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Molecular imaging by radionuclides: applications to the investigation of *in vivo* biological processes and to the early diagnosis of cancer

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The human genome mapping is expected to boost a deeper understanding of human disease and physiology. The effective exploitation of this potentiality of medical science demands new tools for the investigation of biological processes. In fact, the conventional analysis of the genetic information does not permit *in vivo* analysis. On the other hand, the application of the molecular imaging techniques to the study of small animal models is considered an important and efficient way to investigate genetic and biochemical processes. However, radionuclide imaging methods are technologically complex; they needs specific detection systems with challenging characteristics in terms of efficiency and spatial resolution. The design and development of these detectors can take great advantage from the advanced techniques used in high energy and nuclear physics research. The present report summarizes aspects of the applied research in the molecular imaging for early breast cancer diagnosis and small animal imaging studies.
Key words: Molecular imaging, Coded aperture

Istituto Superiore di Sanità
***Imaging* molecolare con radionuclidi: tecnologie avanzate per lo studio di processi biologici *in vivo* e la diagnosi dei tumori.**
A cura di Maria Lucia Magliozzi, Evaristo Cisbani, Francesco Cusanno e Franco Garibaldi
2006, iii, 19 p. Rapporti ISTISAN 06/14 (in inglese)

La mappatura del genoma umano consentirà una comprensione profonda della fisiologia e patologia umana ma sono necessari mezzi nuovi per comprendere i processi biologici a livello cellulare ed applicare queste informazioni allo studio delle malattie dell'uomo. L'analisi convenzionale della espressione genica, infatti, non consente studi di processi biologici *in vivo*, spesso indispensabili. L'applicazione delle tecniche di *imaging* molecolare allo studio di modelli di piccoli animali è uno dei mezzi che consentono di comprendere, *in vivo*, aspetti importanti dei processi biologici. Tali tecniche risultano particolarmente complicate perché i sistemi di rivelazione necessitano di caratteristiche molto spinte in termini di risoluzione spaziale ed efficienza. È necessario quindi progettare e costruire rivelatori dedicati facendo uso delle tecniche avanzate derivanti dalle ricerche nel settore della fisica nucleare delle alte energie. Questo rapporto sintetizza alcune delle ricerche in questo campo e le applicazioni di queste alla diagnosi precoce del cancro alla mammella e all'*imaging* di piccoli animali.
Parole chiave: SPECT di piccoli animali, Aperture codificate

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La responsabilità dei dati scientifici e tecnici è dei singoli autori.

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FOREWORD

The human genome mapping is expected to boost a deeper understanding of human disease and physiology.

The effective exploitation of this potentiality of medical science demands new tools for the investigation of biological processes at the cellular and structural levels.

In fact, the conventional analysis of the genetic information generally requires ex vivo essay by biopsy or post mortem tissues. Such studies are time-consuming, use a large number of animals, and do not permit *in vivo* analysis.

On the other hand, the application of the molecular imaging techniques to the study of small animals (mainly mice) models is considered an important and efficient way to investigate genetic and biochemical processes. Moreover, similar imaging techniques can be applied successfully in early tumour diagnosis with high specificity.

Bio-medical imaging methods include planar nuclear medicine, single photon or positron emission tomography – SPECT (Single Photon Emission Computed Tomography) and PET (Positron Emission Tomography) –, Computer Tomography (CT) by X-rays, optical imaging, nuclear magnetic resonance (Magnetic Resonance Imaging, MRI) and related spectroscopy (Magnetic Resonance Spectroscopy, MRS).

The imaging techniques by means of radionuclides present a specific and some time unique role: they are extremely sensitive (at the picomolar level typical of the *in vivo* processes) to the metabolism of the investigated system, other than to their morphology.

However, radionuclide imaging methods are technologically complex; they needs specific detection systems with challenging characteristics in terms of efficiency and spatial resolution. The design and development of these detectors can take great advantage from the advanced techniques used in high energy and nuclear physics research.

The present report summarizes aspects of the applied research, carried on by the Unit of Nuclear Physics and Technology for Health of the Department of Technology and Health, in the molecular imaging for early breast cancer diagnosis and small animal imaging studies.

MOLECULAR IMAGING: HIGH RESOLUTION DETECTORS FOR EARLY DIAGNOSIS AND THERAPY MONITORING OF BREAST CANCER

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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-centimetre 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 in imaging breast under compression (4, 5). After thorough optimisation 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. The optimisation procedure of the intrinsic properties of the gamma detector includes the selection of the scintillator material and its degree of segmentation, as well as proper light sampling characteristics. Electronics, Data AcQuisition (DAQ) system and image reconstruction techniques can also play an important role.

In this paper we report about such an initial 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 optimisation 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.

Equipments and methods

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

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 the main results of the new study.

