cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_L}}{R(\Theta_L)\cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_H} - R(\Theta_H)\cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_L}}$$

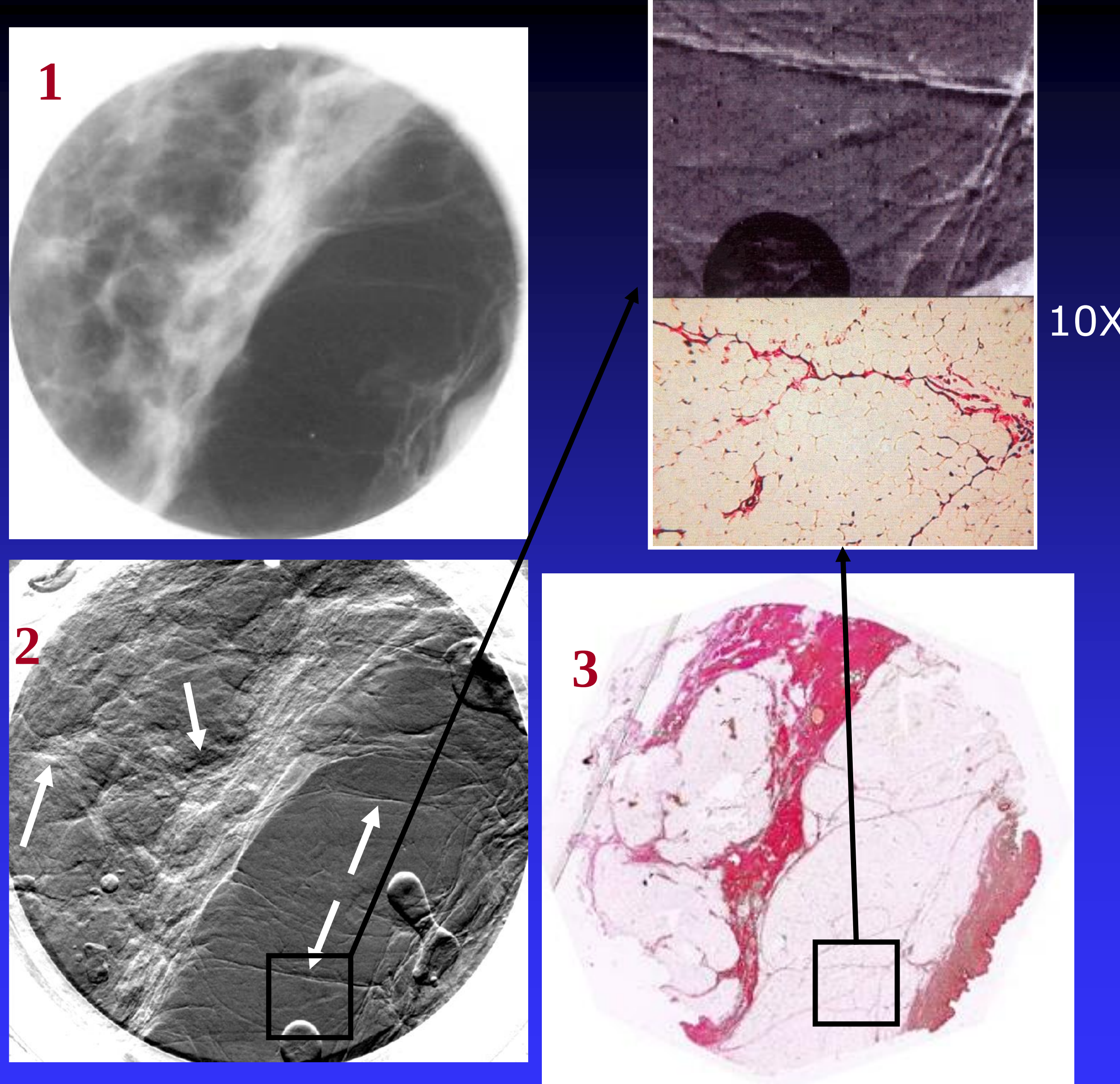




$$\Delta\Theta_Z = \frac{I_H \cdot R(\Theta_L) - I_L \cdot R(\Theta_H)}{I_L \cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_H} - I_H \cdot \left.\frac{dR}{d\Theta}\right|_{\Theta_L}}$$

Carcinoma Medullare

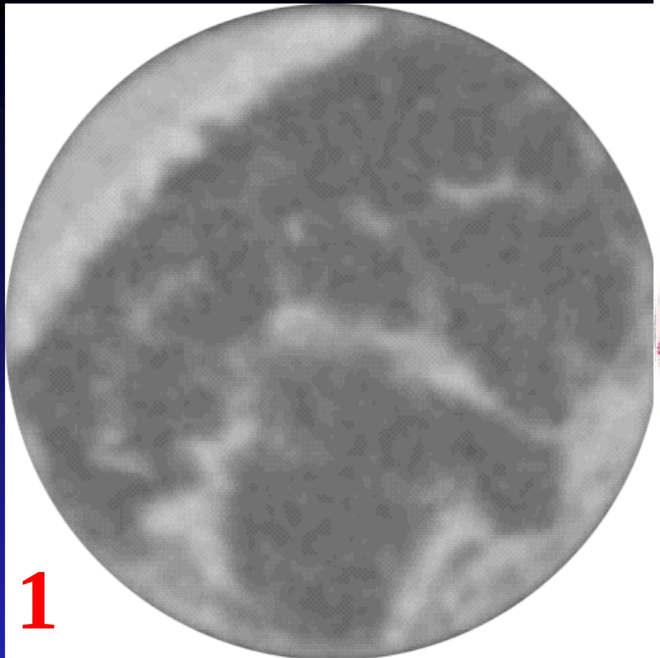
- 1 Siemens Mammomat 3000 -23 kVp 5.6 mAs MGD=0.4 mGy
- 2 ABI 25 keV minus 0.7 μrad Si(333) MGD= 0.6 mGy
- 3 Histology

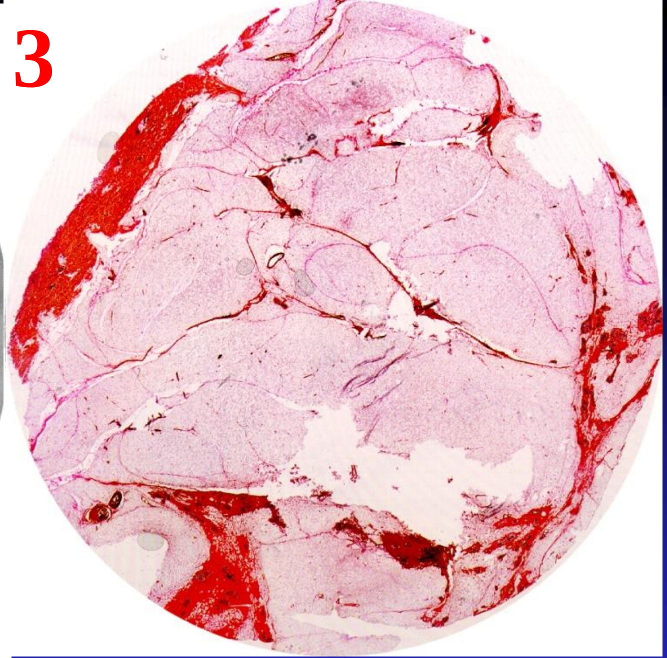


Keyriläinen et al. European Journal of Radiology 53, 226-237 (2005)

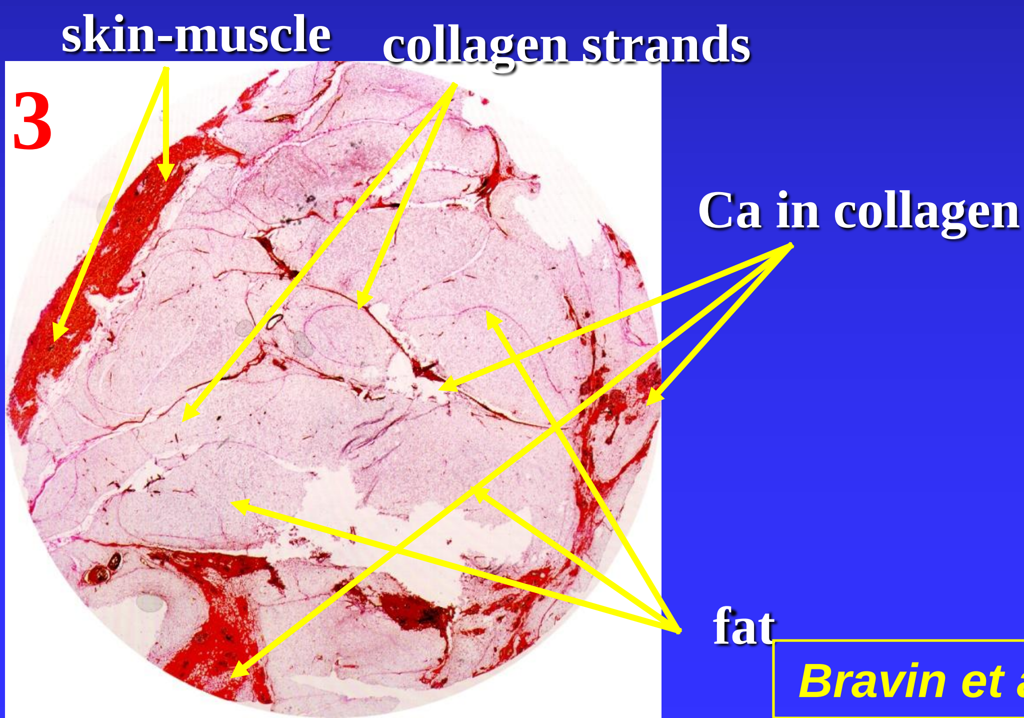
ABI-CT

Breast cancer





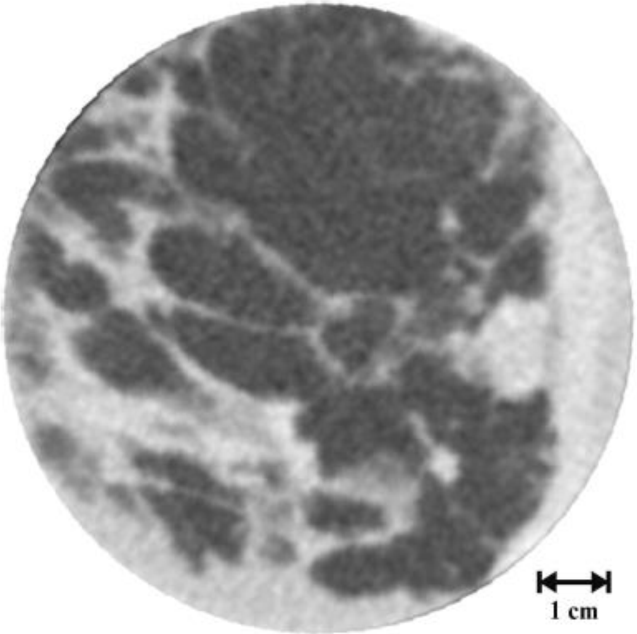
- 1 Hospital scanner
- 2 SR technique
- 3 Histology (reality)



Bravin et al. Phys.Med. Biol. 2007 52 (8) 2197

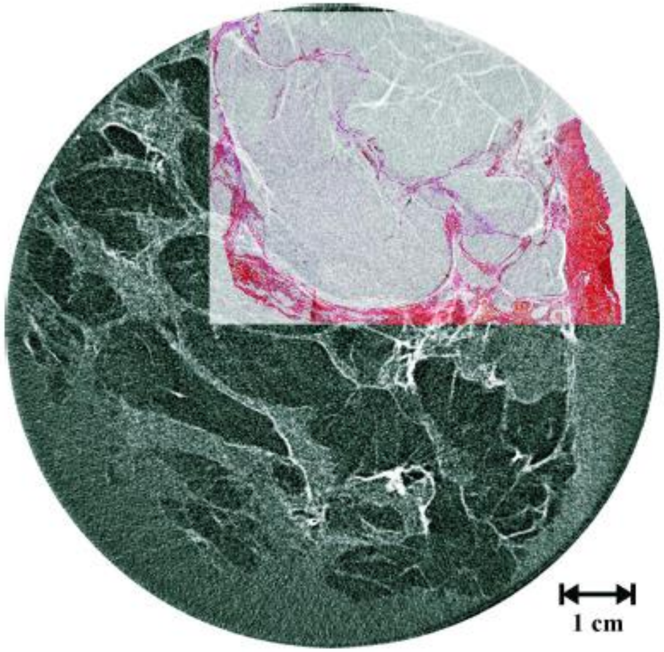
FIRST LOW DOSE CT DEMONSTRATION ON FULL MASTECTOMY

Conventional



MGD=6.9 mGy

Phase contrast (ABI)



