Molecular imaging: high resolution detectors for early diagnosis and therapy monitoring of breast cancer


1. Istituto Superiore di Sanita’ and INFN - gr. Sanita’ – Rome, Italy
2. University La Sapienza, Rome, Italy
3. University Tor Vergata, Rome, Italy
4. CNR Napoli, Napoli, Italy
5. Jefferson Lab, Newport News, VA, USA
6. Massachusetts Institute of Technology, Cambridge, MA, USA

Abstract

Dedicated high resolution detectors are required for detection of small cancerous breast tumours by molecular imaging with radionuclides. Absorptive collimation is normally applied in imaging single photon emitters, but it results in a strong reduction in detection efficiency. Systems based on electronic collimation are complex and expensive. For these reasons, the simulations and measurements have been performed to design optimised dedicated high resolution mini gamma camera. Critical parameters are contrast and Signal to Noise Ratio (SNR). Intrinsic performance (spatial resolution, pixel identification, and response linearity and uniformity) were first optimised. Pixellated scintillator arrays (NaI(Tl)) of different pixel size were coupled to arrays of PSPMT’s with different anode pad dimensions (6 x 6 mm$^2$ and 3 x 3 mm$^2$). Detectors having a Field Of View (FOV) of 100 x 100 mm$^2$ and 150 x 200 mm$^2$ were designed and built. The electronic system allows read out of all the anode pad signals. The collimation technique was then considered and limits of coded aperture option were studied. Preliminary results are presented.

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1. Introduction

Breast cancer is a major health problem especially for women from developed countries. Early detection leads to early and thus more efficient treatment leading to better outcomes. The most widely used screening technique for asymptomatic women is mammography, which is in general very sensitive but not specific. In addition, it cannot detect efficiently lesions in women with dense breast or after surgical interventions. As a result, majority of mammography-directed biopsies are performed on benign lesions and a significant number of biopsies are therefore unnecessary. Hence, additional adjunct diagnostic methods need to be applied. Among them molecular imaging with radionuclides has a central role to play. Standard gamma cameras were initially used and have shown the ability to differentiate malignant from benign lesions, but they do not offer sufficient resolution to detect small lesions when used in breast imaging scintimammography procedure with $^{99m}$Tc-sestamibi. Several designs of dedicated gamma cameras have been implemented, tested and shown to substantially increase the detection sensitivity for sub-centimeter size lesions [1-3]. Nevertheless, there is still high level of interest in novel technologies for these compact gamma cameras to further improve their performance in the breast imaging tasks. Key parameters for detecting small lesions are: spatial resolution, Signal to Noise Ratio (SNR) and contrast. Energy resolution plays only a secondary additional role when imaging breast under compression [4,5]. After thorough optimization of intrinsic detector properties, the collimation technique has to be carefully designed in order to maximize the SNR, which is critical in the detection of small lesions with low uptake. Optimisation procedure of intrinsic properties of the gamma detector includes selection of scintillator material and its degree of segmentation, as well as proper scintillation light sampling characteristics. Electronics, Data AcQuisition (DAQ) system and image reconstruction techniques also play an important role and have to be properly selected to match the imager sensor performance. In this paper we report about such an initial optimisation study, funded by the Italian Ministry of Health for the Italian National Institute of Health, in collaboration with the Imaging Departments of Rome and Naples Universities. Simulations for the optimization of the scintillator/photomultiplier array based detector intrinsic properties, phantom measurements, as well as pilot clinical trials in early cancer detection were performed, as described below.

2. Equipment and experimental methods

Our aim is to design a system optimized for its intrinsic performances: spatial resolution, pixel granularity, response linearity etc.

2.1 Simulation

Extensive simulations have been performed in the past by our group by means of EGS4, TracePro and IDL software. Results are reported elsewhere [6,7].

The work continued using the GEANT4 code. A complete report can be found in [8]. Here we report main results of the new study.

2.2 Detectors

NaI(Tl) scintillators have been used because of the good match between scintillation emission and response of bialkali photocathodes used in photomultipliers. Arrays made of NaI(Tl) with different pixel sizes (down to the present technological limits for NaI(Tl) arrays fabrication) with pixel pitch of 2.0, 1.5 and 1.2 mm) were coupled to arrays of Position Sensitive PhotoMultiplier Tubes (PSPMT) with two anode pad dimensions (6 x 6 mm$^2$ and 3 x 3 mm$^2$). The obvious choice for the photodetectors was the Hamamatsu H8500 and H9500 (“flat panel”) PSPMT’s. They are very compact having a metal envelop of 51.7 x 51.7 x 15.4 mm$^3$. The photocathode in these PMTs is bialkali and it has 12 stages of metal channel dynodes for electron multiplication. H8500 active area of 49.7 mm$^2$ (effective area of 97%) is covered by an anode array consisting of a 8 x 8 matrix in which each individual anode is 6 x 6 mm$^2$. H9500 has the same size and main internal structure but it has higher granularity anode consisting of a 16 x 16 matrix of individual anode pads of size 3 x 3 mm$^2$. 
2.2 Electronics