Detectors

NaI(Tl) scintillators have been used because of the good match between scintillation emission and response of bialkali photocathodes used in photomultipliers. Arrays of NaI(Tl) of 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 (6×6 mm^2 and 3×3 mm^2). The obvious choice for the photodetectors was the Hamamatsu H8500 and H9500 (“flat panel”) PSPMTs. They are extremely compact with an active area of 5.08×5.08 cm^2. The H8500 is very compact having a metal envelop of 51.7×51.7×15.4 mm^3. The photocathode in these PMTs is bialkali and it has a 12 stages of metal channel dynodes for electron multiplication. The PMT active area (effective area of 97%) is covered by an anode array consisting of a 8×8 matrix in which each individual anode is 6×6 mm^2. The H9500 has the same size and main structure but it has different anode consisting of a 16×16 matrix of individual anodes of size 3×3 mm^2.

Electronics

The PMT anode pad channels are read-out 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 and spatial distortions of the centroids maps). Multiplexing permits to reduce complexity and cost of electronics, providing, in the adopted solution, a 2 kHz event rate of 1024 channels, limited by the write access speed of the mass storage sub-system. 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.

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 equalized channels after a proper spatial windowing (peculiar of the independent readout) that reduces distortion effects of the background and noisy channels. The centroid map of a flood calibration run defines the crystal (pixel) centres 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.

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 22 mm length (1.5 mm hole). 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 technique for small breast tumour detection.

Results

Simulations

Figure 1 and 2 show the main results, the SDV of the reconstructed-measured centroid *vs* the photodetector anode dimension for different scintillator pixel sizes (Figure 1) and the SNR *vs* scintillator pixel size (Figure 2).

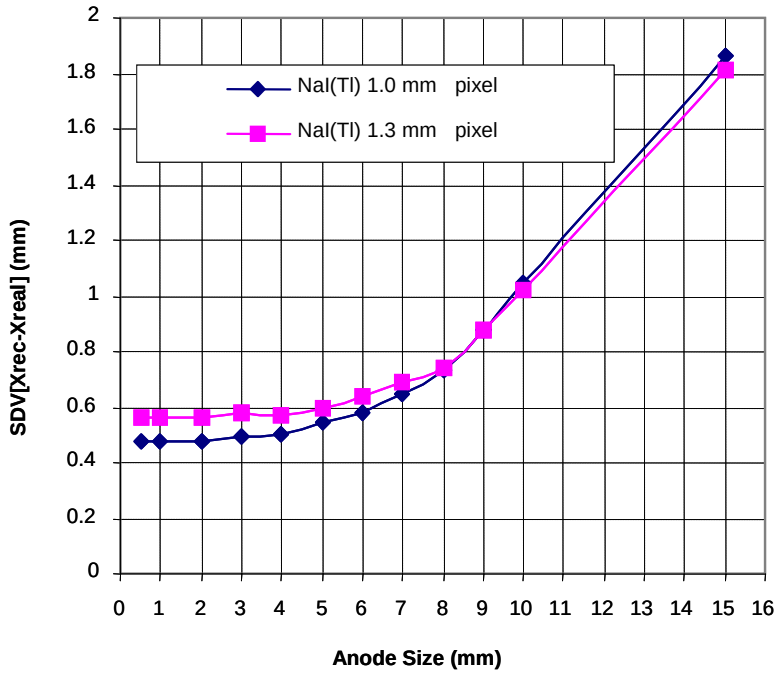


Figure 1. SDV of the reconstructed-measured centroid *vs* anode pixel size for different NaI(Tl) scintillator pixel size

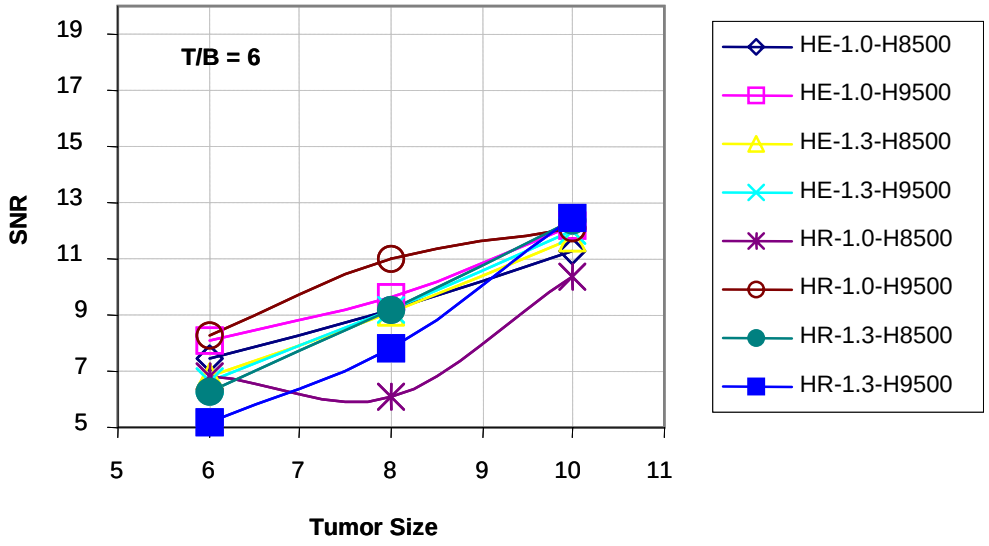


Figure 2. SNR *vs* tumor size for uptake 6:1 for different scintillator pixel size, phododetector's anode pixel size and collimators

Figure 1 shows that anode pixel size (at least) as small as 3×3 mm^2 is needed for sampling the light coming from 1.0×1.0 mm^2 NaI(Tl) scintillator pixels. The anode dimension is the one that minimized the SDV of the difference between the reconstructed and measured centroid.