MGD=1.9 mGy

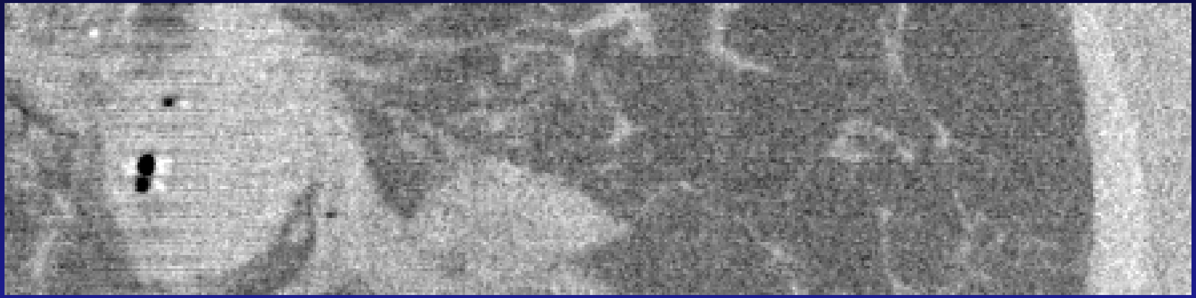
Full breast : 8 cm

33 keV

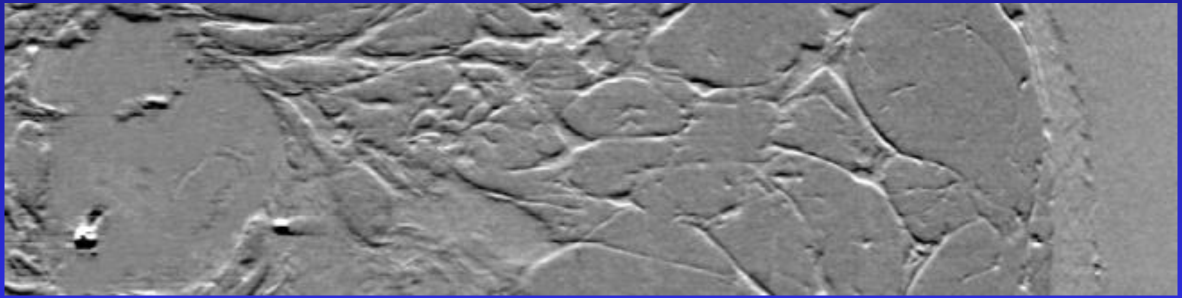
Keyriläinen et al. Radiology, 2008

Breast-CT: PCI-CT vs conventional CT vs histology

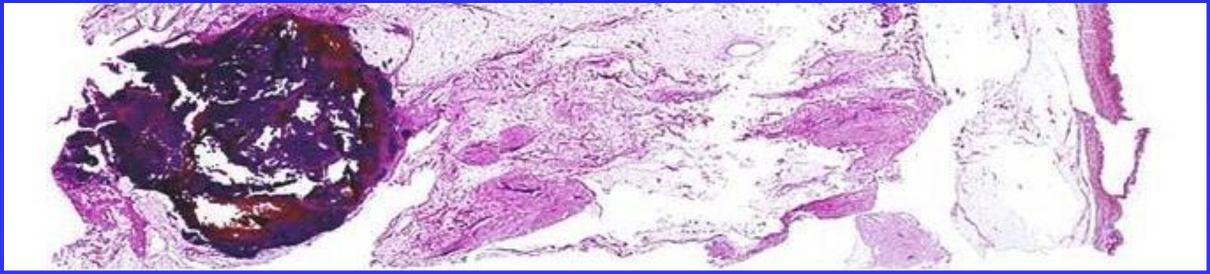
PCI CT outperfoms conv. CT and it is in strong correlation with histology



Conventional Absorption



PCI CT



Histology

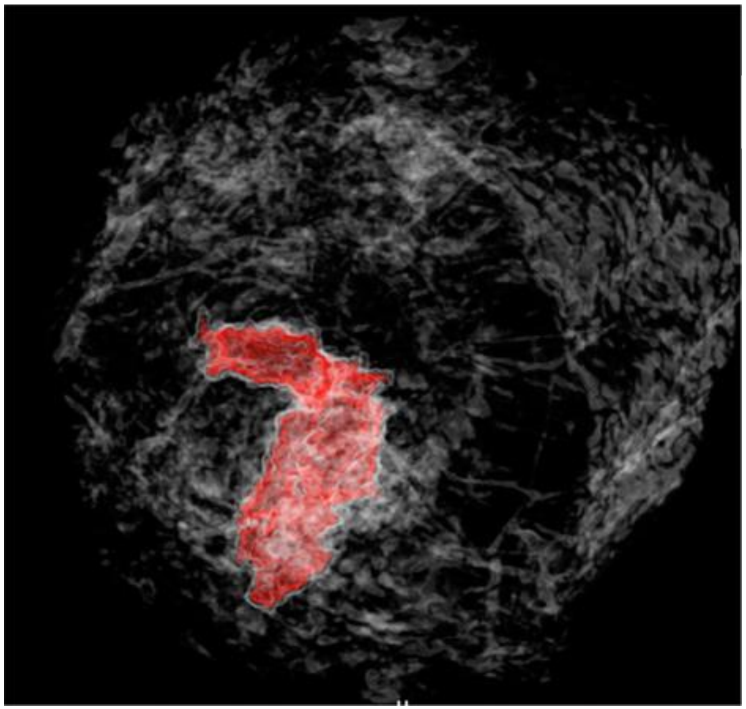
A. Sztrokay et al *Physics in Medicine and Biology*, 57(10) 2931 - 2942, 2012

LOW DOSE AND HIGH RESOLUTION HUMAN BREAST CT

PNAS

High-resolution, low-dose phase contrast X-ray tomography for 3D diagnosis of human breast cancers

Yunzhe Zhao[a,1], Emmanuel Brun[b,c,1], Paola Coan[c,d], Zhifeng Huang[a], Aniko Sztrókay[d], Paul Claude Diemoz[c], Susanne Liebhardt[d], Alberto Mittone[c], Sergei Gasilov[c], Jianwei Miao[a,2], and Alberto Bravin[b,2]



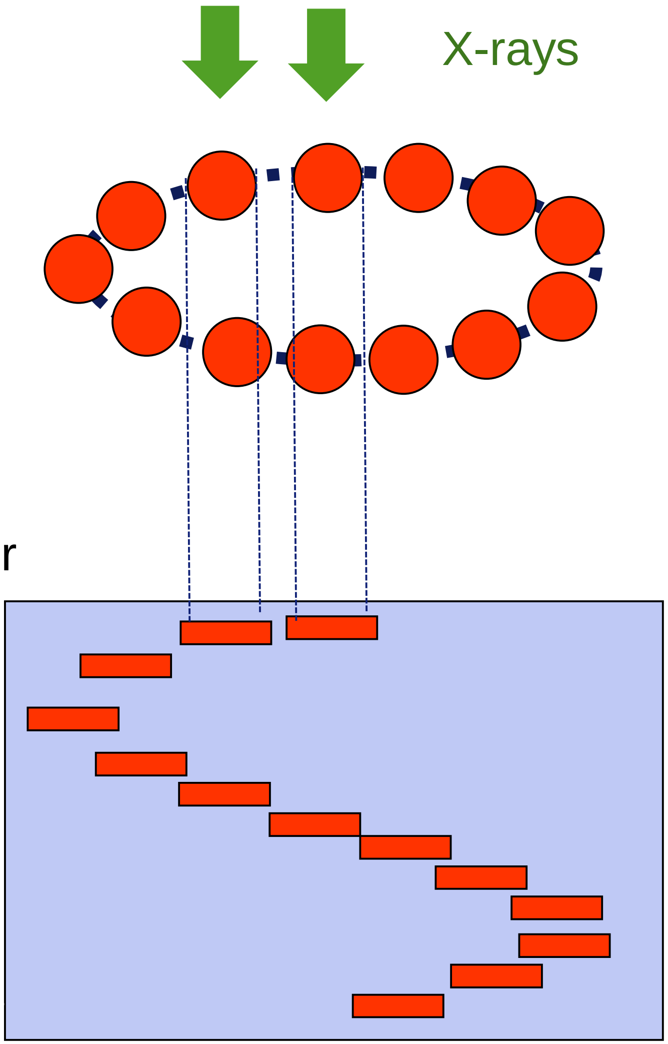
PNAS | November 6, 2012 | vol. 109 | no. 45 | 18293

Phase contrast CT
+ iterative reconstruction method

Dose = 2.0 ± 0.1 mGy
25 times dose saving vs clinical breast CT at same resolution

CT BASIC PRINCIPLES

Rotating sample



Detector

3D image

Computing
(reconstruction
algorithms)

Sinogram

❑ LOW DOSE CT

Combination of *3 ingredients*:

“Phase contrast imaging”	+	Advanced CT reconstruction algorithms	+	High X-ray energies
⇩		⇩		⇩
Highly sensitive imaging techniques		Iterative algorithms for CT reconstruction - less projections than normally used		Tissues more radio-transparent -> less dose

- **Breast imaging needs high resolution**
    - High number of projections for CT (Shannon Nyquist criterion):

$$\text{Proj} = \frac{\mathbf{D\pi}}{\mathbf{p\ 2}}$$

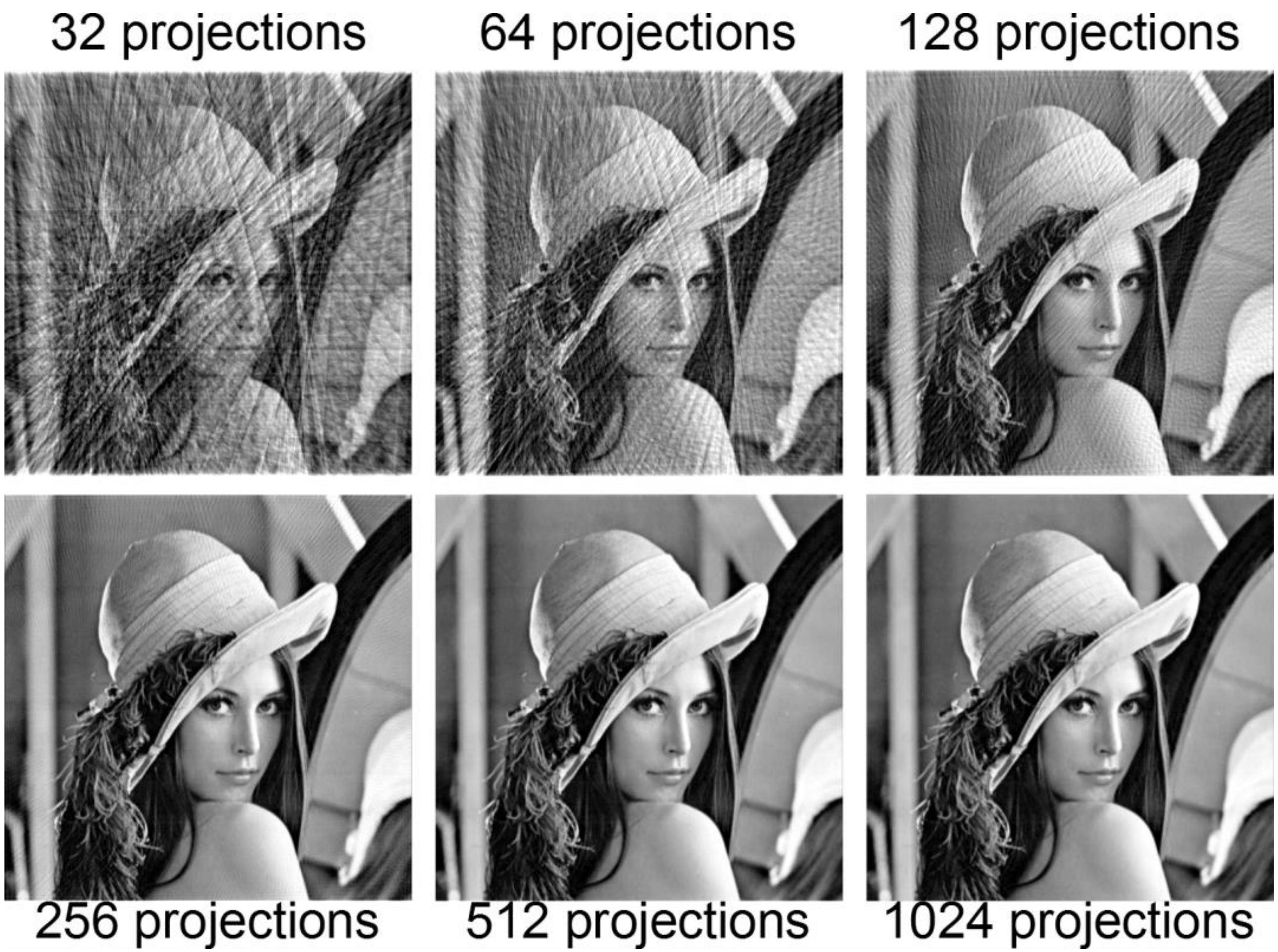
D: sample thickness
P: pixel size

- **Can we reduce the number of projections?**

2 possible strategies :

- To reduce the number of projections for a CT data set:
    - Shannon-Nyquist criterion not valid anymore
- To reduce the number of photons onto the detector per each angular projection