The PMT anode pad channels are read independently by a track-and-hold multiplexed system (based on the VATA IDE AS system). This solution significantly improves the quality of imaging (in particular in terms of peak-to-valley ratio and correction of spatial distortions of the centroids maps). Readout multiplexing permits to reduce complexity and cost of electronics, providing, in the adopted solution, an up to 2 kHz event rate for 1024 channels, limited by the write access speed of the mass storage subsystem. Higher rates can be obtained with more recent, still cost-effective solutions (that are under evaluation) where a sparse readout logic is introduced at the track-and-hold stage or after the multiplexed ADCs.

2.3 Data processing

Higher flexibility of the independent channel readout (with respect to the conventional resistive chain) is exploited at different levels during the processing of the data: the collected charge centroid is computed on gain-normalized anode pad channels after a proper spatial windowing (specific feature of the independent pad readout) that reduces distortion effects of the background and impact by noisy channels. The centroid map of a flood calibration run defines the crystal (pixel) centers and, therefore, a local mapping of the PMT channels on the regular crystal grid. Border and residual spatial distortions are then compensated by a projection of the centroid image from the PMT channel to the crystal grid defined by the above mapping.

2.5 Collimation Technique

The role of collimation system has been studied. Two parallel hole collimators have been used. First, a general purpose (22 mm length, 1.9 mm hexagonal holes) and a second with 22 mm long 1.5 mm holes. Then the coded aperture option has been considered. In fact once the intrinsic detector performances have been optimised, the only way for improving the contrast and the SNR of a detector is the collimation system. It has been shown [9-11] that it is possible to increase sensitivity by careful design of the collimator system, maintaining very good spatial resolution. We have started studying the limits of this techniques for small breast tumour detection.

3. Results

3.1 Simulations

Fig.1 and 2 show the main results: the SDV of the reconstructed – measured centroid vs the photodetector anode dimension for different scintillator pixel sizes (Fig. 1), and the SNR vs scintillator pixel size (Fig. 2). Results in Fig. 1 show that anode pixel size at least as small as 3x3 mm$^2$ is needed for sampling the light coming from 1.0 x1.0 mm$^2$ NaI(Tl) scintillator pixels. The anode element dimension is the one that minimized the SDV of the difference between the reconstructed and measured centroids.

Fig.2 shows the SNR vs tumour size for different scintillator pixel sizes, different photodetector anode pixels and different collimators. SNR improves with smaller scintillator pixel size, provided small anode pixel size is used, especially for small tumours. The superior performances of the larger pixel size for 1.3 mm, for tumours larger than 6 mm, seems to be due to insufficient sampling of the smaller scintillation pixel by the 3 x 3 mm$^2$ anode pixels.

![Fig. 1: SDV of the reconstructed – measured centroid vs anode pixel size for different scintillator pixel sizes (NaI(Tl)).](image-url)
PSPMT model H9500 from Hamamatsu has 3x3 mm$^2$ anode pad size and has acceptable active area, unlike the previously used small anode pad PSPMT model Hamamatsu R5900 M64 (with even smaller 2 x 2 mm$^2$ anode pad size) which has too small active area to be seriously considered for our application.

Nevertheless further studies, as well as comparison with measurements have still to be performed.

### 3.2 Measurements

Two detectors of different dimensions (100 x 100 mm$^2$ and 150 x 200 mm$^2$) have been built to be able to use a “dual detector head system” for clinical trials. In fact it has been shown in phantoms [12] that using two opposed detector heads increases the efficiency of the system in detecting tumours located anywhere in the breast.

Measurements have been performed with $^{57}$Co sources as well as with $^{99m}$Tc filled phantoms.

Fig. 3 shows the two detectors and the gantry ready for calibrations in one of the Hospitals involved in the project.

![Fig. 3: The detectors and the gantry.](image)

![Fig. 4: Light sampling of 1.5 x 1.5 mm$^2$ CsI(Tl) scintillator crystal-pixels coupled to PSPMT’s with different anode pixel size. (a) Hamamatsu C8, (b) M16 (anode pixel: 4 x 4 mm$^2$), (c) M64 (anode pixel: 2 x 2 mm$^2$).](image)

Fig. 4 shows the importance of light samplings. Smaller scintillator pixels require smaller photodetector anode pixels. Proper digitization of the image is possible only after good pixel identification.

