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EPIC

NEW TECHNOLOGIES AND STRATEGIES TO ENHANCE QUALITY IN MAMMOGRAPHY

NKI, December12, 2019

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CONTENTS

What could be an ideal system for breast imaging ?

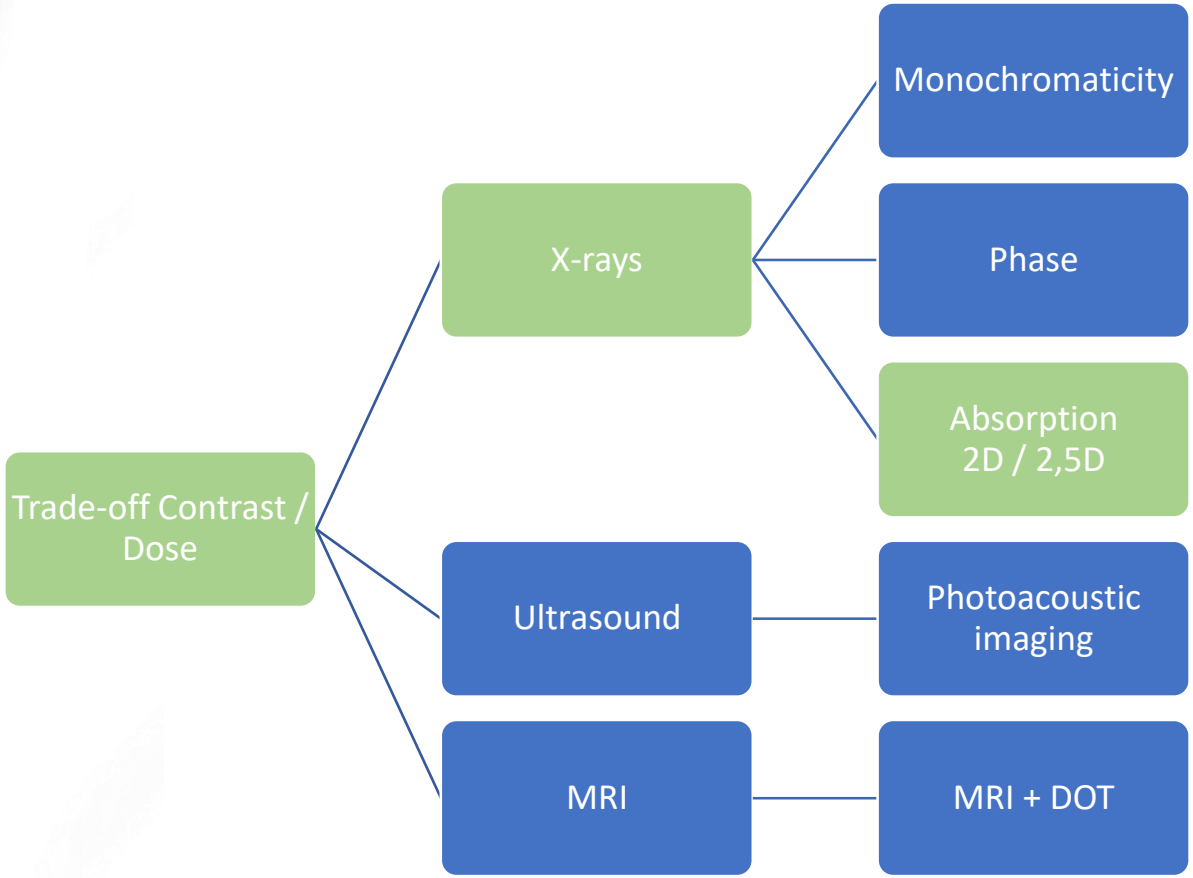
- Today existing system are :
  - Ionizing => could induce radiocancer and so limited number of exams are possible
  - Heavy => MRI
  - Costly (MRI)
  - Time consuming
  - Bad contrast (X ray)
  - Xray dose are too high
  - Low sensitivity for dense breast (X ray)
- Is photonics and other technics are able to improve and to get an breast imaging system:
  - Without hazard and risk and that can be repeatable, non ionizing
  - With high contrast, high deep penetration and high resolution,
  - Label free,
  - With short acquisition time,
  - With less pain for patients (compression),
  - Acceptable cost (purchase and maintenance) with respect to the improvement
  - Easy to use

Using lower dose while preserving image quality

Source	Year	Protocol for screening	Estimation	Induced Radiocancer	Trade-off
NHS UK	1995	1mGy per breast each 3 years	32 new cancers for 1 million women		
Feig & hendrick	1997	4mGy each year during 1 years between 40 & 50	20 new cancers for 100.000 women	8 deaths	
Yaffe	2011	3,7mGy each year between 40 and 55 then each 2 years till 74	86 new cancers for 100.000 women	11 deaths	136 years lost 10670 years gained
Hauge	2014	2,4mGy each two year between 50 and 69	10 new cancers among 100.000 women	1 death	350 saved lives
US	2016	Screening Each two years between 50 and 74	27 new cancers among 100.000 women	4 deaths	627 saved lives

Retrospective based on analogid devices / on digital devices

Technology landscape (incumbent and emerging)



Mammography Figures (2018)

Recent literature reports a sensitivity between 69% and 94% and a specificity between 78% and 95% for digital mammography, depending on patient age and breast density.