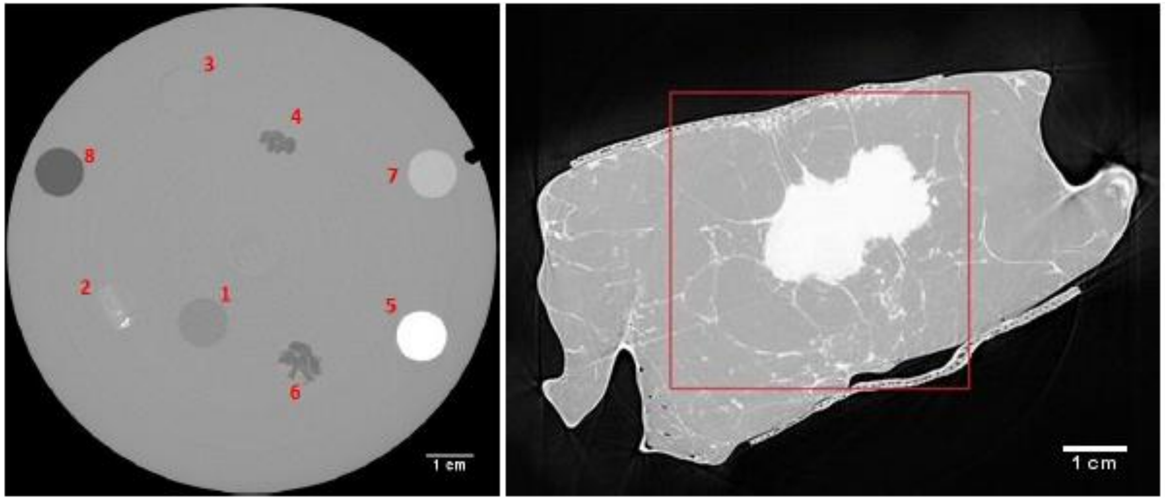
REDUCING THE NUMBER OF PROJECTIONS OF A CT DATA SET



Using FBP: prone to the appearance of artefacts

REDUCING THE NUMBER OF PROJECTIONS

- **Filtered Back Projection (FBP)**
- Simultaneous Iterative Reconstruction Technique (SIRT)
- Simultaneous Algebraic Reconstruction Technique (SART)
- Conjugate Gradient Least Squares (CGLS)
- Total Variation (TV) minimization
- Iterative FBP algorithm based on the image histogram updates
- **Equally Sloped Tomography (EST)**



S. Pacile et al, Biomed Opt Express. 2015 Aug 1; 6(8): 3099–3112

REDUCING THE NUMBER OF PROJECTIONS

Table 4. Qualitative assessment of the considered images performed by expert supervisors.

	Radiol. 1	Radiol. 2	Radiol. 3	Pathologist	Mean Score
FBP	1	1	1	1	1
FBP-ITER	1	1	1	0.5	0.87
SIRT	1.5	1	1.5	1.75	1.43
SART	1.5	1.25	1.5	1.75	1.5
CGLS	1	1.25	1.5	1.5	1.31
EST	1	1.25	1.5	1.5	1.31
phr FBP-ITER	3	3	2.5	2	2.62
phr FBP-ITER $Epan17$	2.5	3.25	2.5	2.5	2.68
phr FBP-ITER $Susan5$	2.5	3.25	3	2.5	2.81
phr TV-MIN	1.5	2.75	2.75	2.75	2.43
phr FBP	2.5	2.5	2.75	3.5	2.81
phr SIRT	3.25	3.25	3.5	3	3.25
phr SART	3.25	3.25	3	3	3.12
phr CGLS	2.5	3.25	3	3	2.93
phr EST	3.5	3.25	3.5	3.5	3.43

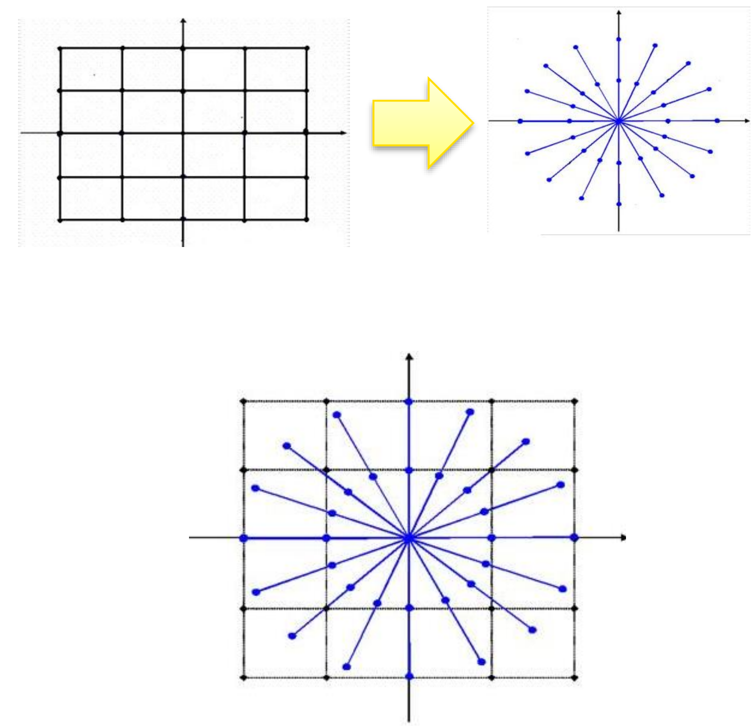
0: worst case; 4: best image

All algorithms available in X-TRACT software:
http://www.ts-imaging.net/Services/SignUp.aspx

S. Pacile et al, Biomed Opt Express. 2015 Aug 1; 6(8): 3099–3112

Observation:

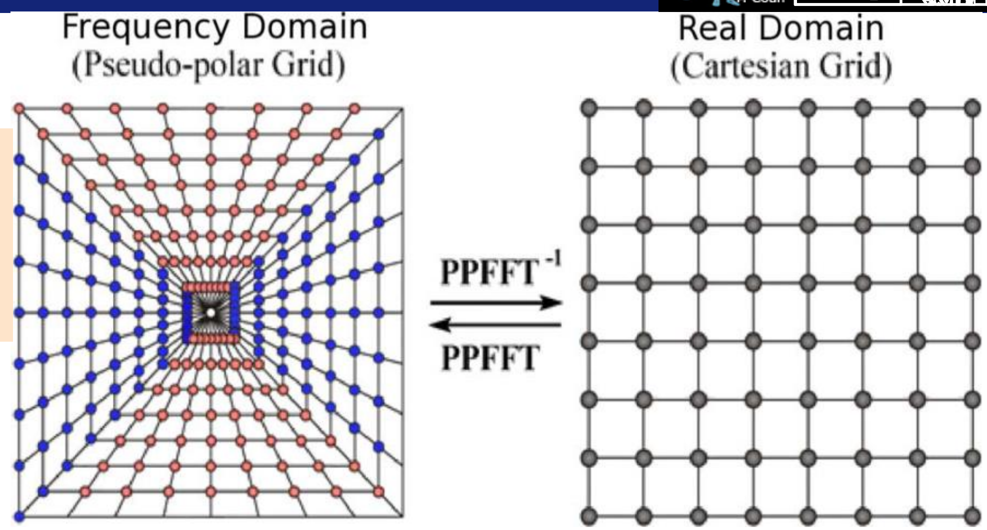
- Real space image is in Cartesian grid while the Fourier space data is in Polar Grid
- There is no exact and direct FFT between polar and Cartesian Grid [1]



[1] Briggs, W.L., Henson V.E. The DFT: An owners' Manual for the Discrete Fourier Transform. SIAM, Philadelphia. 1995

Slides provided by Prof. P. Coan

Idea : “a polar like” grid that enables direct and exact Fourier transform
=> **PSEUDO POLAR GRID**



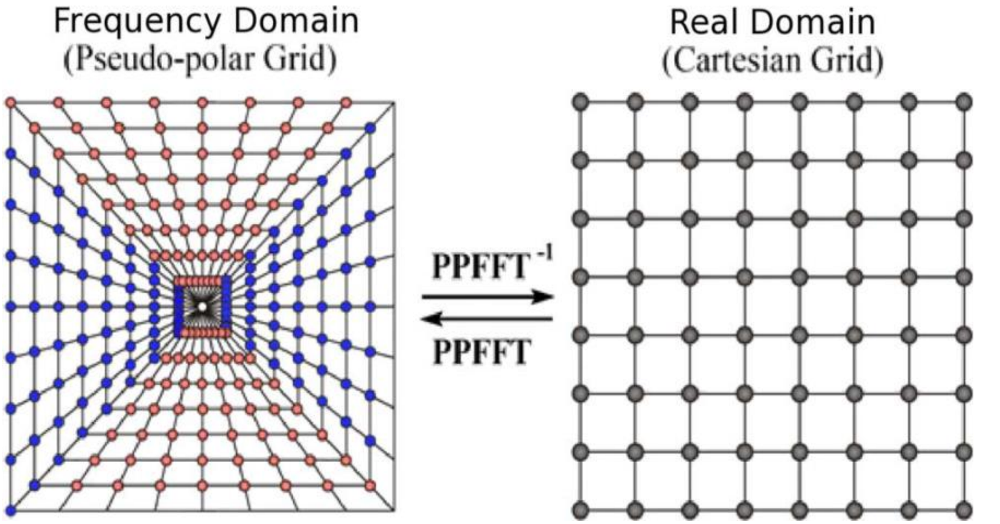
- Grid points in the Fourier domain are lying on the **equally-sloped lines instead of equally-angled lines**
- N*N Cartesian grid -> 2N*2N Pseudo polar grid (PPG) points
- There exist a PPFFT between PPG and Cartesian Grid
  - algebraically exact
  - geometrically faithful
  - Invertible

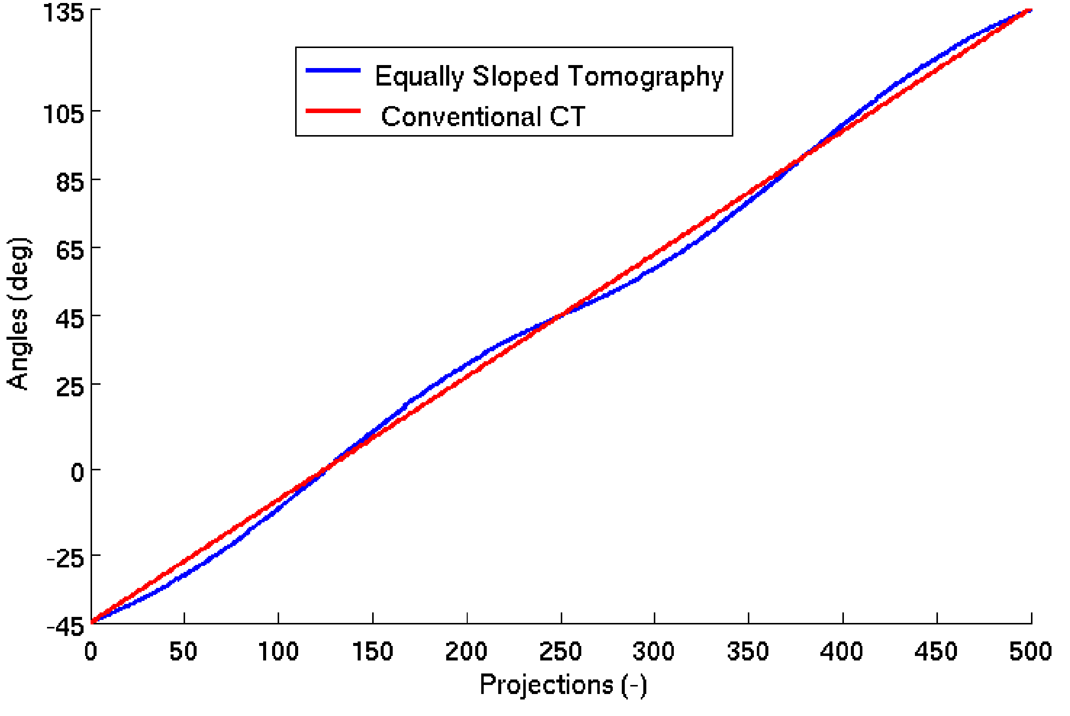
Slides provided by Prof. P. Coan

Miao et al. Phys Rev B ,72 (2005)

PNAS, Zhao, Brun, Coan et al., 109 (45) 6 Nov 2012

Idea : "a polar like" grid that enables direct and exact Fourier transform
=> **PSEUDO POLAR GRID**

