Development of ClearPEM-Sonic, a multimodal mammography system for PET and Ultrasound

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ABSTRACT: ClearPEM-Sonic is an innovative imaging device specifically developed for breast cancer. The possibility to work in PEM-Ultrasound multimodality allows to obtain metabolic and morphological information increasing the specificity of the exam. The ClearPEM detector is developed to maximize the sensitivity and the spatial resolution as compared to Whole-Body PET scanners. It is coupled with a 3D ultrasound system, the SuperSonic Imagine Aixplorer that improves the specificity of the exam by providing a tissue elasticity map. This work describes the ClearPEM-Sonic project focusing on the technological developments it has required, the technical merits (and limits) and the first multimodal images acquired on a dedicated phantom. It finally presents selected clinical case studies that confirm the value of PEM information.

KEYWORDS: Gamma camera, SPECT, PET PET/CT, coronary CT angiography (CTA); Multimodality systems
Breast cancer can be considered as the first cancer as occurrence among women (almost 40 cases per 100,000 women per year compared to the second one, cervix uteri cancer, with a rate of 15.2 per 100,000 per year) [1]. Its mortality is 23% of all cancer cases but an early detection can greatly reduce this number [2]. This is why a frequent screening (once every 1–3 years) is highly recommended for women from the age of 50 in most countries. Different techniques are adopted for breast cancer detection and the most common ones include radiography, ultrasound or magnetic resonance imaging. Anyway, these modalities present different problems. The detection of breast cancers by x-ray imaging is difficult in women with high breast density, since healthy tissues and cancer appear very similar in these cases [3]. Ultrasound tests show the same issues since the image is created by waves reflections where tissues have density variations. MRI can detect small lesions missed by the other techniques and without irradiation of the patient, but unfortunately cannot distinguish some difference between cancerous abnormalities. In order to avoid missed cancers detections, false positives are preferred and patients undergo a large number of unnecessary biopsies [4]. Whole-body positron emission tomography is able to provide metabolic information, but high cost and poor spatial resolution reduces its use only as support to the previous one. This problem can be solved with dedicate PET machines for mammography (PEM), less bulky and with a better spatial resolution.

ClearPEM-Sonic [5] has been designed and developed to answer these requirements. The ClearPEM [6, 7] module consists of a compact PET scanner designed for breast analysis with high spatial resolution. Developed by the Crystal Clear Collaboration [8] it is coupled with 3D ultrasound and elastography system Aixplorer from the SuperSonic Imagine company [9]. The combination of the two systems allows to perform multimodal exams where metabolic information (PET result) can be merged and compared with the morphological images provided by the US device. This combination may allow the detection of those cancers that are not visible in standard
imaging devices. This innovative scanner was born as an international project in the frame of CER-IMED (European Center for Research in Medical Imaging) and with the collaboration of partners from academic, clinical and industrial world:

- academic partners: CERN, Geneva, CH; the Aix-Marseille University, Marseille, FR; the Vrije Universiteit Brussels (VUB), Brussels, BE; the Laboratorio de Instrumentacao e Fisica Experimental de Particulas, Lisbon, PT; the Laboratoire de Mecanique et Acoustique, CNRS, Marseille, FR; the University of Milano-Bicocca, Milano, IT.
- industrial partners: PETsys, Lisbon, PT and SuperSonic Imagine, Aix-en-Provence, FR
- clinical partners: Assistance Publique Hopitaux de Marseille, Marseille, FR; Institut Paoli Calmettes, Marseille, FR

Two prototypes have been built up to now, the first is currently placed at ICNAS, Coimbra [10], PT. First clinical tests were performed at Hopital Nord (Marseille, FR), where the second prototype was initially installed (see figure 1), and are now being carried out at the San Gerardo Hospital (Monza, IT) where the machine was recently moved.