The positive predictive value is between 7% and 13% in screening examinations.

A non-invasive second-level examination is needed to clarify questionable or suspicious findings and avoid unnecessary invasive procedures such as biopsies.

How to increase detection by keeping dose at lower levels ?

Patient-assisted compression (PAC) versus technological compression (TC)

- Patients aged 40-90 years coming for bilateral mammography were included prospectively in the study. After positioning each breast, the technologist performed the compression and exposure of the first breast, initiated the compression of the other until 3 daN and then let the patient complete the compression using a remote control device.
- Image quality, compression force, breast thickness, average glandular dose and pain value for each breast were assessed for PAC and technologist compression (TC).
  - The compression level was significantly higher with PAC than TC for both craniocaudal
  - Breast thickness was reduced with PAC
  - The image quality was rated equivalent for both modes in 85% (85/100) of cases, superior for PAC in 10% (10/100) of cases and inferior in 5% (5/100) of cases.
- No significant difference in discomfort or pain felt between PAC and TC modes.
- 74% of patients reported that the self-compressing device would facilitate their reattendance
- **Moreover, as the breast compression level is increased, PAC may help reduce breast thickness, hence glandular dose.**
- The fact that patients have control over the procedure may change their perception of mammography and improve uptake and compliance.

Europena Journal of Cancer, Novembre 2018, Volume 103, Pages 137-142, Author Corinne Balleguier

Looking for other contrast than absorption

- The quality of the x-ray images is ultimately limited by **two** opposing factors
  - increased image spatial and contrast resolution requires an increased number of detected x-ray photons per image resolution unit,
  - direct dependence between the increased dose deposited by x-rays and the increased risk of tissue damage and further cancer development.

Strategies for optimization:

- Monochromatic x-rays instead of *Bremsstrahlung*
  - By eliminating x-ray frequencies outside of the range required for a specific application, the dose may be significantly reduced. It has been estimated that mammographic examinations performed with near mono-energetic x-rays will deliver a dose to the patient that will be from one-tenth to one-fiftieth of the dose delivered by a conventional x-ray system. This estimate is similarly applicable to angiography and other radiography studies.
- Utilization of x-ray refractive index – phase sensitive imaging
  - For materials of low atomic number, the variation of refractive index (phase shift) is about 1000 times higher than the variation of density (absorption): phase imaging has thus the potential to significantly increase the contrast of details in such materials. This gain in contrast is in particular even more significant for high energies, since phase shift decrease more slowly than absorption with increasing energy.

Issue : How to reduce synchrotron footprint

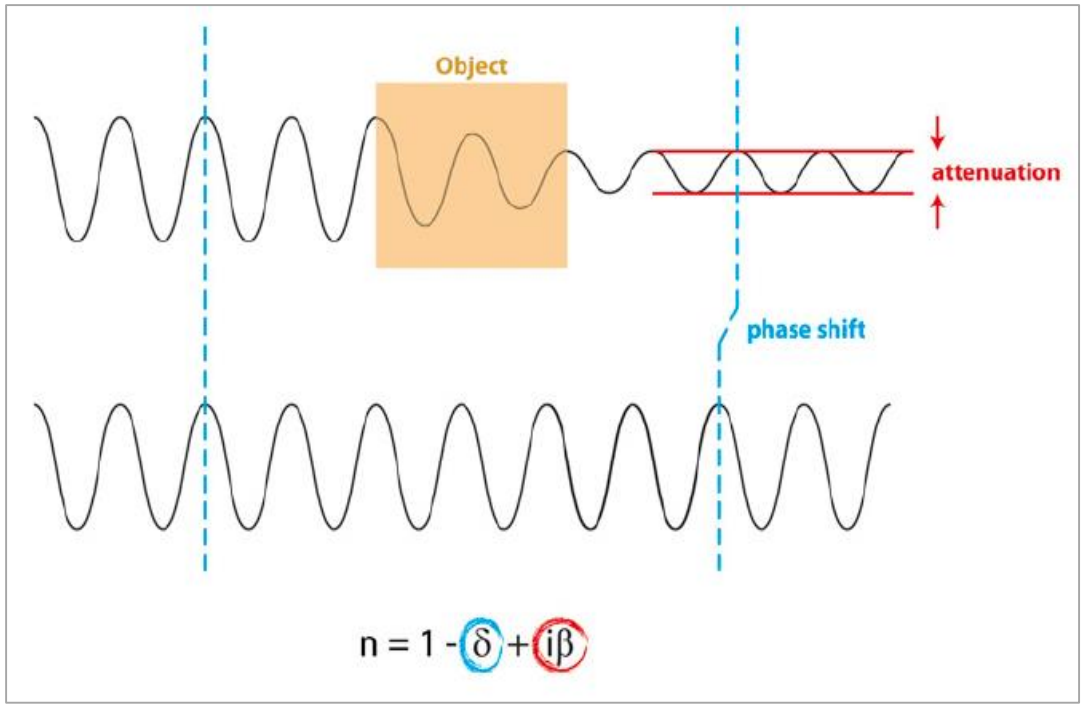
- Commercial
  - Munich Compact Light Source (MuCLS) from Lyncean Technologies inc.
- On-going development of high brightness X-ray sources,
  - cERL-based laser Compton X-ray source at KEK (Akagi *et al.*, 2016)
  - STAR (Bacci *et al.*, 2014, 2016)
  - Tsinghua Thomson Scattering X-ray Source (Du *et al.*, 2013)
  - ASU Compact XFEL (Graves *et al.*, 2017)
  - LLNL Laser Compton X-ray Source (Hwang *et al.*, 2016)
  - Smart*Light (Luiten, 2016)
  - NESTOR (Shcherbakov *et al.*, 2013)
  - SPARC_LAB Thomson Source (Vaccarezza *et al.*, 2016)
  - ThomX (Variola *et al.*, 2014)
  - Xpulse (2019)