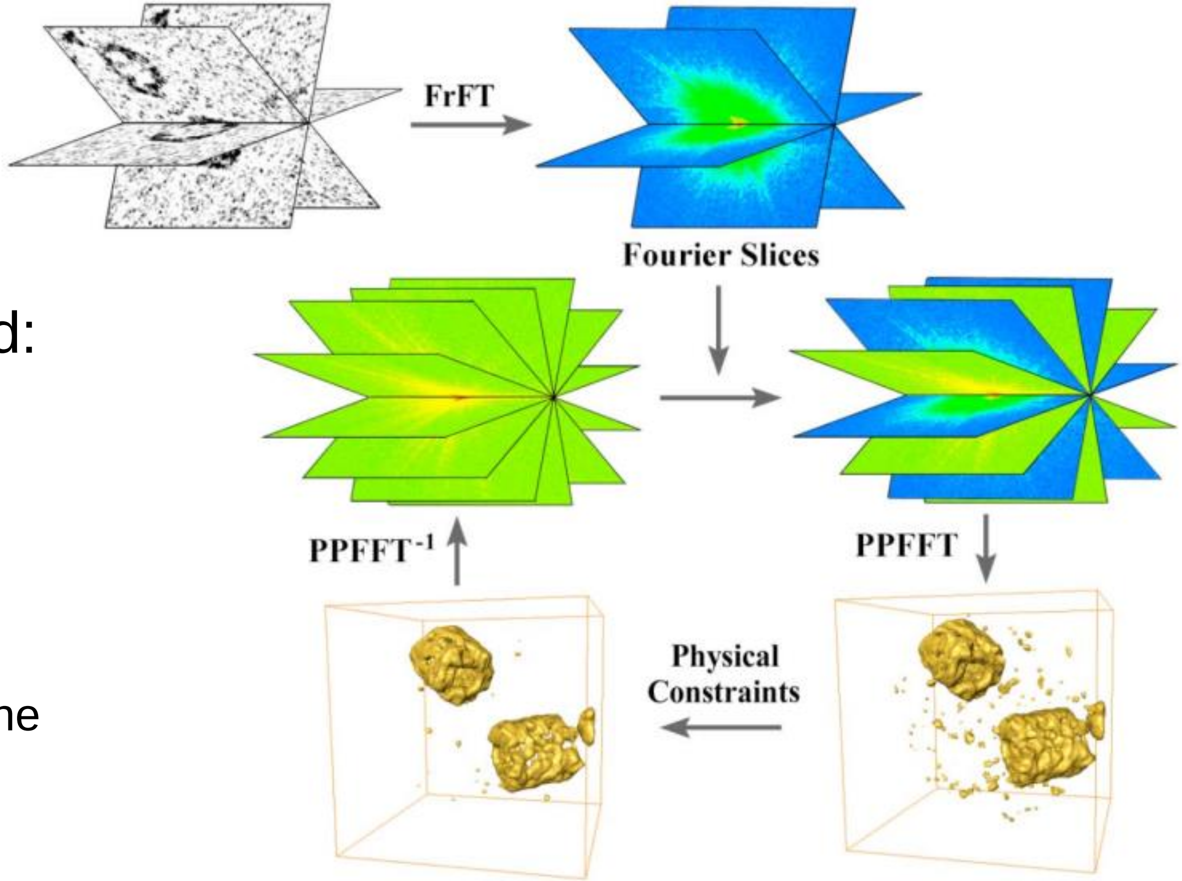




Miao et al. *Equally sloped tomography with oversampling reconstruction.* Phys Rev B ,72 (2005)

EST iterative algorithm

Starts with the conversion of the projections to Fourier slices in the pseudo polar grid fractional FFT



Iterative process is initiated:

- Inverse PPFFT is applied to the frequency data
- A new object is obtained through constraints. Forward PPFFT onto modified image
- Frequency data is updated with the measured Fourier slices

Real domain constraints:

- Minimization of the coefficients
- Real values as result

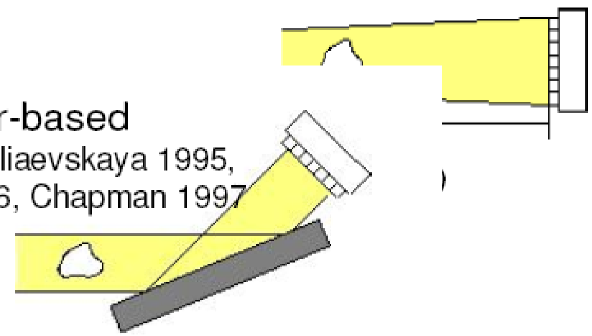
Iterations are monitored by an error function

WE TESTED EST ON DIFFERENT CASES

→ On both synthetic and experimental data

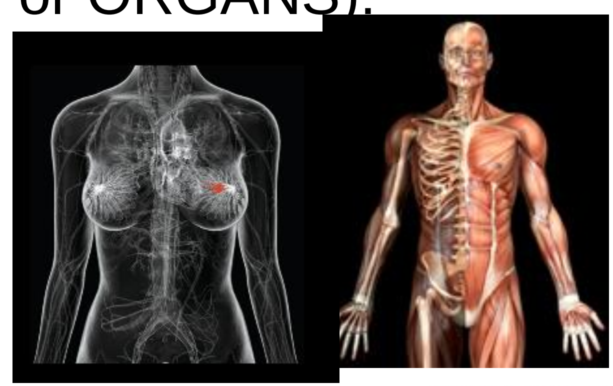
→ Different Phase Contrast Imaging techniques

- Propagation based imaging
- Analyzer based imaging



→ Different clinical cases (FULL JOINTS or ORGANS):

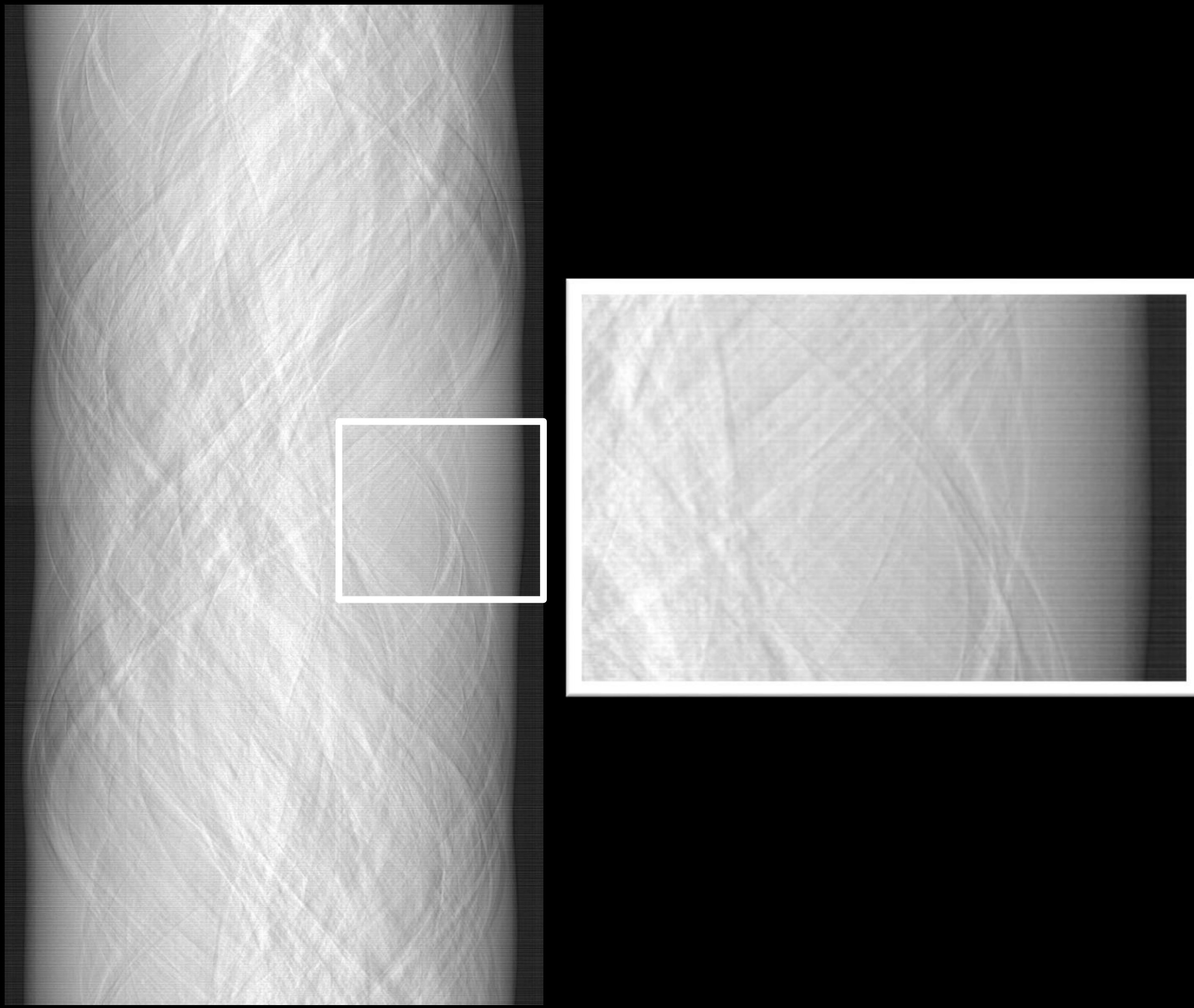
- Breast imaging
- Musculoskeletal imaging



Slides provided by Prof. P. Coan

The raw data

The sinogram

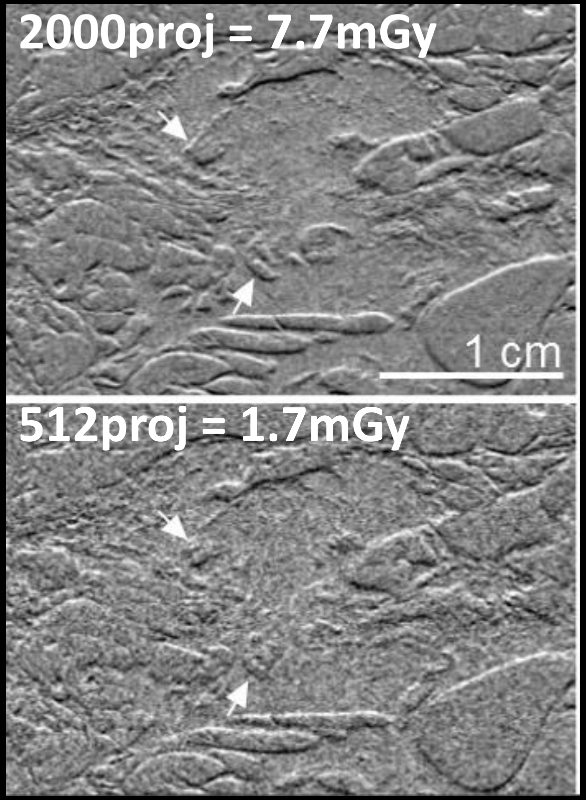


Visual Comparison

Zoomed view in a 92 µm thick slice **an excised full human tumor bearing breast**

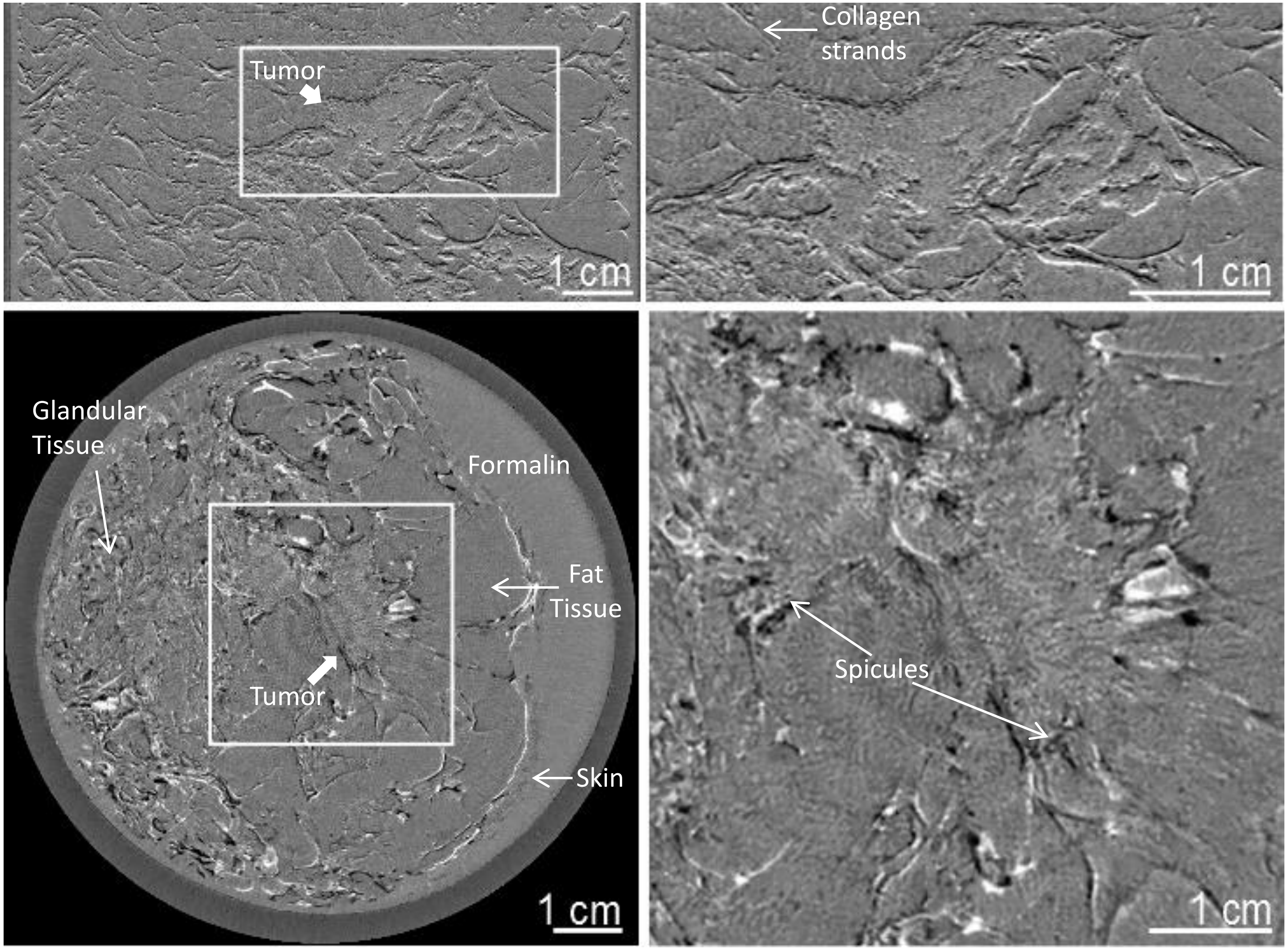
FBP

- FBP - 512 exhibits high noise degraded features and blurred boundary of the tumour