Fig. 5 shows the importance of the electronics. Individual readout improves light sampling and the pixel to valley ratio and then the digitization.

![Fig. 5: Comparison between results obtained with a 1 x 1 x 6 mm$^3$ 1.2mm step NaI(Tl) pixel arrays and H8500 PMT’s using different readout electronics: resistive chain (a) and individual readout (b).](image)

Fig. 6: Image of multisource $^{99m}$Tc phantom.
In Fig. 6 image obtained with multi-source phantom is showed, with spherical tumours of 12, 10, 9, 8, 7, 6 mm for uptake ratio of 10:1 (lesion to background). 1.3 x 1.3 x 6 mm\(^3\) NaI(Tl) scintillator pixels sampled by H8500 PSPMT’s (6 x 6 mm\(^2\) anode pixel) were used to obtain this result.

Higher combined detection efficiency will produce better images. Moreover the present detector structure with H8500 PSPMT’s is not yet optimized. Indeed as previously shown, better SNR can be obtained if H9500 PSPMT is used. This will however require new electronics with more readout channels is not yet available.

3.2.2. Coded aperture collimation

Coded aperture collimation option has been considered. Simulations and measurements show that much better SNR and contrast can be obtained in principle but a reduction of field of view (FOV) is unavoidable. Moreover, further work is needed to prove the applicability of such a technique [13].

3.2.3 First clinical trial

In Fig. 8 we show the very first imaging result from the clinical trial at the Imaging Department of University of Tor Vergata. In this uncorrected image, a tumour of 1 cm in diameter is clearly visible at the chest wall at the top of the image. The image has been taken with the upper detector shown in Fig. 3 (100 x 100 mm\(^2\), NaI(Tl) 1.3 x 1.3 mm\(^2\) sampled with H8500 (6 x 6 mm\(^2\))). The shown image is without any uniformity correction, which is especially important in the dead areas between the PSPMT’s. During operation the image from this smaller detector will be combined with the one taken from the detector positioned on the other side of the breast.

Fig. 7: SNR vs tumour dimension.

Fig. 7 shows the SNR for different tumour sizes. Tumours of 6 mm are “visible” (SNR > 5).

4. Summary and conclusions

Detectors for imaging breast tumours have been designed and built in the framework of the study, funded by the Italian Ministry of Health for the Italian National Institute of Health, in collaboration with the Imaging Departments of Rome and Naples Universities. The system is practically ready for clinical trials. Optimization has been performed in order to find the best configuration of the scintillator type, pixel dimension, photodetector pixel size, electronics readout and collimation system.

Simulations show that NaI(Tl) scintillator pixel size as small as 1 x 1 mm\(^2\) gives the best SNR, provided that correct light sampling is performed. This means using small PSPMT anode pixels (not larger than 3 x 3 mm\(^3\)). First generation electronics readout system able to read all the individual channels has been used.

Phantom studies have been performed with 1.3 mm NaI(Tl) scintillator pixels coupled to H8500 Hamamatsu PSPMT’s. Tumours as small as 6 mm were visible with uptake ratio of 10:1. Using smaller scintillator pixels requires new readout with higher number of readout channels, therefore new multi-channel electronic readout has to be built. In fact a new system for reading out an even higher number of...
channels (~ 5000) with high rate capability (up to ~ 20 kHz) is under study.

4.1 Future plans

According to the performed simulations and based on the preliminary measurements we believe that new multi-channel electronics will enable using high performance breast imagers built from arrays of smaller anode pixel size PSPMTs (Hamamatsu H9500) and smaller scintillator pixel sizes (1.0 mm or so). Our goal is to build such a system.

In a near future we plan full optimization of the dual head detector layout is under development.

We will continue study of an alternative collimation system (coded aperture). It could be the key parameter in detecting small tumours (< 5 mm in diameter) provided better radiopharmaceuticals are available. In fact Bombesin has been already shown to be a possible alternative to MIBI [14-16].

Moreover, we will evaluate better scintillators such as LaBr₃:Ce with higher number of produced photons that recently appeared on the market.

We will also perform comparative simulations continue of the best scintillation layout (continuous scintillator vs small pixels).

Finally, photodetectors with even smaller anode pixel (1.6 x 1.6 mm²) are now available (Model 85021 PSPMT from Burle). This would allow better light sampling and higher number of pixels in the image with possible improvements in the coded aperture collimation case. We are indeed planning to perform evaluations of this high granularity PSPMT.

References

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