Figure 2 shows the SNR *vs* tumor size for different scintillator pixel size, different photodetector anode pixel and different collimators.

SNR improves with smaller scintillator pixel size, provided small anode pixel size is used, especially for small tumors. The superior performance of the larger pixel size for 1.3 mm, for tumours bigger than 6 mm, seems due to insufficient sampling of the smaller pixel by the 3×3 mm^2 anode pixel.

Practical photodetectors PMT model H9500 from Hamamatsu has 3×3 mm^2 anode pad size and has acceptable active area unlike another PMT model Hamamatsu R5900 M64 (with even smaller 2×2 mm^2 anode pad size) which has too small active area to be seriously considered.

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

Measurement

Two detectors of different dimensions (100×100 mm^2 and 150×200 mm^2) were built to be able to use a "dual detector head" for clinical trials. In fact, (12) using a "dual head detector" in phantoms increases the efficiency of the system in detecting tumours located in any position in the breast.

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

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

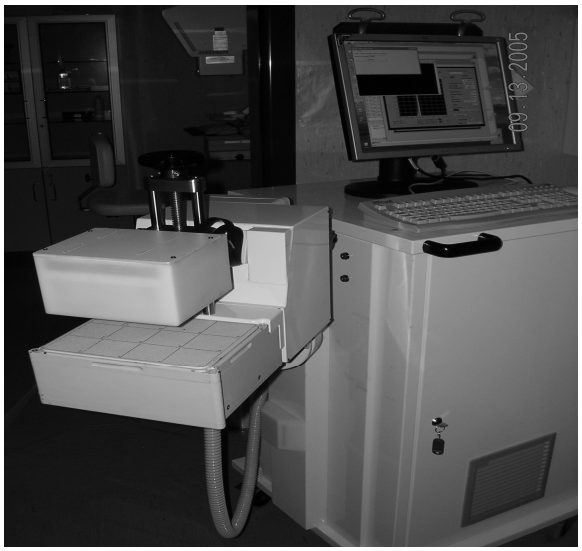


Figure 3. The detectors and the gantry

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

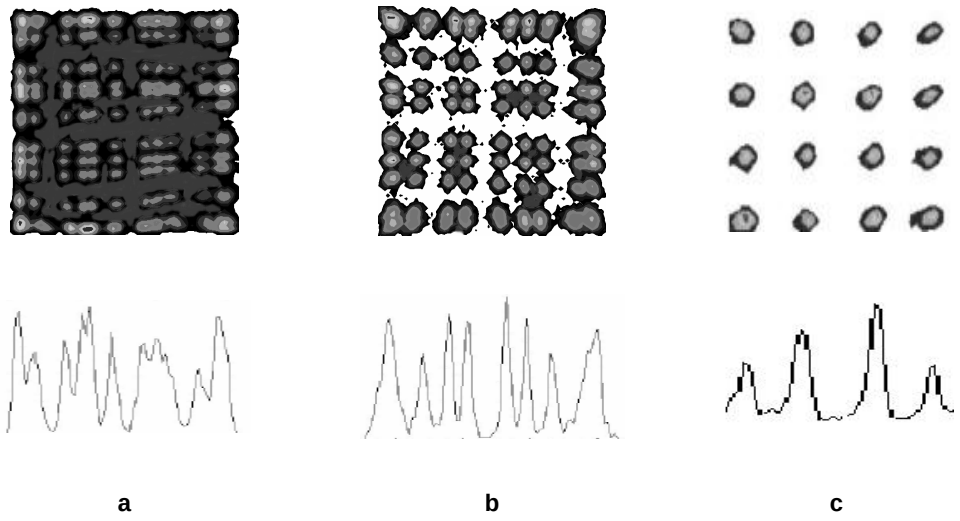
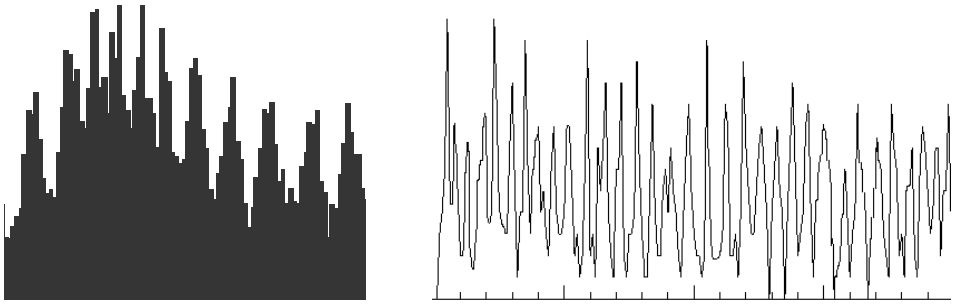