PNAS, Zhao, Brun, Coan et al., 109 (45) 6 Nov 2012

Result of reconstruction by EST 512projections



<u>MGD</u>

<u>1.7mGy</u>

Quantitative Comparison

Blind Test made by 5 radiologists (Radiology department of Ludwig Maximilians University)

Radiologist were asked to mark form 1 (worst) to 5 (best) on the following criteria

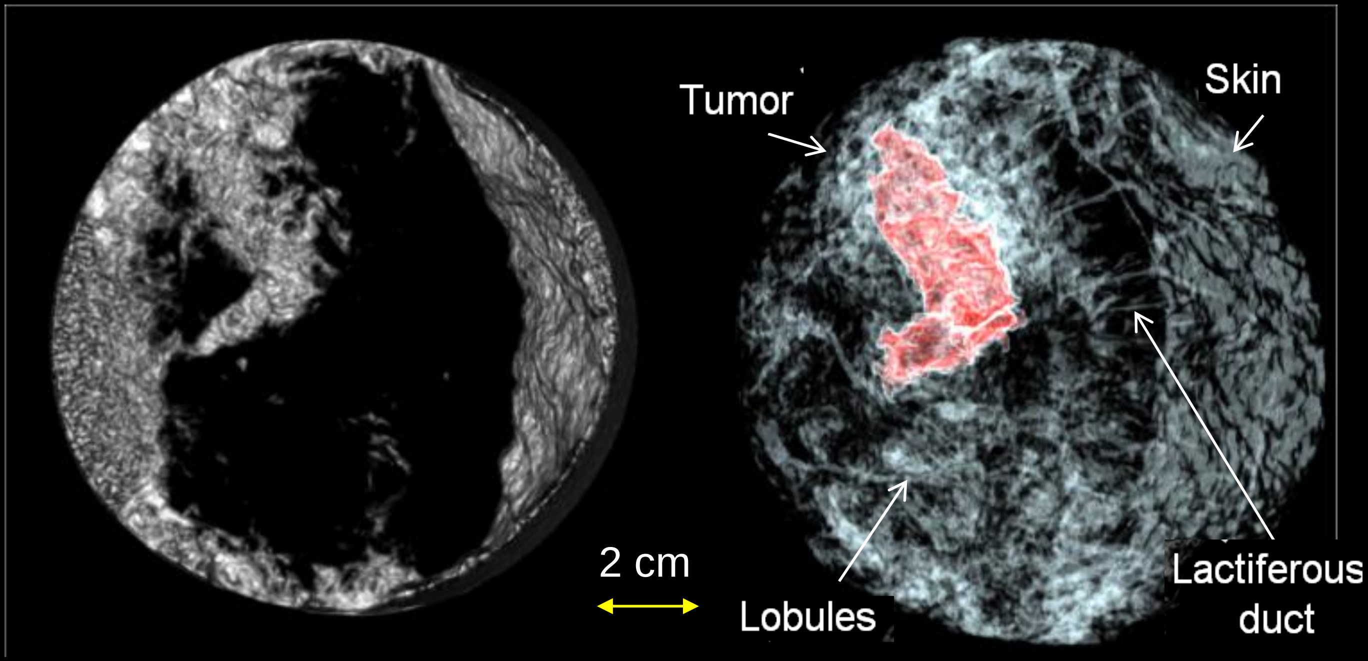
	FBP 512	EST 200	FBP2000	EST512
Image quality	2.2 ± 0.4	2.7 ± 0.9	**4.3** ± 0.9	**4.5** ± 0.5
Sharpness	3.3 ± .0	2.2 ± 0.8	**4.0** ± 0.7	**4.3** ± 0.5
Contrast	3.0 ± 0.7	3.4 ± 0.9	**4.0** ± 0.5	**4.8** ±0.4
Evaluation of different structure	2.7 ± 0.5	2.9 ± 1.	**4.1** ± 0.6	**4.8** ± 0.4
Noise	1.8 ± 0.7	3.3 ± 0.8	**4.2** ± 0.7	**4.8** ± 0.3

3D CT breast tumor detection at high resolution and at a dose even lower then conventional 2D mammography (~3.5 mGy)!

Fourier based iterative Equally Slopped Tomography (EST) algorithm

Conventional CT
Dose 49 ± 1 mGy

Phase contrast CT + EST
Dose = 2.0 ± 0.1 mGy



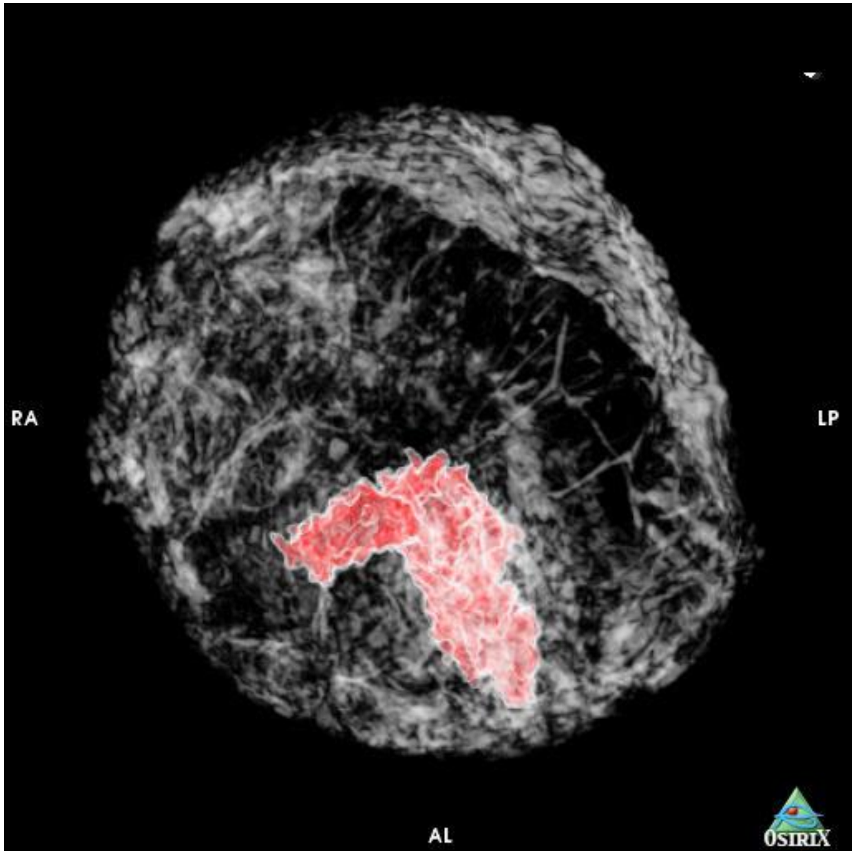
25 times dose saving vs clinical breast CT at same resolution

P. Coan

PNAS, Zhao, et al., 109 (45) 6 Nov 2012

Summary

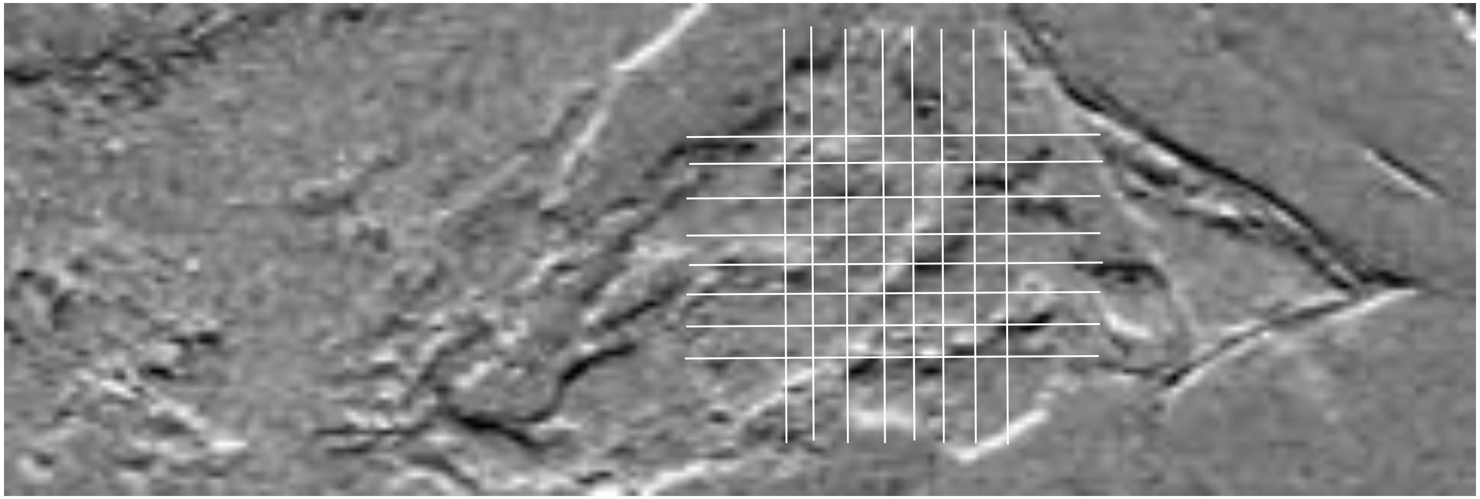
- 3D information of soft tissues at **higher resolution** and **better contrast**, but also deliver **less radiation** doses to the sample
- A step towards the clinical application of PCT for 3D screening and diagnosis of human breast cancer
- Very low dose **(<1mGy)** 3D imaging is possible if one is ready to loose a bit of spatial resolution and noise



PNAS, Zhao, Brun, Coan et al., 109 (45) 6 Nov 2012

Sparsity

image is intrinsically sparse when it can be approximated as a linear combination of a small number n of basis functions, with n=N, where N is the image dimensionality



Good case: when image has large constant parts: the basis can be small pieces varying only on the borders

How many patches?

mxm<< NxN (pixel size)

- Fast calculation
- Image not well reproduced
- Very low noise (noise has little sparsity)

mxm>> NxN (pixel size)

- Heavy computation
- Image well reproduced
- Very smooth transition at the patches borders if the patches are overlapping
- Also noise is reproduced, to be treated with a denoisy method

Submethods:

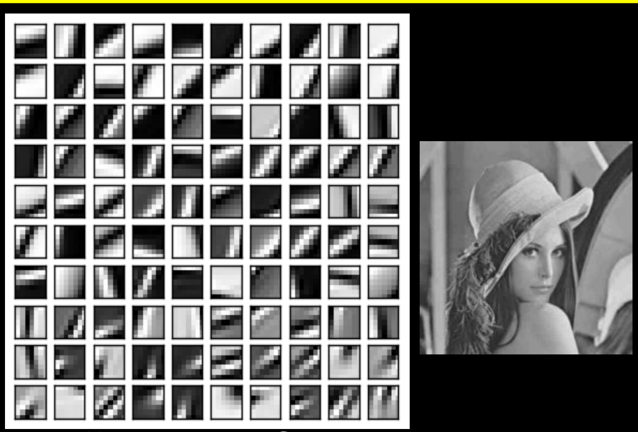
- **Dictionary learning**
- **Total Variation penalization (TV):** introduces a regularization parameter

All mathematics can be found in

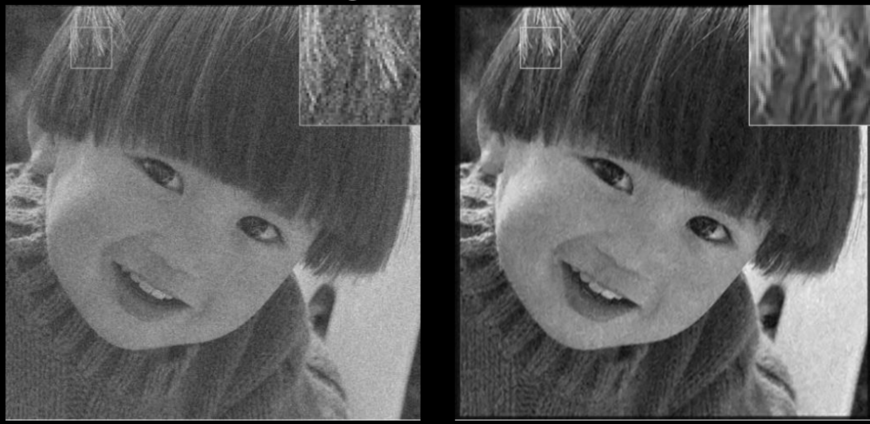
A. Mirone, E. Brun, P. Coan. PlosOne, 9(12) e114325