The Lyncean CLS assembled at Lyncean Technologies' former headquarters in Palo Alto, CA

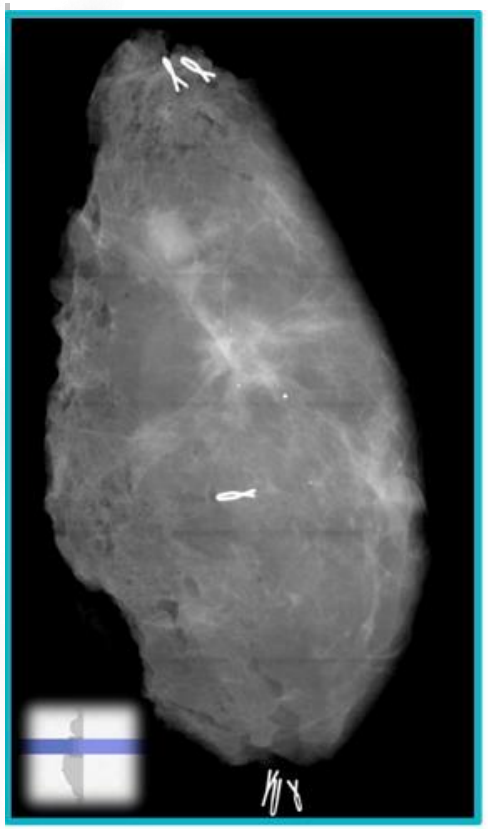
https://journals.iucr.org/s/issues/2019/05/00/yi5067/ - « Dos compatible grating-base phase-contrast mammography on mastectome specimens using a compact synchotron source »

How to use Phase contrast ?

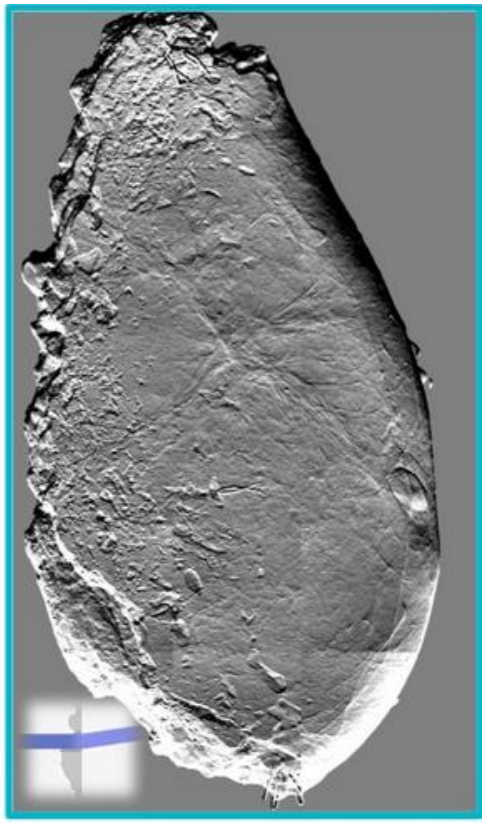
- The complex refractive index in the X-Ray range can be written using the formula: **n=1-δ+i.β** where δ is proportional to the phase shift and i.β is proportional to the absorption. The impact of an object on an X-Ray wave is represented in the opposite figure: the density is responsible for a decrease in the amplitude of the wave, while the refractive index creates a phase shift of the incoming wave.
- The phase shift is not directly detectable using conventional detectors that are sensitive to intensity, so that, when targeting phase imaging, it is necessary to implement a method that converts a phase shift to a modulation of intensity.



Results : Talbot interferometry (Pfeiffer)



Conventional radiography



Differential phase contrast image

The differential phase contrast image clearly enhances the spiculations features of the breast lesion.

This enhancement is diagnostically very relevant since spiculations are usually appearing in relation to malignant formations sometimes difficult to detect in conventional mammography