Figure 4. Light sampling of 1.5×1.5 mm^2 CsI(Tl) scintillator crystal-pixels coupled to PSPMT's with different anode pixel size: (a) Hamamatsu C8, (b) M16 (anode pixel: 4×4 mm^2), (c) M64 (anode pixel: 2×2 mm^2)

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



a **b**

Figure 5. Comparison between results obtained with a 1×1×6 mm^3 NaI(Tl) pixel arrays and H8500 PMT's using different readout electronics: resistive chain (*a*) and individual readout (*b*)

In Figure 6 measurement with multisource phantom is showed, with spherical tumors of 12, 10, 9, 8 7, 6 mm with uptake ration of 10:1 (lesion to background). 1.3×1.3×6 mm^3 NaI(Tl) scintillator pixels sampled by H8500 PSPMT's (6×6 mm^2 anode pixel) are used.

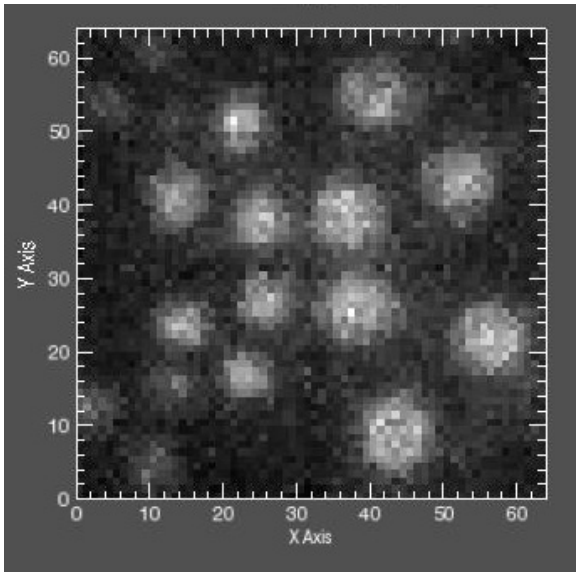


Figure 6. Image of multisource ^{99}Tc phantom

Figure 7 shows the SNR for different tumour sizes. Tumours of 6 mm are "visible" (SNR>5).

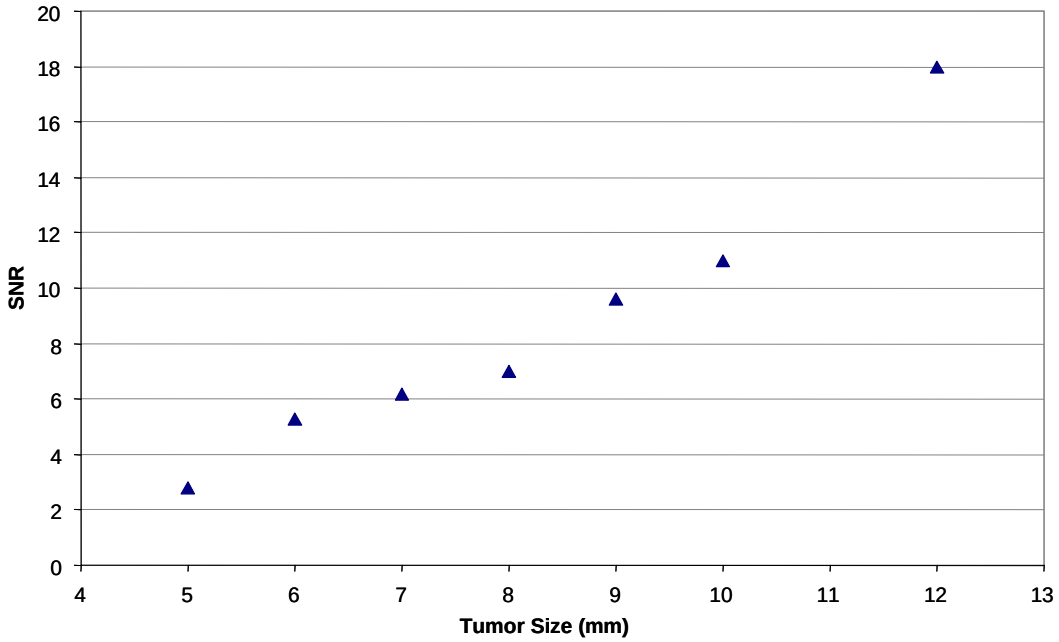


Figure 7. SNR *vs* tumor size with uptake ratio of 10:1. 1.0×1.0×6 mm^3 NaI(Tl) scintillator pixels sampled by H8500 PSPMT's (6×6 mm^2 anode pixel) are used

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.