Dictionary Learning reconstruction

- Idea of the method :
  - To create a database of patchworks starting from images close to the images to be reconstructed
  - To decompose the slice to be reconstructed in a patchwork of sub-images
  - To express a given sub-image at position "*r*" as a linear combination of the basis patches
  - To find the solution which gives the maximum Likelihood by minimizing the number of entries in the dictionary
  - Minimization is done toggling between slice and sinogram
  - A regularization included to assure fidelity



Dictionary "learnt" from Lena image and used for reconstructing the image of interest



Noisy image **Denoised image**

A. Mirone, E. Brun, P. Coan. PlosOne, 9(12) e114325

Reconstructing Lena

- **Experiment :**
  - 512*512 pixel Lena image
  - 80 projections

- **Remark :**
  - To avoid aliasing 800 projections should be used (Nyquist-Shanon sampling criterion)

Lena image to reconstruct

A. Mirone, E. Brun, P. Coan. PlosOne, 9(12) e114325

Results

FBP

EST

TV

DL

NO noise

80 projections

Zoom views in two different image regions

FBP EST TV DL Original

A. Mirone, E. Brun, P. Coan. PlosOne, 9(12) e114325

Results

FBP

EST

TV

DL

Noisy data

Additive White Gaussian Noise = 0.3% max of sinogram

80 projections

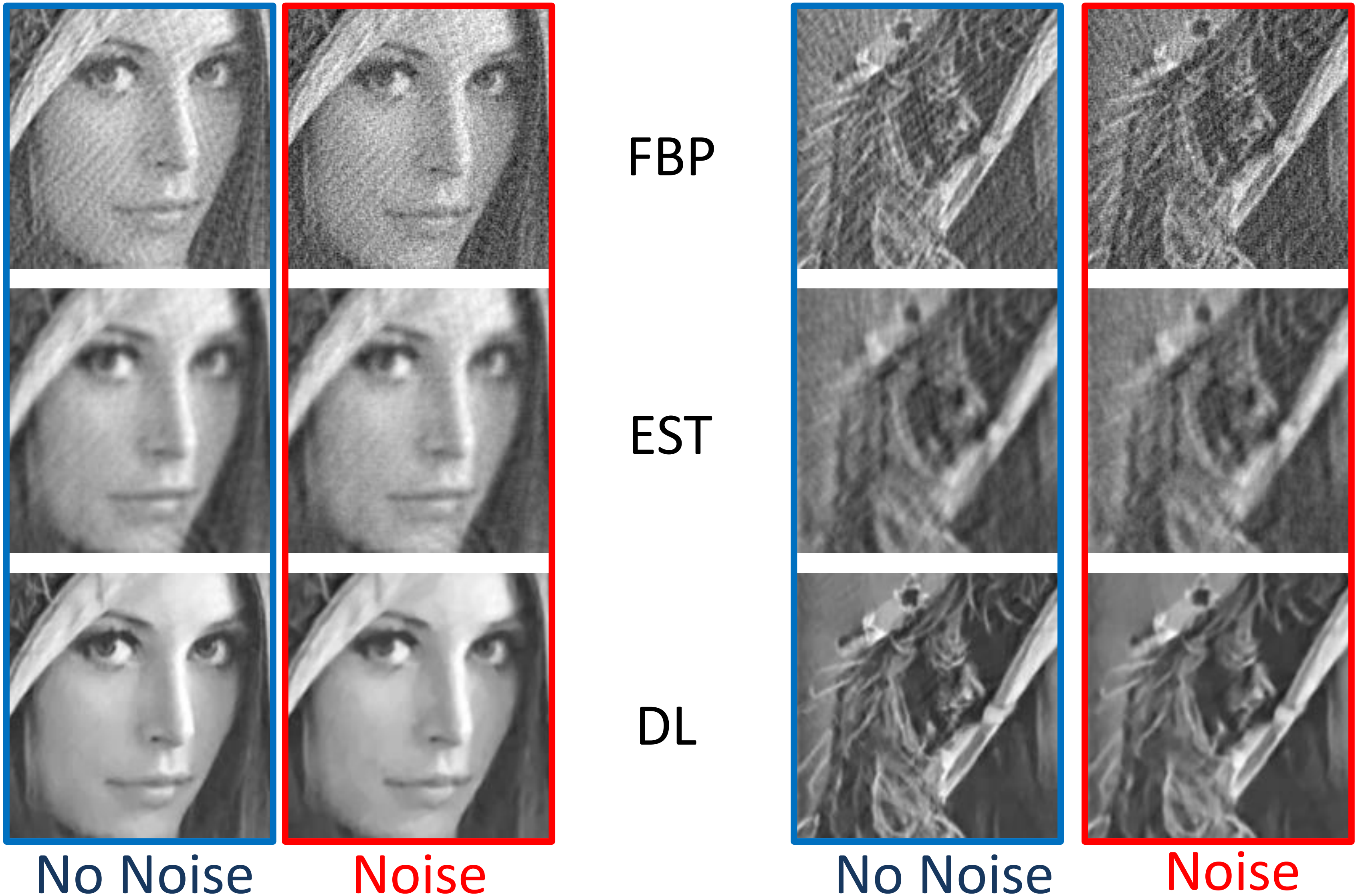
Zoom views in two different image regions

Additive White Gaussian Noise = 0.3% max of sinogram

FBP | EST | TV | DL | Original

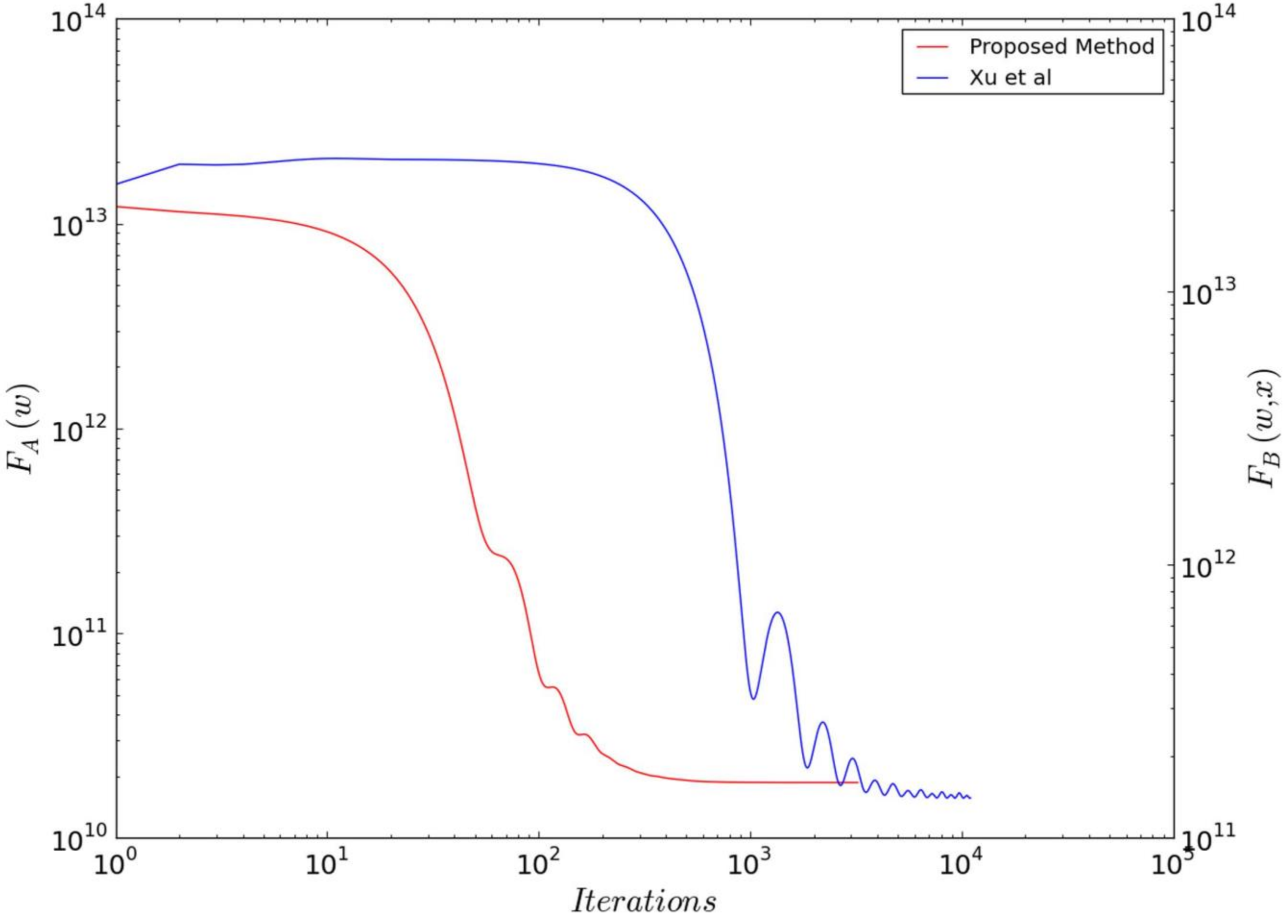
A. Mirone, E. Brun, P. Coan. PlosOne, 9(12) e114325

Direct comparison



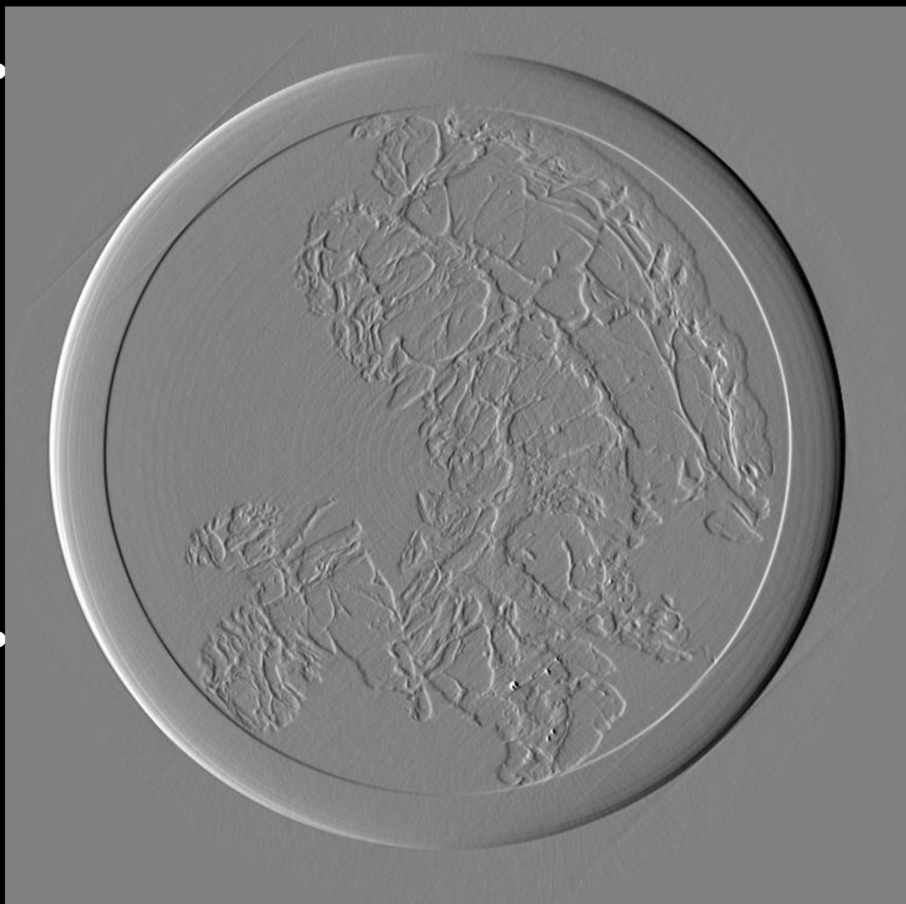
A. Mirone, E. Brun, P. Coan. PlosOne, 9(12) e114325