Source : Website GratXRays

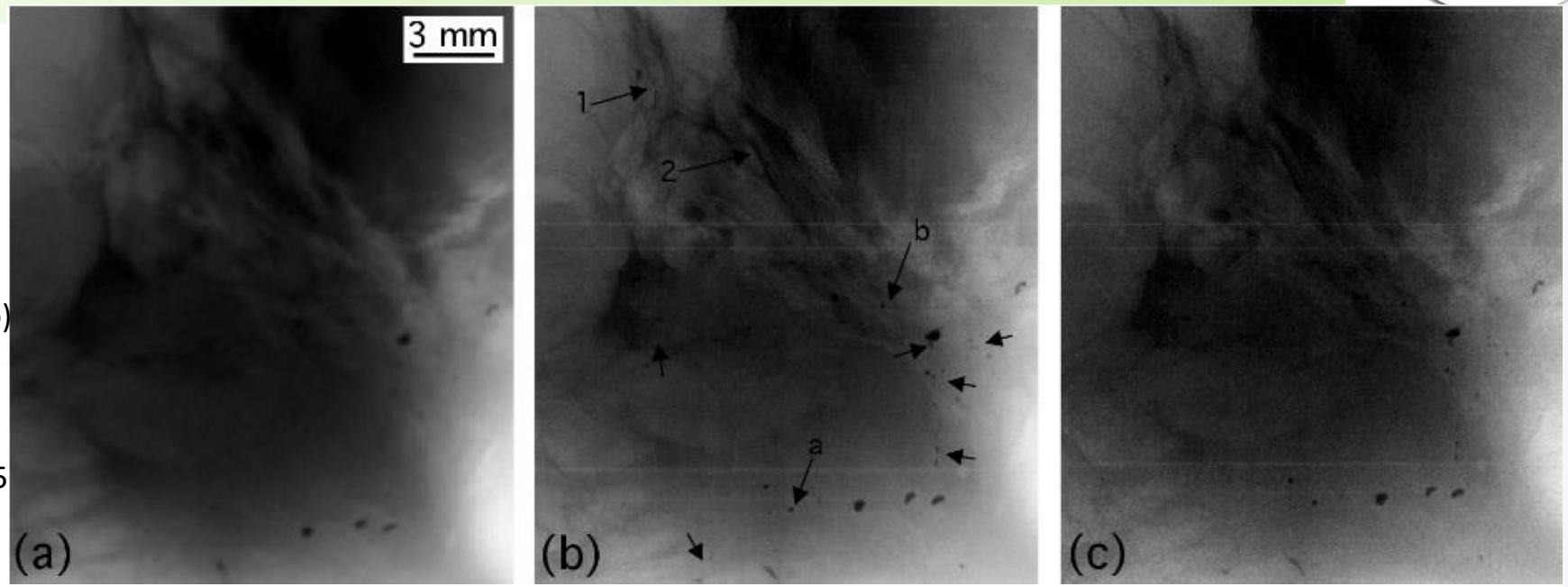
Pfeiffer & al

Results : Edge Illumination (Olivo)

XPCi image is apparent, in terms of both tissue definition (arrows labelled “1” and “2”) and increased microcalcification detection (unlabelled arrows).

Moreover, practically all calcifications detected in Figure 2(b) are still visible in Figure 2(c), obtained with reduced dose.

As the pixel size was 100 µm and 85 µm in the conventional and XPCI systems respectively, the increased microcalcification detection is **not due to a difference in spatial resolution, but is rather a phase effect**: the calcium/soft tissue interface generates x-ray refraction that deviates x-rays on the absorbing septa of the detector mask, thus leading to reduced detected intensity.



Absorption, 3mGy | Phase, 5mGy | Phase, 1mGy

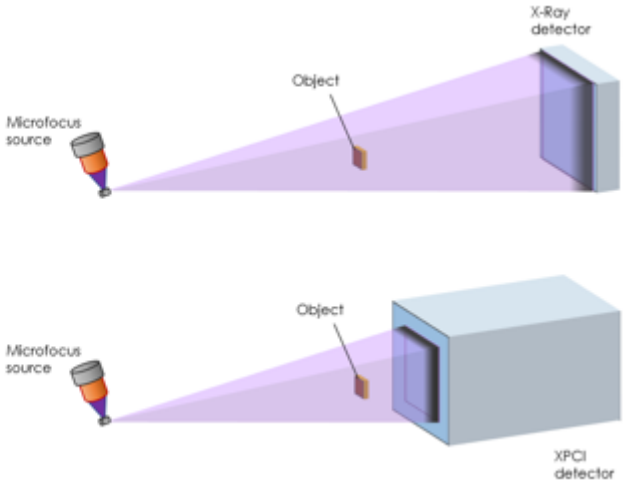
Specimen Tissue thikness : 2cm

Olivo & al

“Low-dose phase contrast mammography with conventional x-ray sources”, Olivo & al

Emerging : Snapshot Phase imaging

The following figure describes how a conventional X-Ray imaging system is modified to provide phase imaging using Imagine Optic's technology: basically, a specific mask is positioned between the object and the detector, at a certain distance (typically 50cm), so that a phase contrast imager can be roughly seen as an elongated X-Ray detector.



A single-shot phase/phase contrast X-ray image, achieved using a simple system with minimal technical differences vs. conventional X-Ray imaging systems based on local absorption measurement, would provide the following benefits:

- **Additional image contrast in a single acquisition,**
- **Capability to reveal details in samples of homogeneous density,**
- **Capability reveal details at high energies,** where samples mostly become transparent
- **Limited additional complexity/cost** when compared to other technical approaches,
- **Wide range of applications,** theoretically all applications where conventional X-Ray imaging fails to identify details, structures that do not show absorption contrast: biomedical imaging both ex-vivo and in-vivo, preclinical imaging, non-destructive testing, quality control, etc.