First clinical trial

In Figure 8 we show the very first obtained imaging result from the clinical trial at the Imaging Department of University of Tor Vergata. In this uncorrected image, a tumor 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 (100×100 mm^2, NaI(Tl) 1.3×1.3 mm^2 sampled with H8500 (6×6 mm^2)).

The shown image is without any uniformity correction especially important in the dead areas between the PSPMTs. During the operation the image from this smaller detector will be combined with the one taken from the detector positioned in the other side of the breast. Higher combined detection efficiency will produce better images. Moreover the present detector structure with H8500 PSPMTs 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 optimized yet. In fact as previously shown, better SNR can be obtained if H9500 PSPMT is used.

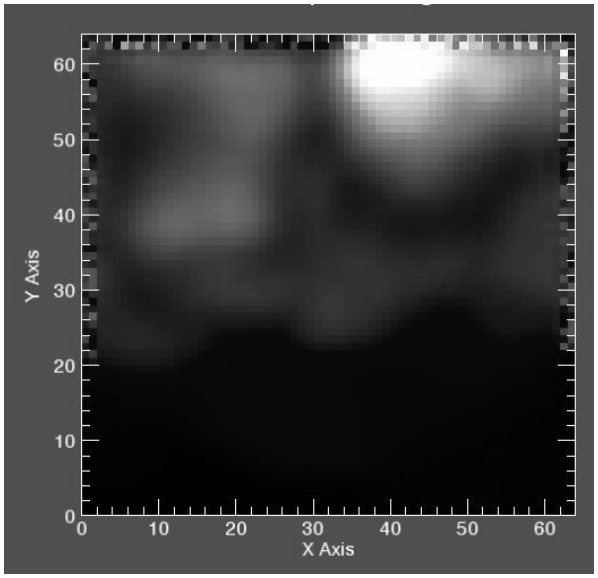


Figure 8. A tumor of ~10 mm is cleary detected

Conclusion

Detectors for imaging breast tumors have been designed and built in the framework of the study, funded by the Italian Ministry of Health for the Istituto Superiore di Sanità (the National Institute of Health in Italy), in collaboration with the Imaging Departments of Rome and Naples Universities. The system is practically ready to start 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 1×1 mm^2 gives the best SNR, provided the correct light sampling is performed. This means using small PSPMT anode pixels (at least 3×3 mm^2). The electronic system able to read out all the individual channels has been used.

Measurements with phantom have been performed with 1.3 mm NaI(Tl) scintillator pixels coupled with H8500 Hamamatsu PSPMT's. Tumors as small as 6 mm are visible with uptake 10:1. Using smaller scintillator pixel size requires an higher number of channels, so a new electronics. 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.

The new electronics will allow using smaller anode pixel size (Hamamatsu H9500) so smaller scintillator pixel size (1.0 mm) that, according to the simulations seems to improve the SNR.

Full optimization of the dual head detector layout is under development.

Study of an alternative collimation system (coded aperture) has been performed. It could be the key parameter for the real possibility of detecting small tumors (< 5 mm in diameter) provided better radiopharmaceuticals are available. In fact Bombesin has already shown to be a possible alternative to MIBI.

Moreover better scintillators ($LaBr_3$:Ce) appear in the market and will be used as soon as they become available.

Simulations are underway to for choosing the best layout (continuous *vs* pixellated).

Photodetectors with very small anode pixel (1.6×1.6 mm^2) are now available (Model 85021 from Burle). This would allow better light sampling and higher number of pixels in the image with possible improvements in the coded aperture collimation.

References

1. Pani R, *et al*. Multi-PSPMT scintillation camera. *IEEE Trans Nucl Sci* 1999;46:702-8.
2. Kieper D, Majewski S, *et al*. Optimization of breast imaging procedure with dedicated compact gamma cameras. *Nucl Instr Meth* 2003;A 497:168-73.
3. Gruber GJ, *et al*. A discrete scintillation camera module using silicon photodiode readout. *IEEE Trans Nucl Sci* 1998;NS-45:1063-8.
4. Garibaldi F, *et al*. Optimization of compact gamma cameras for breast imaging. *Nucl Instr Meth* 2001;A 471:222-8.
5. Gruber GJ, *et al*. Monte Carlo simulation of breast tumor imaging properties with compact, discrete gamma cameras. *IEEE Trans Nucl Sci* 1999;46(6):2119-23.
6. Cusanno F, *et al*. Preliminary evaluation of compact detectors for hand-held gamma cameras. *Phys Med* 2004;XX(2):65-70.
7. Lo Meo S. Imaging *molecolare ad alta risoluzione con radionuclidi, per l'applicazione alla diagnosi precoce del tumore della mammella* [thesis]. Rome: University of Rome "La Sapienza", 2005.
8. Magliozzi ML, *et al.* (Ed.). *High resolution, high sensitivity detectors for molecular imaging of small animals and tumor detection*. Proceeding of 9th International Conference of Advanced Detectors. Como (Italy), October 17-21, 2005.
9. Accorsi R, Gasparini F, Lanza RC. A coded aperture for high-resolution nuclear medicine planar imaging with a conventional anger camera: experimental results. *IEEE Trans Nucl Sci* 2001;48(6):2411.
10. Accorsi R, Gasparini F, Lanza RC. Optimal coded aperture patterns for improved SNR in nuclear medicine. *Nucl Instr Meth* 2001;A 474:273-84.
11. Garibaldi F, *et al*. Small animal imaging by single photon emission using pinhole and coded aperture collimation. *IEEE Tran Nucl Sci* 2005;52(3 Pt1):573-9.
12. Kieper D, *et al*. (Ed.). Improved lesion visibility in a dedicated dual head scintimammography system – Phantom results. In: Metzler S (Ed.). *2002 IEEE Nuclear Science Symposium Conference Record*; Norfolk, Virginia, November 10-16, 2002.
13. Fenimore EE, Cannon TM. Coded aperture imaging with uniformly redundant arrays. *Appl Opt* 1978;17:337-47.
14. Cinti MN, *et al*. Tumor SNR analysis in scintimammography by dedicated high contrast imagers. *IEEE Trans Nucl Sci* 2003;50(5):1618-1623.
15. Accorsi R. *Design of near-field coded aperture camera for high resolution medical and industrial gamma ray imaging* [PhD thesis]. Cambridge, MA: Massachusetts Institute of Technology; 2001.
16. Garibaldi F, *et al*. Scintillator and photodetector array optimization for functional breast imaging. *Nucl Instr Meth* 2003;A:497:51-59.