THE IMPORTANCE OF THE FAST CONVERGING

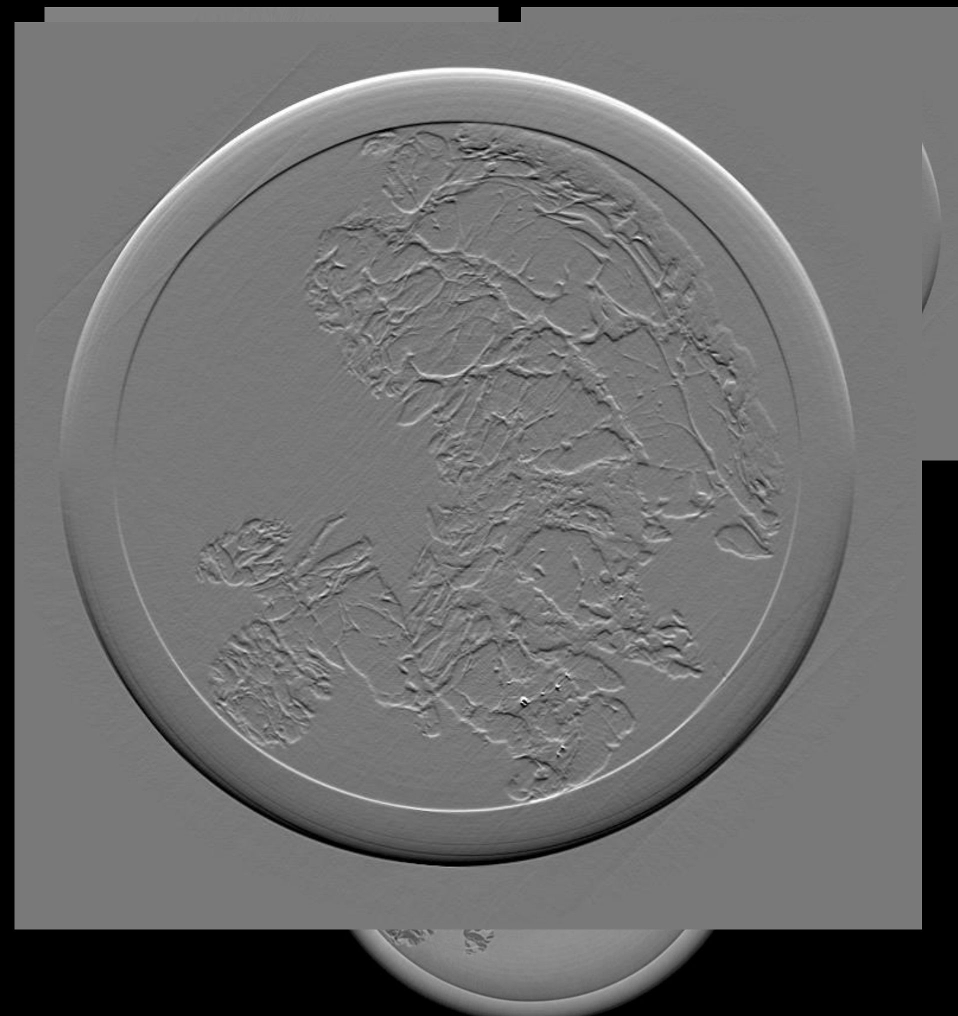


APPLICATION ON EXPERIMENTAL DATA

Reconstructing phase gradient images



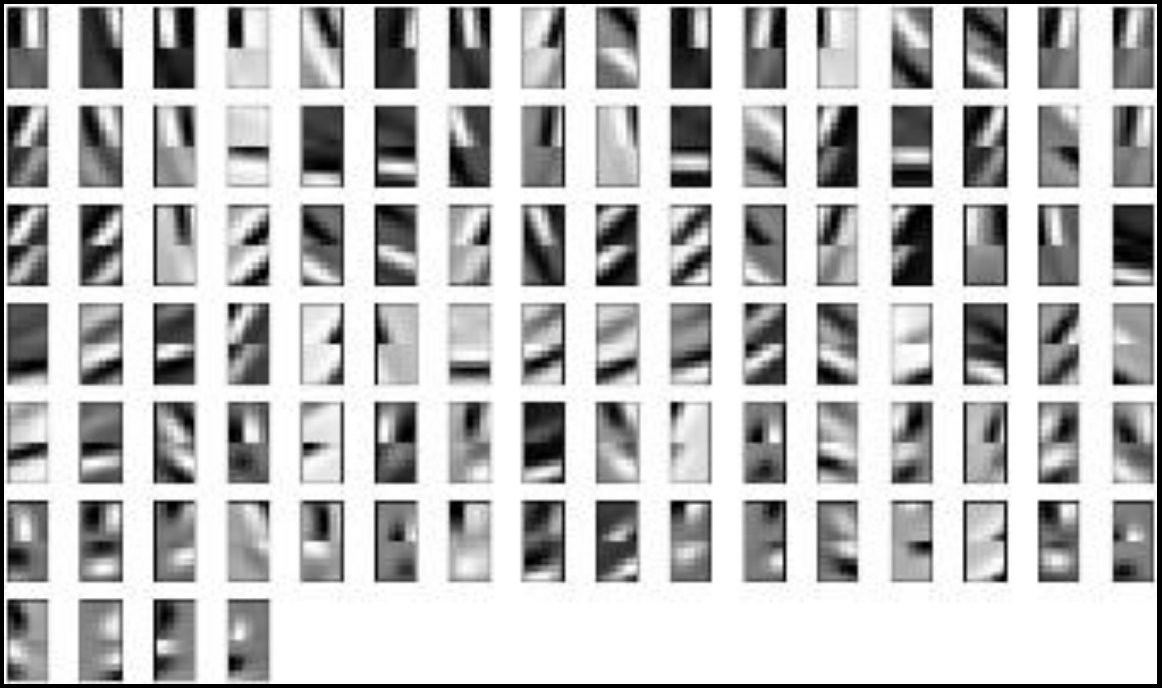
Shannon criterion: 2335 projections
(pixel: 47 microns)



Diameter: 7 cm

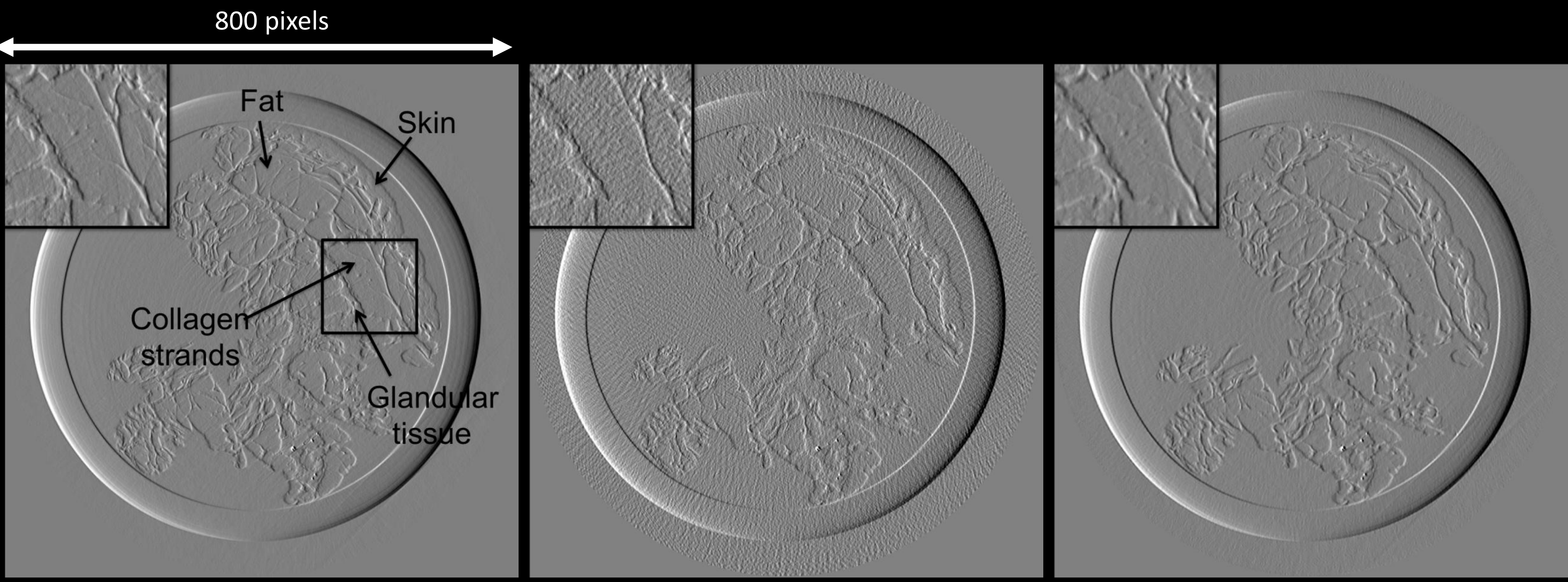
Prof. P. Coan

Vectorial Set of Patches



Set of 2* 7*7 pixels patches learnt from another breast sample

Phase Contrast Reconstruction using DL



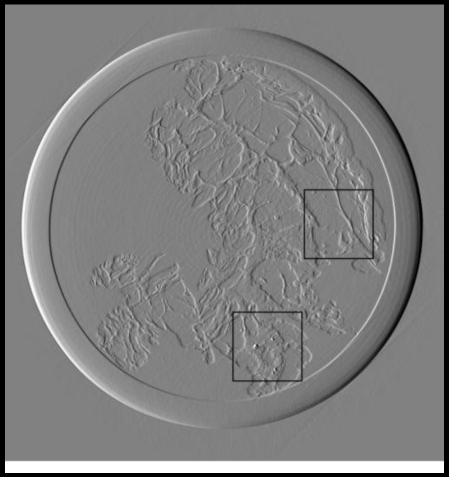
FBP 1000 Projections **FBP 250 Projections** **DL 250 Projections**

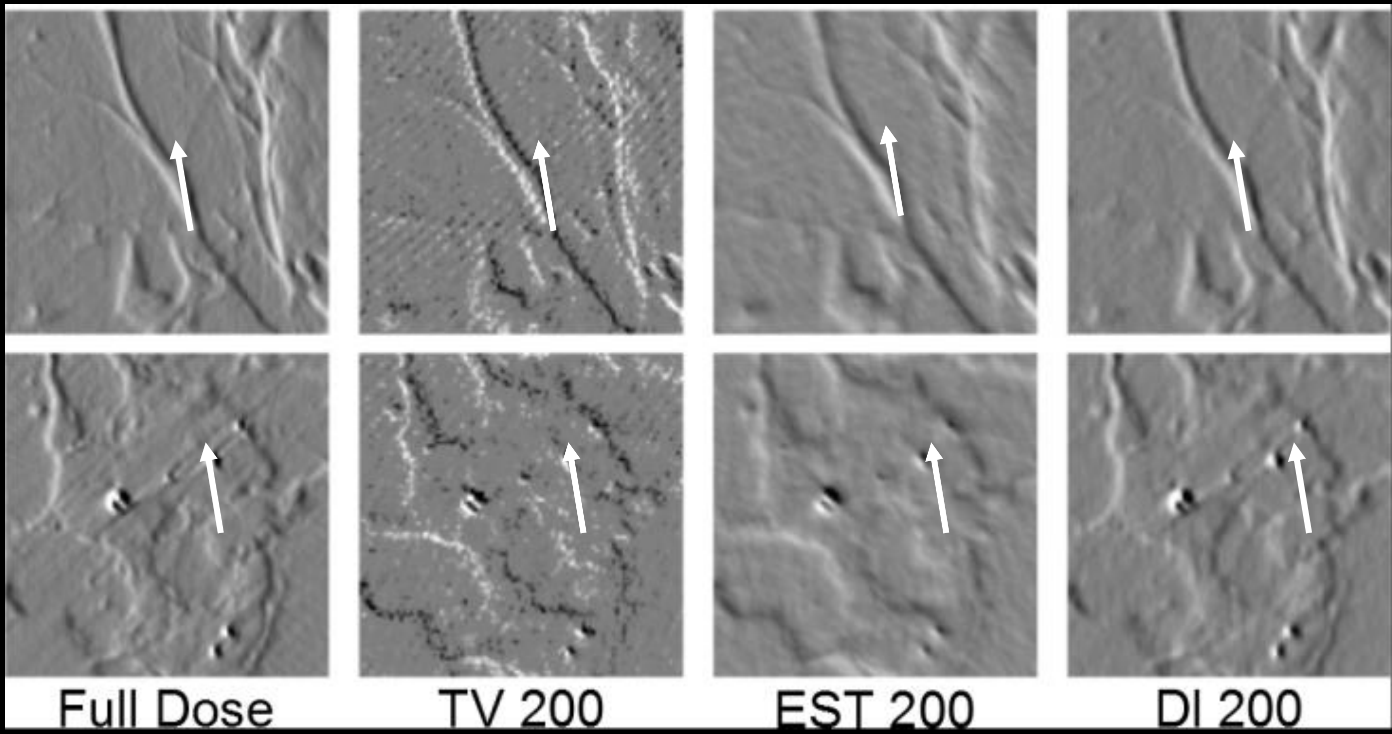
Analyzer Based Imaging of a full (7cm) human tumor bearing breast tumor

Prof. P. Coan

A. Mirone, E. Brun, P. Coan. PlosOne, 9(12) e114325

Closer Look





Small Structures are preserved in the Dictionary Learning reconstructions
Global Image quality is higher in DL

A. Mirone, E. Brun, P. Coan. PlosOne, 9(12) e114325

Tomographic reconstruction of the refractive index with hard X-rays: an efficient method based on the gradient vector-field approach

Sergei Gasilov,[1,*] Alberto Mittone,[1,2] Emmanuel Brun,[1,3] Alberto Bravin,[3], Susanne Grandl,[2] Alessandro Mirone,[3], and Paola Coan[1,2]

Optics Express Vol. 22, Issue 5, pp. 5216-5227 (2014)

Phase retrieval converting the problem to Poisson equation, robust to noisy data

Boundary value problem for phase retrieval from unidirectional X-ray differential phase images

Sergei Gasilov,[1,*] Alberto Mittone,[2,3,4] Annie Horng,[4] Alberto Bravin,[3] Tilo Baumbach,[1] Tobias Geith,[4] Maximilian Reiser,[4] and Paola Coan[2,4]

18 May 2015 | Vol. 23, No. 10 | DOI:10.1364/OE.23.013294 | OPTICS EXPRESS 13294

Application of a finite element technique to solve The boundary value problem in phase retrieval

On the possibility of quantitative refractive-index tomography of large biomedical samples with hard X-rays

Sergei Gasilov,[1,*] Alberto Mittone,[1,3] Emmanuel Brun,[1,2] Alberto Bravin,[2] Susanne Grandl,[3] and Paola Coan[1,3]

1 September 2013 | Vol. 4, No. 9 | DOI:10.1364/BOE.4.001512 | BIOMEDICAL OPTICS EXPRESS 1512

PhC vs conventional CT: accuracy in refraction Index calculation in noisy data

A single-image method for x-ray refractive index CT

A Mittone[1,2,4], S Gasilov[1,3], E Brun[1,4], A Bravin[4] and P Coan[1,2]

Phys. Med. Biol. 60 (2015) 3433–3440

Fast and low dose phase retrieval using a single Image dataset

The problem of the radiation delivered

How to perform fast dose simulations?