Claimed Parameter	
Resolution : FOV	20 µm : FOV 2mmx2mm / **50µm : FOV 11cm x 14cm**
Sensitivity (Δn)	0,1-10 µrad (exp required to transform it in optical indice variation)
Measurement time	Typ. 1 second depending of Source brightness and detector sensitivity
Compatible source	Microfocus X-ray tube (5-20µm emitting surface)
Detector	Flat Panel : 22 cm x 28 cm
	Reduced dose at higher energy (60keV versus 20-30keV)

Sources : « L'imageire de Phase pour les rayons X », Jerome Primot, ONERA, ImagineOpic contriubtions

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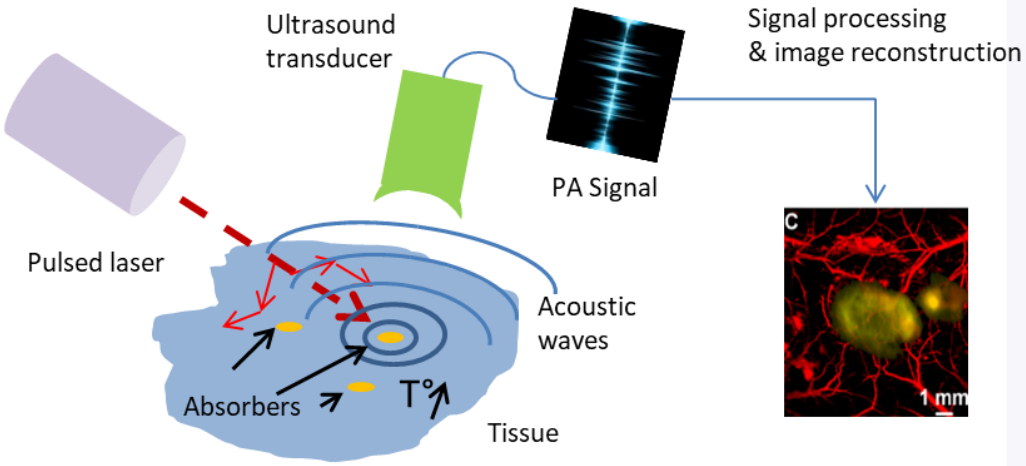
Photonics and business issue to overcome

- Mainly mask fabrication (pattern and size) for Snapshot Phase imaging
- Validation of the added value of Phase Imaging in Breast cancer diagnostics
- Understanding from medical experts what is missing in Various design tested
  - Momose (interferometry) – 20 years ago
  - Olivo (edge illumination) – 15 years ago
  - Pfeiffer (Talbot Laue interferometry) – 15 years ago

Principles of Photoacoutic imaging

- Photoacoustic Imaging is a biomedical imaging technics using a pulsed laser as an illumination source which is selectively absorbed by chromophore within the tissue.
- Absorbed energy produces a local and small temperature increasing, then yields a slight expansion of the object.
- This thermoelastic expansion produces a pressure increasing within the object which relaxes by launching acoustic waves into the surrounding media.
- Acoustic waves are weakly absorbed and scattered by the tissues and propagate through them up to tissue surface.
- They are detected by ultrasound transductors yielding to time resolved measurements
- Using appropriate signal processing and specific algorithms of back projection an image of the absorbed energy image is obtained.



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Properties of PAI

- PAI doesn't required contrast agent or biomarker, because all the molecules of the tissue absorb light at **specified wavelength**. They are important contrast agents for anatomic or functional studies.
- By choosing the right wavelength of excitation, the component of the tissue we want to see with a **high contrast** is selected.
- As the acoustic wave intensity is directly linked to the level of laser absorption by the targeted chromophores, non-absorbing molecules produces any signal. PA resulting images are obtained with **no background signal**.
- PAI can be used on small animal and human tissue :In vivo, (external or endoscopic), ex vivo and in vitro.
- PAI can be used to: Diagnostic a lot of diseases and pathologies at early stages, Monitor drug efficiency or pathology evolution: repeated examination are safe and also drug development.
- Due to its remarkable capabilities PAI with different devices and approach allows to get plenty of information : Anatomic or structural, Functional, Molecular, Kinetic and Monitoring image.

Structural information	Vasculature anatomy
Functional information	Blood Oxygenation
Molecular information	Glucose uptake monitoring
Kinetic information	Dynamic of probe perfusion
Monitoring information	Evolution of tumor angionesis