HIGH RESOLUTION, HIGH SENSITIVITY DETECTORS FOR MOLECULAR IMAGING WITH RADIONUCLIDES: THE CODED APERTURE OPTION

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Introduction

Molecular imaging with radionuclides is very powerful because it is sensitive to imaging biological processes *in vivo*. A wide range of human diseases can be studied in animal models and early detection of small tumours with high specificity is in principle possible, provided an adequate detection system is available. In fact, simultaneous requirements in terms of high spatial resolution and high sensitivity make the technique challenging. The limitation of the sensitivity due to collimation is well known and affects the performances of detector systems. The "electronic" collimation technique used in Positron Emission Tomography (PET) is limited only to positron emitters with intrinsic limitations in terms of spatial resolution and is also more complicated and expensive. Another electronic collimation method applied to single gamma emissions using Compton Camera techniques is rather complicated too, expensive and not yet fully developed.

Coded aperture collimation can be a solution in many cases, for example when imaging objects having a small thickness as compared to the object-detector distance, as it is typical in small animal imaging.

In this paper simulations performed to optimize the intrinsic performances of dedicated detectors affecting the coded aperture collimation option (essentially: intrinsic spatial resolution, dimension of scintillation pixels, and pixel identification) are presented. Different masks have been designed for different applications (small animal imaging and tumour detection). Phantom measurements have been performed to compare the technique to parallel hole collimation, showing the advantages of the technique in terms of sensitivity and spatial resolution (1).

Equipment and methods

We have performed quite extensive simulations, first to optimize the intrinsic performances of the detectors (2-4), and then the coded aperture option for collimation has been studied (5-7).

Detectors

Different detector configurations have been studied. Essentially they are pixellated NaI(Tl) scintillators with different degree of segmentation, coupled with different photodetectors having anode pixel of different size (1-4,8). One of the detector systems used, based on a flat panel PSPMT (Position Sensitive PhotoMultiplier Tubes) is shown in Figure 1.

Figure 1. One of the detector systems used, based on a flat panel PSPMT. Collimation masks can be seen to the right of the detector box

Coded aperture collimation

The spatial resolution of single photon systems is limited to the sum in quadrature of intrinsic spatial resolution of the detector and collimator hole size if parallel hole collimator is used, but significant improvements are possible if a pinhole collimator is used. The major drawback is the limited sensitivity one can get with a pinhole collimator. It has been shown that it is possible to increase the collimator sensitivity, while maintaining a good spatial resolution, by using multi pinhole or coded aperture technique (9, 10).

Coded Aperture (CA) imaging uses multiple pinholes to improve the signal throughput of single-pinhole cameras.

In brief, in CA imaging each pinhole forms a copy of the projection of the object onto the detector, where copies may overlap. This superposition must be undone to form a clear image. For this reason, the acquired data are post-processed (decoded) by taking their correlation with a decoding array associated to the aperture's transmission function. If this array is chosen carefully, for a 2D object it is indeed possible, as shown below, to completely undo the overlap. The reason for going through this complication is that since more photons are collected, under conditions of uniform background (10), noise in the resulting image is reduced.

The use of multiple pinholes has a second implication, specifically that, in near-field geometry, different viewing angles for each point in space are present even in a single projection. This is different from classic pinhole imaging, where in each projection all points are seen from a single vantage point. Single-view CA data, then, are richer than single-view pinhole data in a sense that at least some partial information is available for 3D reconstruction.