Conventional Monte Carlo
Long computational time

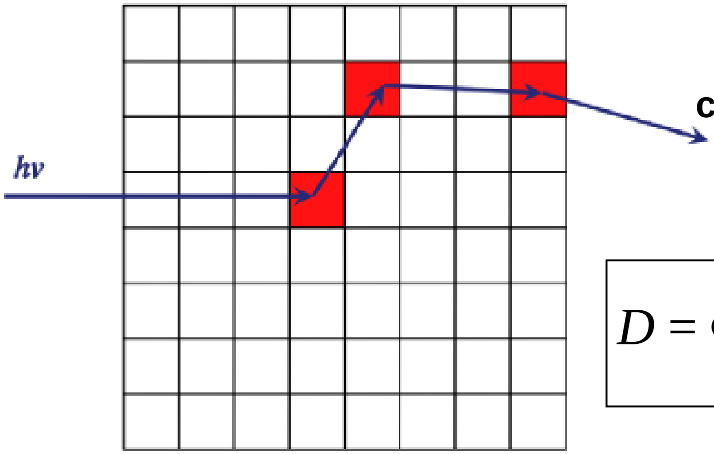
→

- **The track-length estimator (TLE)**
- **Electrons production cut**

How to perform fast dose simulations?

Conventional Monte Carlo
Long computational time

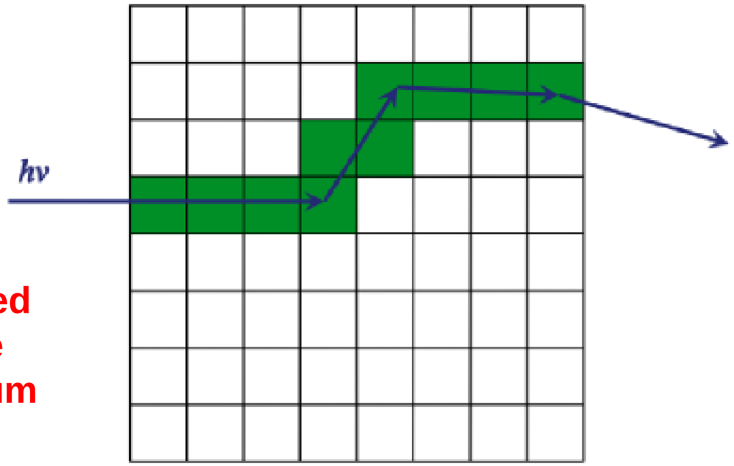
- **The track-length estimator (TLE)**
- **Electron energy is deposited locally and are not tracked**



Local deposition
vs
continuous deposition

$$D = \Phi E \frac{\mu_{en}}{\rho}$$

In charged particle equilibrium

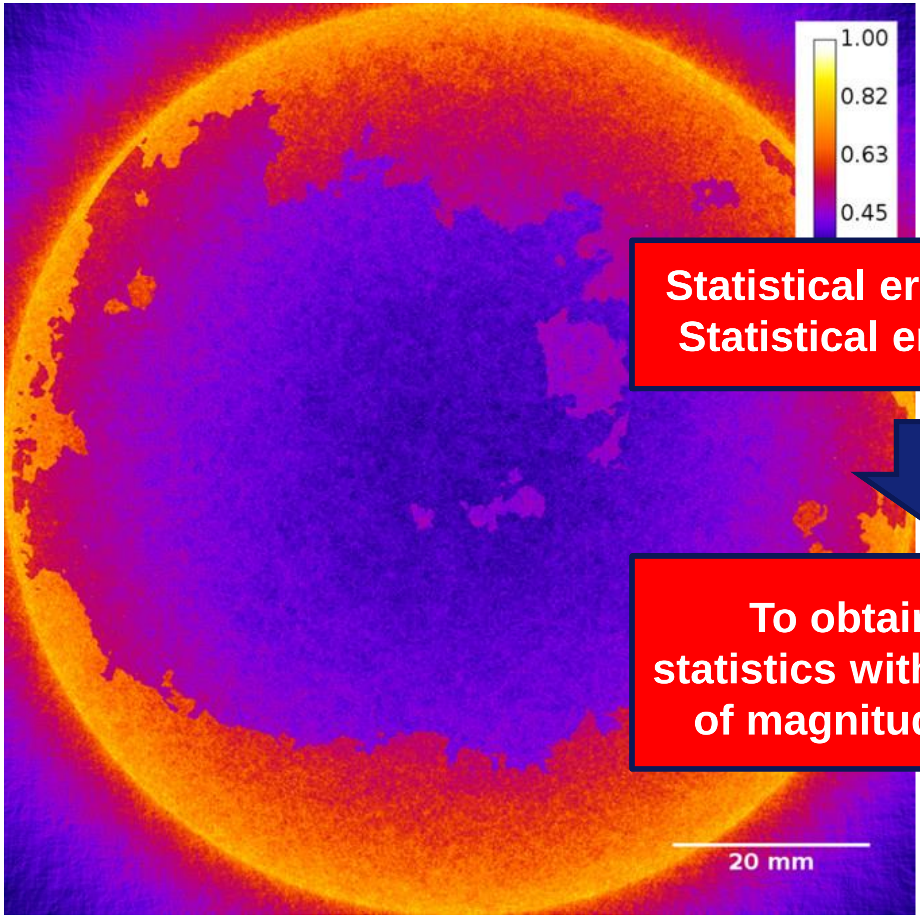


- ➢ **It requires fewer particles to converge**
- ➢ **Works when electron range is < spatial resolution (<100 keV)**
- ➢ **No significative energy escape (radiative, atomic deexcitation): Z<20; E<1 MeV**

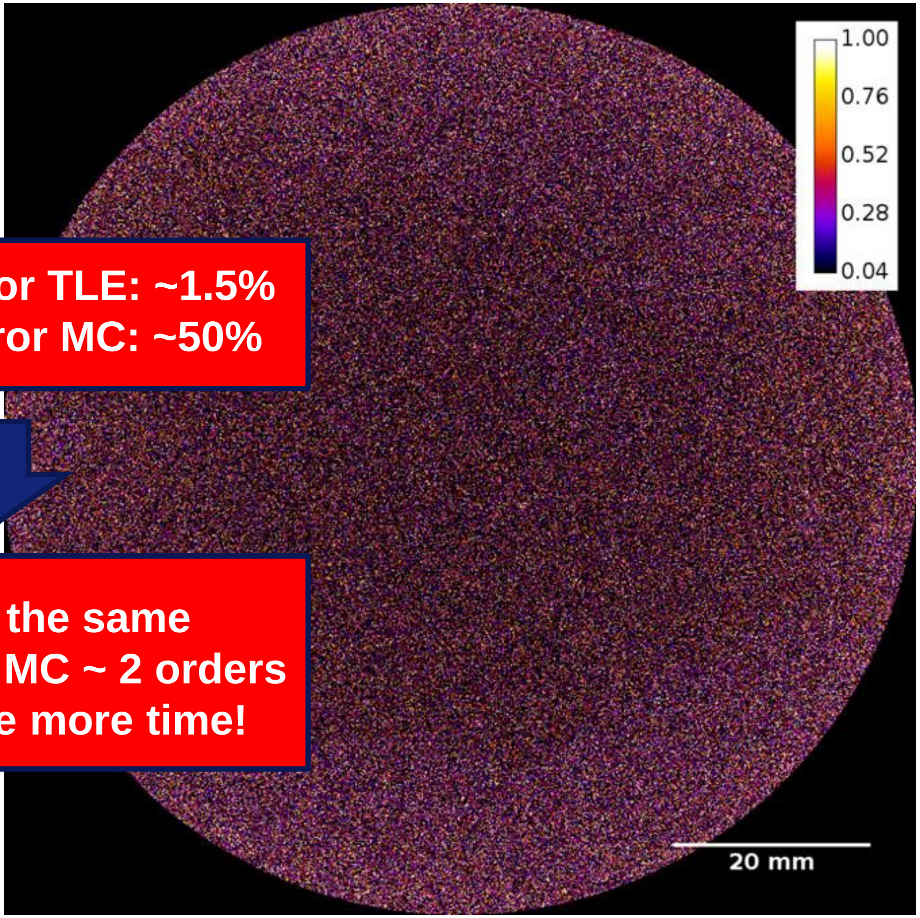
The TLE code (C++) has been integrated in <u>GATE</u> (Geant4)

10^7 events on segmented CT data of experimental <u>breast sample</u>

TLE Method[8,9]



Standard Monte Carlo

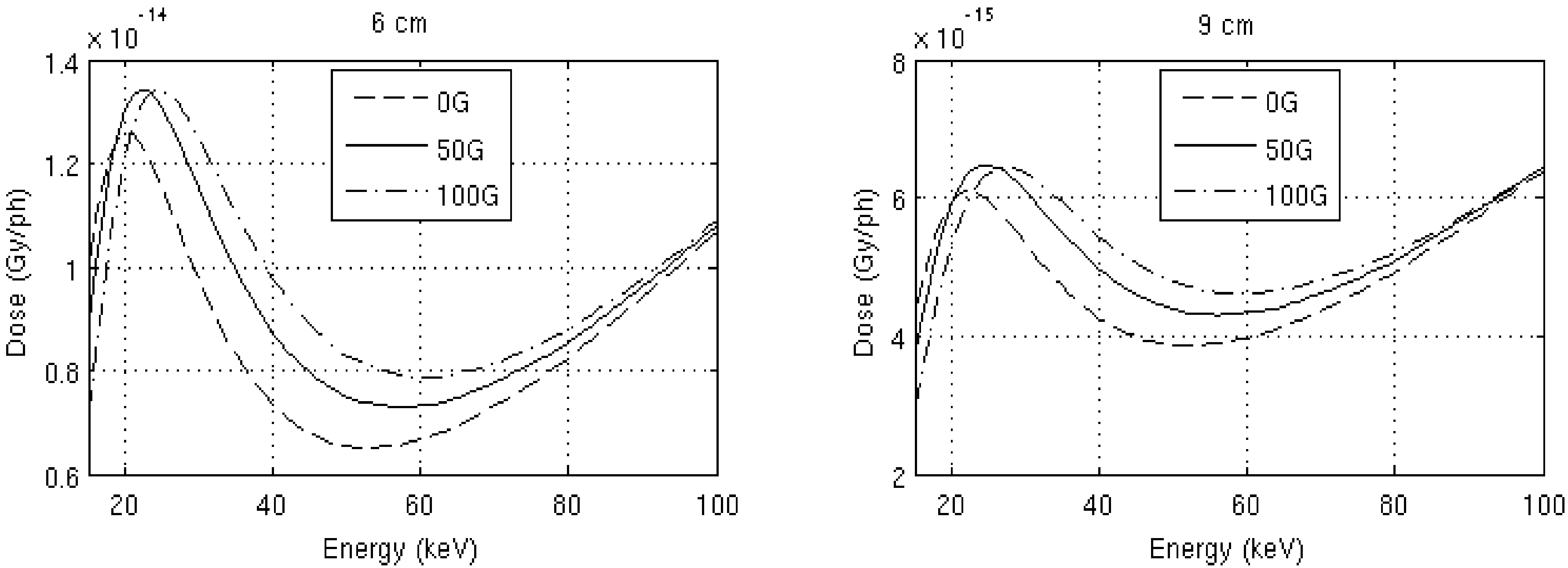


Statistical error TLE: ~1.5%
Statistical error MC: ~50%

To obtain the same statistics with MC ~ 2 orders of magnitude more time!

[8]**A. Mittone** et al, *J. Synchrotron Radiat.* 2013.
[9]F. Baldacci, **A. Mittone** et al, *Z. Med. Phys.*, 2015.

DOSE DATABASE FOR BREAST IMAGING[10]



Estimation of the average dose in a breast (monochromatic radiation):

-Range of energy: 15-100 keV
-Different geometries (thickness)
-Different compositions (fraction of glandular tissue)

A. Mittone et al, Phys. Med. Biol. **59** (2014) 2199–2217.

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