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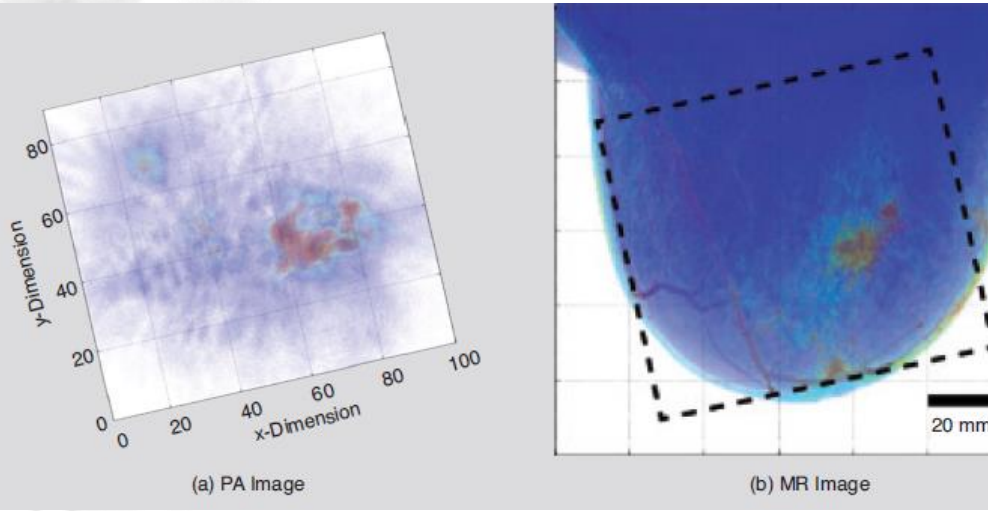
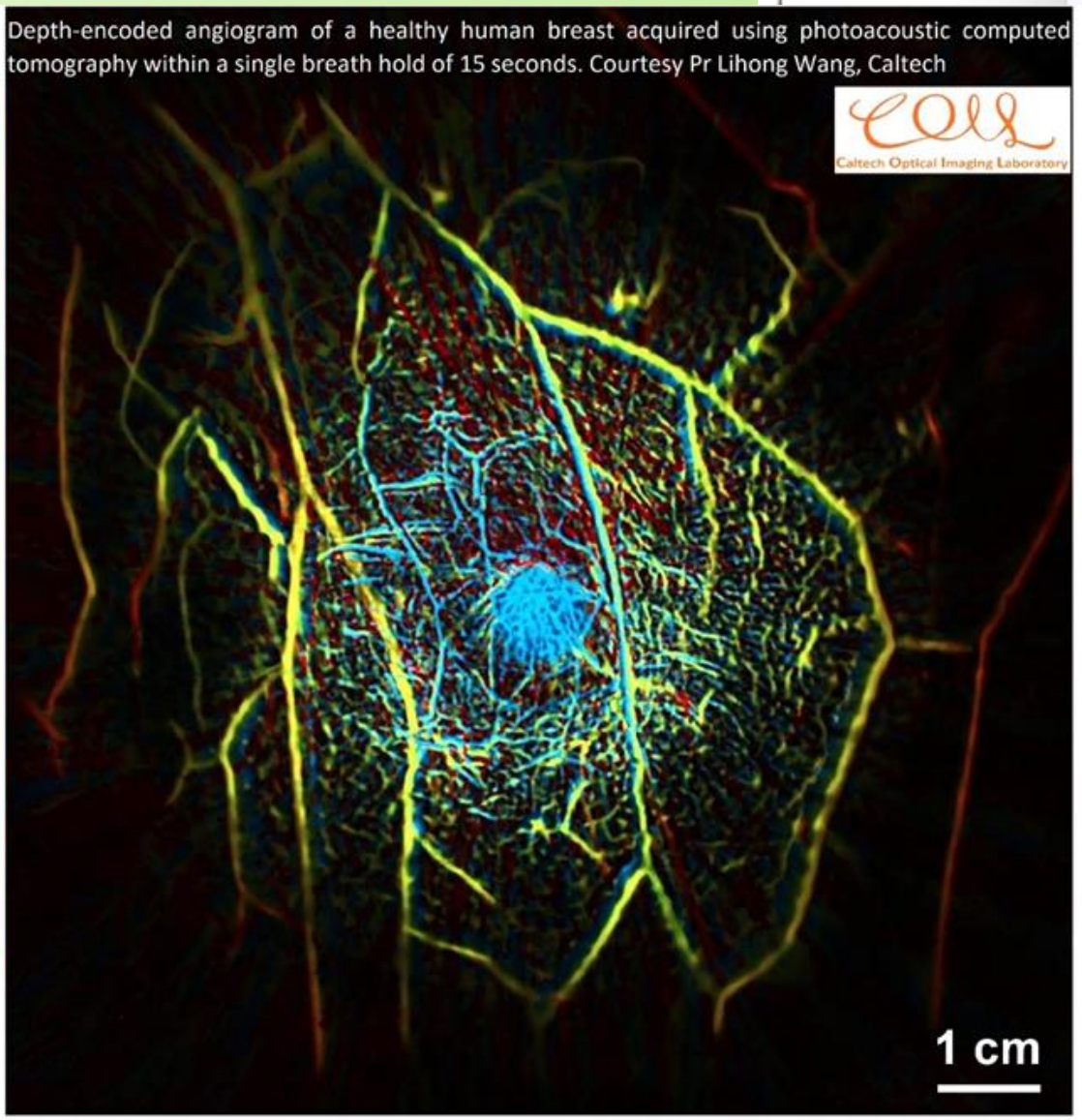
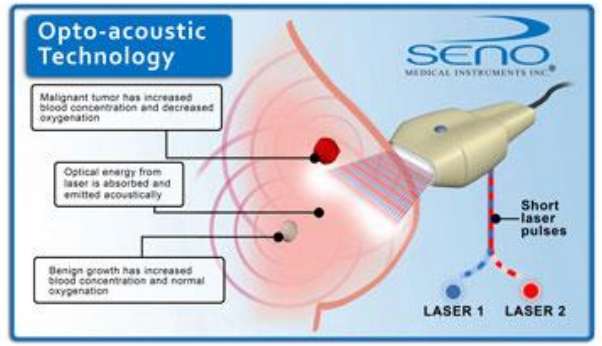


PAI and MRI of 63 year-olds patient with IDC (Infiltrated Ductal Carcinoma)
IEEE Pulse, May 2015, M. Heijblom et al., U. Twente)



Clinical Breast cancer diagnostic and Monitoring

- First photoacoustic product for Handheld systems (SENO)
- 2nd generation of photoacoustic mammography (PACT) devices which were or are in clinical trial and should soon leads to clinical product :
  - PA mammography system from Optosonic
  - « Laser Optoacoustic Imaging System » LOIS-64 from Tomowave
  - « Twente Photoacoustic mammoscope » from University of Twente PAM
  - PA mammography system from Canon
- These 4 systems are externally similar; typically they have a patient examination table with an aperture to suspend the patient's breast when lying in prone position.
- They differ in laser illumination, geometry of transducers arrays and geometry of the imaged volume,and signal processing and image reconstruction.
- Resolution < 200 - 400µ, penetration : some cm (4 - 8), acquisition time : 45s to 3'
- With tunable wavelength, image of tissue oxygenation is obtained.