This information is actually equivalent to that obtained, in a much longer time, with a single pinhole visiting sequentially all the positions of the holes in the aperture in the case of a point source, for which no overlap can be present in CA data. A simple approach to recover 3D information relies on the property that each point in the object projects the aperture onto the detector with magnification uniquely related to its distance from the plane of the aperture. A 3D image, then, can be obtained plane by plane, each plane being the result of decoding the acquired data with the decoding arrayscaled to match the size of the projection of the aperture corresponding to the distance of the plane from the aperture.

From theory, if O is the irradiance (number of photons emitted per unit area) of the object, A is the transmission of the coded aperture (a function ranging from 0 for complete opacity to 1 for complete transparency) and R is counts recorded by the detector, we have $R = O \times A$ ($\times$ indicates non-periodic correlation). Let G be a decoding pattern, such that $A \otimes G = \delta$ ($\otimes$ indicates a periodic correlation).

A and G are both in the hands of the designer. The reconstructed image is $O' = R \otimes G = (O \times A) \otimes G = O * \mathbf{(A \otimes G)}$ where * indicates correlation. $A \otimes G$ is the convolution kernel or Point Spread Function. If $PSF = \delta$ we have perfect reconstruction, because $O = O'$.

Of course, ideal reconstruction is only possible after a number of approximations.

First is the far-field approximation. The second hypothesis is that detector and mask are ideal, for example zero-dimensional pinhole. In realistic cases resolution is slightly worse and we have blurring.

Pixel size p_d of the detector is very important because the reconstruction is well performed only when $\alpha > 2$, where α is the number of detector pixels sampling projection of a mask aperture.

If p_m is the mask pixel size, a is the distance from object to mask, and b is the mask-detector distance, the Depth Of Field[1] (DOF) increases when p_m decreases:

$$DOF = \frac{b}{2.0\dfrac{p_d}{p_m} - 1} - \frac{b}{\dfrac{a+b}{a} - 1} \qquad [1]$$

We have studied different masks for different applications. It is evident that detecting small tumors in humans requires different mask designs than small animal imaging where better spatial resolution is required. However, in some situations sensitivity is less critical in small animal imaging than in humans where acquisition time can limit image statistics.

Results

We have designed essentially high-resolution and (relatively) high Field of View (FOV) masks.

We have simulated the performance of the high-resolution MURA-14 mask, having a pixel size of 0.69 mm, with a mask-detector distance of 45 mm and a source-mask distance of 15 mm.

[1] DOF is the axial range where the image reconstruction can be correctly performed.

In this setup we measured spatial resolution as good as 0.88 mm FWHM (1), with 16 mm FOV and 9 mm DOF.

We started simulating a 2D source of different size and two possible uptake ratios within a background of 500 nCi/cm^2. In Figure 2 the 2D-simulation results of tumours of different sizes (uptake ratio 1:6) are shown.

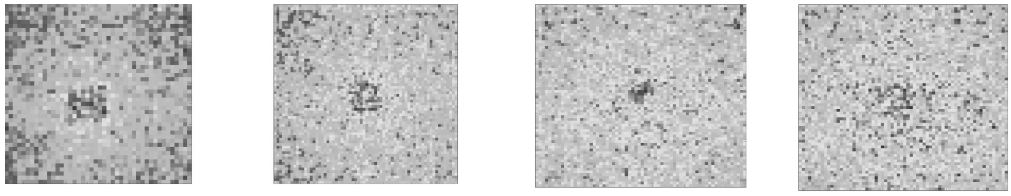

Figure 2. Simulation of 12 mm, 9 mm, 6 mm and 3 mm square source, respectively, corresponding to 1:6 uptake ratio with respect to a background of 500 nCi/cm^2, simulating 6 cm thick surrounding tissue

In Figure 3, 3D-simulations (laminography) results of tumour (uptake 1:10) of 12×12×12 mm^3 in size, at different positions in the DOF are shown. We have used the mask-antimask technique (10) to reduce near-field artefacts. In the 3D case artefacts are still present because of the activity out of the focus and out of the FOV. Measurements have been performed according to the specifications of the previous paragraph with a 50×50mm^2 imaging detector. We have used a phantom for breast tumour detection with 8 mm diameter "lesion" source at different "depths" (detector to tumour distances: 15 mm, and 0 mm) and different absolute uptakes with 12:1 uptake ratio relatively to a background as thick as the DOF (30mm).

The measurements show an agreement with the simulation, but the residual artefacts are slightly different, probably due to the different amount of background activity out of the FOV. The problem is under investigation.