2 The project

2.1 ClearPEM

The fulcrum of the ClearPEM module is composed by the two heads holding the PET detectors [6, 7]. Each of them consists of 96 matrices of $8 \times 4 \times 2 \times 2 \times 20 \text{ mm}^3$ LYSO:Ce crystals with a casing of $BaSO_4$ acting as matrix structure and reflector for optical photons. It was chosen to couple each matrix with 2 Hamamatsu S8550 $4 \times 8$ APD matrices obtaining an active area about 46% of the total. In this configuration each crystal presents a double readout and depth of interaction information (DOI) is collected. The DOI resolution is determined by the measured light asymmetry per unit length. The first result we obtained, measured with the prototype in Coimbra, is better than 4%/mm, which corresponds to an uncertainty of around 2.8 mm on the exact position of the gamma interaction in the crystal [10]. Depolishing one of the $2 \times 20 \text{ mm}^2$ crystals surface, we are able to achieve a value of 5.21%/mm increasing DOI resolution but without affecting too much the light yield (only a 6% of LY is lost). We used a dedicated 192-channel ASIC for each
crystal signal with a threshold to discriminate low energy signals. The noise level is less than 2% at 511 keV while the average energy resolution is about 15.9%. A 10-bit sampling ADCs trans-
mits the digitized signal to the data acquisition system. The entire process can be computed with
a rate of 0.8 MHz [11]. A 360° complete acquisition can be obtained thanks to the rotation of a
robotic platform where the two heads are mounted on and a full 3-dimensional breast image can be
reconstructed. A rail allows the movement of the heads closer to the subject maximizing the solid
angle coverage while the high interaction probability provided by the high crystal density gives us
a high sensitivity. For instance the global detection efficiency in the centre of the plates has been
determined to be 1.5% at a plate distance of 100 mm [12]. The correction of the parallax error,
through the DOI evaluation, and the small section of the crystals installed make ClearPEM an high
spatial resolution PET scanner.

2.2 SuperSonic Aixplorer

The ultrasound system chosen is the Aixplorer by SuperSonic Imagine, Aix-en-Provence, FR [9].
It can work in a standard way (B-mode) providing a map of the tissues density variation in the
region of interest. Unfortunately, B-mode ultrasound images show limited contrast in the breast.
The reason why this ultrasound platform was chosen is that it can work also in elastographic mode.
Elastography is a technique to study and map elastic properties of tissues whose variation in the
breast are more evident than density one [13]. The principle of this technique is based on an ul-
trasound beam focused under the skin surface behaving as dipolar source of shear waves. Then
it is moved deeper inside the tissue faster than the sound waves it generates. The results is the
propagation of quasi-planar share waves that interfere constructively around a Mach cone. Their
propagation is able to deform regions they cross with an intensity that depends on the tissue stiff-
ness. During this process a standard ultrasound wave is emitted by the transducer, monitoring the
deformations inside the volume of interest. The information registered are computed to create an
elasticity map. A representation of this process is shown in figure 2. The Aixplorer probe used
in ClearPEM-Sonic is composed of a linear array that is able to create 2D images. Moving the
transducer a sequence of images is acquired and a 3D map is reconstructed. Ultrasound and elas-
tographic mode are applied one after the other in a single treatment that required about 20 seconds
to be performed. A typical acquisition covers a small volume ($40 \times 40 \times 40 \text{ mm}^3$) but composed of
very small voxels ($100 \times 100 \times 75 \text{ mm}^3$ size).
2.3 The multimodal system

The idea of this project is to provide physicians a more exhaustive breast exam using a multimodal system that can overcome the limitations of each imaging modality. PET scanners create high contrast maps of the cellular metabolic activity and they are therefore very suitable for the detection of cancer. On the other hand, the spatial resolution they can achieve is very poor if compared to other systems. Also ClearPEM, that is built for a specific exam, is not able to obtain the Aixplorer sub-millimetric precision. Therefore the two systems can cooperate for a better result joining their advantages. It is important to remember that also an elastographic picture carries information that is not visible by standard ultrasound systems.

An important task of this project was the realization of a merging software tool. 3D images of the region of interest (ROI) are computed independently by the two acquisition systems and they can be studied independently by physicians. But more interesting is the overlapping of the information carried by the 18F-FluoroDeoxyGlucose (FDG) density map and the elastographic map that can help the identification of smaller malignant lesions. To obtain this result a common reference system is required. In the ClearPEM-Sonic scanner the ultrasound probe is manually moved by the operator. It is not fixed to the system structure and only a mechanical flexible arm is applied to help the stabilization of the ultrasound probe. In this way the 3D map created by the ultrasound system can be placed and oriented everywhere in space. To follow and register the transducer position the trakSTAR magnetic tracking system (by Ascencion Technologies, Burlington, Vermont, U.S.A.) was chosen. The transducer spatial position is measured with 1.4 mm RMS and its inclination angle with 0.5 degrees RMS. This is possible using a magnetic signal transmitter placed to the base of PEM detectors and a receiver fixed to the ultrasound probe. The software will follow transducer position during an ultrasound acquisition and the data collected will be computed to rotate the 3D image in the PEM reference system. Figure 3 shows the apparatus placed between the two plates. The images merging software was developed in the 3D Slicer framework [14], a multiplatform open source software for image visualization and manipulation. It was integrated in a unique user-friendly interface [15] and with just one platform the user can launch PEM image reconstruction, co-registration of both images and save the results in DICOM file format.