U. Twente

Canon

Photonics and business issues to overcome

- Technical improvements are required :
  - To increase the repetition rate of lasers to reach faster image,
  - To reduce light source volume, laser diode is a good solution but they lack of energy per pulse,
  - To increase bandwidth of US transducers, CMUT should be a good device,
  - On software to be able to receive larger number of data to avoid artefact and increase resolution and to be able to treat them quickly to produce image in real time.
- To address a larger number of country and customers, cost reduction (light source, electronics modules…) are also needed.
- To bring answer to unmet clinical needs and clinicians acceptance are key points for commercial success.
- Funding :
  - Because from lab experiment to approval product around 10 years is needed
  - Because clinical trials and regulatory compliance is always a challenge for small companies.

Very emerging :
Combining Vis-NIR Laser Diodes with MRI for DOT

Hybrid time-domain and continuous-wave diffuse optical tomography instrument with concurrent, clinical magnetic resonance imaging for breast cancer imaging

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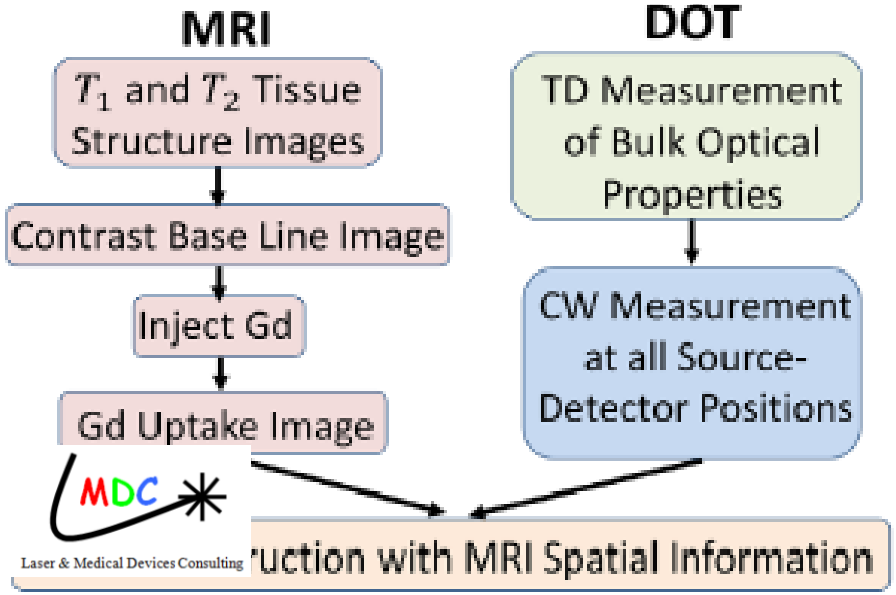