Figure 3. Photograph of trakSTAR magnetic tracking system and of the arm where the transducer is fixed [5].
3 Detector performance

3.1 Phantoms

In order to calculate the spatial resolution that the ClearPEM scanner is able to achieve a standard procedure is applied using mini-Jaszczak phantom produced by Bioscan. The object is composed of rods of different diameters from 1 to 1.5 mm with steps of 0.1 mm as it possible to see in figure 4. Rod with the same diameter are grouped together so that the distance between centres of two adjacent rods is equal to twice the rod diameter. The phantom is filled with FDG, containing 5 MBq of activity. The image is reconstructed with a list-mode file based OSEM algorithm with a voxel size of $0.5 \times 0.5 \times 0.5 \text{ mm}^3$ and an energy window accepting events between 400 and 650 keV, a time window of 4 ns is chosen [16] and a fast Fourier transform bandpass filter is applied to enhance the contrast in the image. An estimation of the spatial resolution was performed on the ClearPEM installed in Marseille and a value better of 1.4 mm was obtained (see figure 5). This result can show the potentiality that ClearPEM has, in particular if it is compared to other commercial PEM devices as PEM Flex Solo II (Naviscan PET Systems, Inc) which is able to reach a spatial resolution of 2.4 mm [19] or Mammi-PEM scanner (Oncovision, Valencia, Spain) with 1.6 mm of spatial resolution [20].

A multimodality test is performed to check the automatic co-registration of the images acquired with both the systems. This kind of test is performed to fully simulate a real breast exam. For this reason a breast shape Agar gelatin phantom [17] is prepared. With this material acoustic properties can be modified just using different amount of gelatin obtaining an object very close to what cancerous lesions surrounded by healthy tissue look like. Moreover 18F-FDG can be injected
Figure 6. a) US image, b) elastography image and c) PEM image of a gelatin/Agar phantom [5].

Figure 7. Images obtained using a Siemens Biograph 15 PET/CT (a), and using MRI (b). Figures (c) and (d) show the coronal and sagittal views respectively, of the ClearPEM images obtained with same breast [18].

and a complete PET+US acquisition may be performed. The separate results of this multimodal exam are shown in figure 6, while the superimposition of the two images is waiting for further tests in order to evaluate in the right way the accuracy of the procedure.

3.2 Patient trial

With due approval, a first clinical trial on 20 patients [18] was started at Hopital-Nord, Marseille. In this work we report one of the clinical trials where ClearPEM has demonstrated its potentialities in breast cancer diagnosis. During the preliminary exam a multifocal breast cancer was detected in this patient (see figure 7). Two lesions have been revealed by the whole-body PET/CT scanner, one in the left breast and the second close to the axilla. Smaller lesions around the first one can be detected only using MRI. The high sensitivity and spatial resolution that ClearPEM can achieve allow the detection of those smaller spots. Unfortunately the second cancerous focus is too close to the thoracic wall and ClearPEM is not able to scan that region since it is out of the field of view of the detector.

4 Conclusion

ClearPEM-Sonic is a multimodal scanner developed to improve the diagnosis of breast diseases. Collaboration efforts have brought to combine a high resolution PEM scanner with an ultrasound system, the SuperSonic Imagine Aixplorer. Metabolic information can be rapidly compared with morphological ones and thanks to a custom dedicate software they can be fused in a single 3D-
image easily accessible by hospital staff. The prototype installed in Hopital Nord, Marseille has been already tested. With calibration phantoms a spatial resolution close to 1.3 mm was measured for the ClearPEM device and the co-registration system was able to acquire images with both modalities. ClearPEM-Sonic has started a first clinical trial to develop an exam protocol and to evaluate the patient safety. The first acquired data are promising since ClearPEM scanner is able to detect small lesion not visible by mean of a WB-PET device.

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