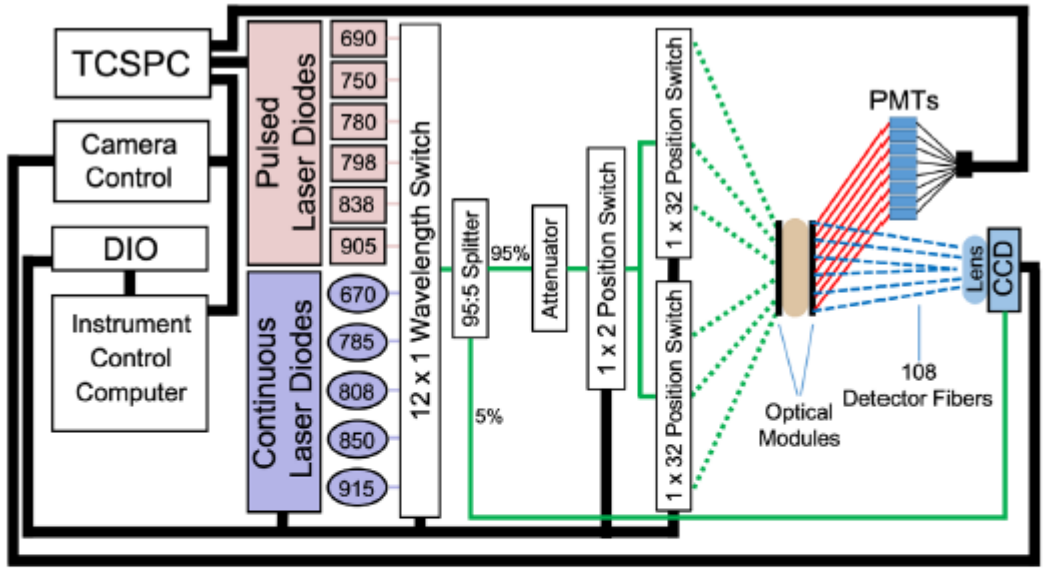
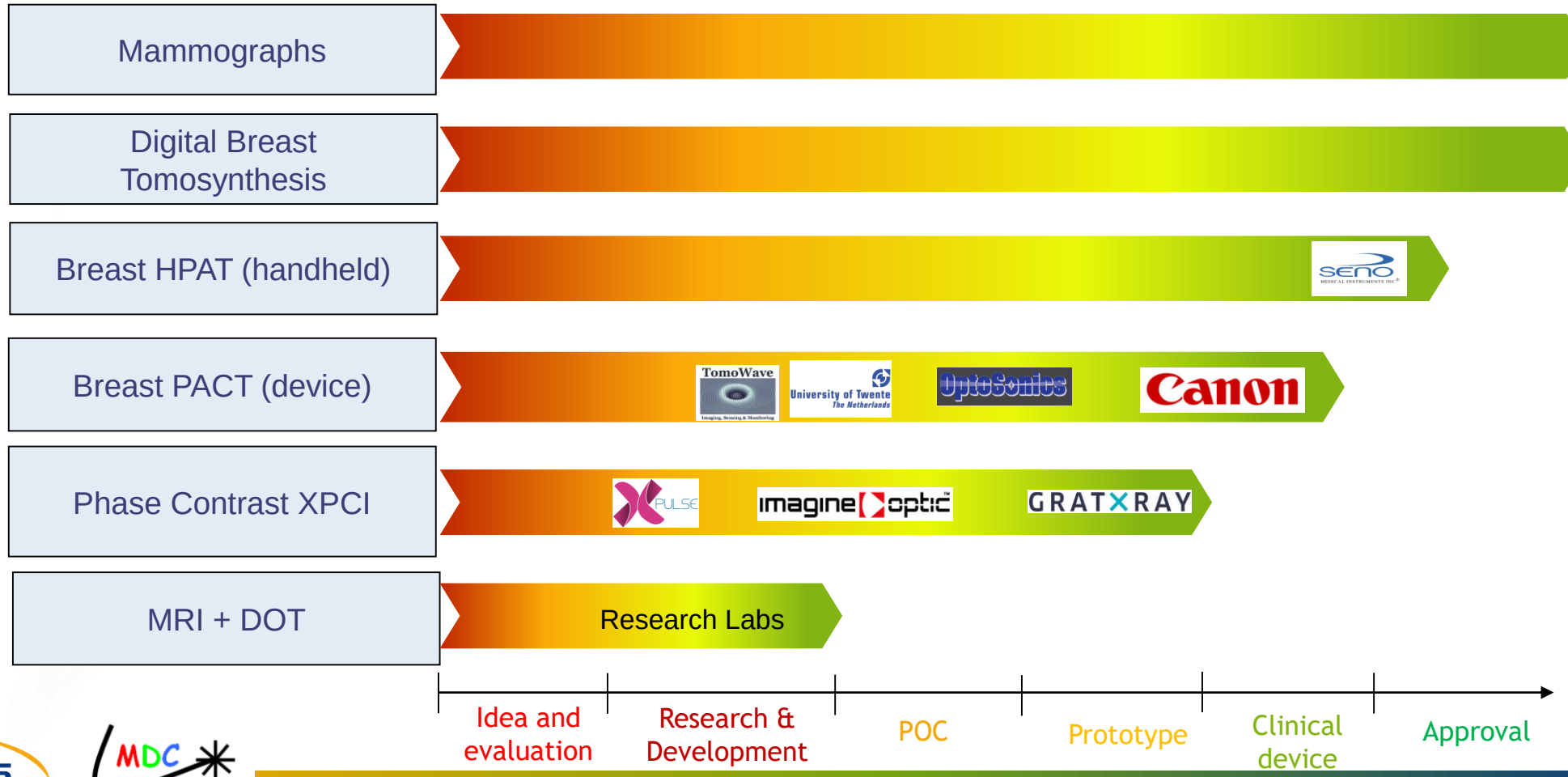


Fig. 1 Schematic of DOT-MRI instrument optics and electronics. This hybrid CW and TD DOT-MRI system employs six short-pulse (<70 ps) laser sources (690, 750, 780, 798, 838, and 905 nm) for TD measurement of absolute bulk optical properties (absorption and scattering) and five CW laser sources (670, 785, 808, 850, and 915 nm) for producing 3-D reconstructions of relative optical properties. The sources are coupled to optical imaging modules via a 12×1 wavelength switch and an effective 1×64 source position switch, i.e., a 1×2 switch and two 1×32 switches. A 95:5 splitter is also used, with the 95% arm coupled to the source position switch and the 5% arm coupled to a reference channel. CW detection is performed via detection fibers (108 positions) mounted on a plate and imaged onto a CCD, and TD detection (8 positions) is accomplished with PMTs and TCSPC modules. All components are controlled via the instrument computer, digital input/output channels, and a National Instruments DAQ board.

"Hybrid time-domain and continuous-wave diffuse optical tomography instrument with concurrent, clinical magnetic resonance imaging for breast cancer imaging," J. Biomed. Opt 24(5), 051409 (2019), doi: 10.1117/1.JBO.24.5.051409.

Commercial Maturity of studied modalities



This presentation was presented at EPIC Meeting on Photonics for Cancer Diagnostics and Treatment 2019

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