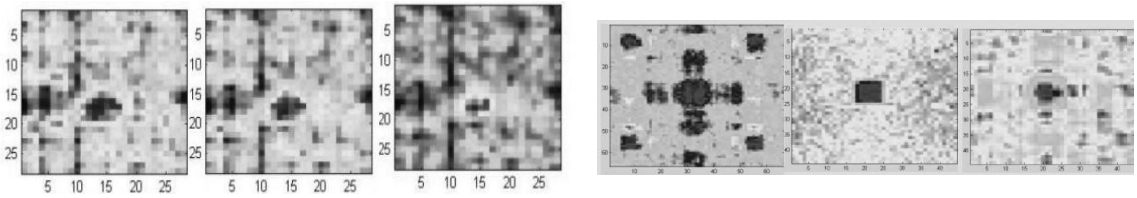

Figure 3. Simulation of 8 mm tumor in different positions of in a phantom as thick as the DOF of 30 mm (uptake ratio 12:1) (*a*); measurements corresponding to the same conditions for 8 mm diameter spherical source (*b*)

Conclusions

We have performed simulations and measurements to study the coded aperture option for radionuclide imaging of a spot inside a background volume with thickness comparable with the DOF of the mask. This is the case for example for detecting small tumours in humans.

Preliminary results are promising; they show that reasonable DOF (few cm) may be feasible. Nevertheless the issue of artefact elimination requires careful studies to show that the technique is really applicable when the volume detection is relatively big. The problem of artefacts due to activity presents out of FOV and out of focus is under study. Moreover the small Field of View shows to be a limitation for the cost of large area high resolution detectors.

References

1. Garibaldi F, *et al*. Small animal imaging by single photon emission using pinhole and coded aperture collimation. *IEEE Tran Nucl Sci* 2005;52(3 Pt1):573-9.
2. Garibaldi F, *et al*. Optimization of compact gamma cameras for breast imaging. *Nucl Instr Meth* 2001;A 471:222-8.
3. Garibaldi F, *et al*. Scintillator and photodetector array optimization for functional breast imaging. *Nucl Instr Meth* 2003;A:497:51-9.
4. Cusanno F, *et al*. Preliminary evaluation of compact detectors for hand-held gamma cameras. *Phys Med* 2004;XX(2):65-70.
5. Lo Meo S. Imaging *molecolare ad alta risoluzione con radionuclidi, per l'applicazione alla diagnosi precoce del tumore della mammella* [thesis]. Rome: University of Rome "La Sapienza", 2005.
6. Accorsi R, Gasparini F, Lanza RC. A coded aperture for high-resolution nuclear medicine planar imaging with a conventional anger camera: experimental results. *IEEE Trans Nucl Sci* 2001;48(6):2411.
7. Accorsi R, Gasparini F, Lanza RC. Optimal coded aperture patterns for improved snr in nuclear medicine. *Nucl Instr Meth* 2001;A 474:273-284.
8. Magliozzi ML, *et al*. (Ed.). *High resolution, high sensitivity detectors for molecular imaging of small animals and tumor detection*. Proceeding of 9th International Conference of Advanced Detectors. Como (Italy), October 17-21, 2005.
9. Fenimore EE, Cannon TM. Coded aperture imaging with uniformly redundant arrays. *Appl Opt* 1978;17:337-47.
10. Accorsi R. *Design of near-field coded aperture camera for high resolution medical and industrial gamma ray imaging* [PhD thesis]. Cambridge, MA: Massachusetts Institute of Technology; 2001.

GEANT4 CODE FOR THE OPTIMIZATION OF MOLECULAR IMAGING DETECTOR

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Introduction

The power of imaging techniques with radionuclides lies in their ability to provide very sensitive measures of a wide range of biologic processes in the body. These techniques allow studies to be targeted to the very specific biologic processes underlying disease; the detection of very small tumors with high specificity is becoming possible.

Moreover the recent availability of genetically modified mice has generated a rapid growth of interest in radio imaging of small animals, because it enables a wide range of human diseases to be studied in animal models. Nevertheless, the technique is challenging due to the concurrent requirements in terms of high spatial resolution and high sensitivity (1).

Spatial resolution at millimeter scale is required for oncological nuclear medicine while many small animal imaging applications need submillimeter spatial resolution. Good sensitivity is also required, especially for small tumor detection (breast for example). PET (Positron Emission Tomography) technique, regardless of intrinsic limitations in terms of spatial resolution, suffers for high cost and complexity, while SPECT (Single Photon Emission Computed Tomography) is less expensive and can be improved accordingly to the final purpose (1, 2).

The performance of compact discrete gamma camera is strongly influenced by camera geometry, so both collimator configuration, scintillator pixel size and PMT (PhotoMultiplier Tube) anode size, affect breast tumor images. The preliminary simulations discussed in this paper have been designed to study how imaging is affected by camera components but also by tumor size and Tumor to Background uptake ratio (T/B).

Monte Carlo simulation program and image reconstruction

A GEANT4 (3) program has been coded to simulate a scintimammography detector, schematically shown in Figure 1, together with a real system. The gamma rays are generated in a large 3D phantom breast of 10×10×6 cm^3, including a spherical tumor, and simulates all possible physical interactions in the world volume. In order to simulate a clinical scintimammography scan, the number of generated 140 keV gamma rays are calculated assuming a background activity density of 80 nCi/cm^3 for breast phantom, T/B, of 6, 10, 12 and an imaging time of 10 minutes (4).

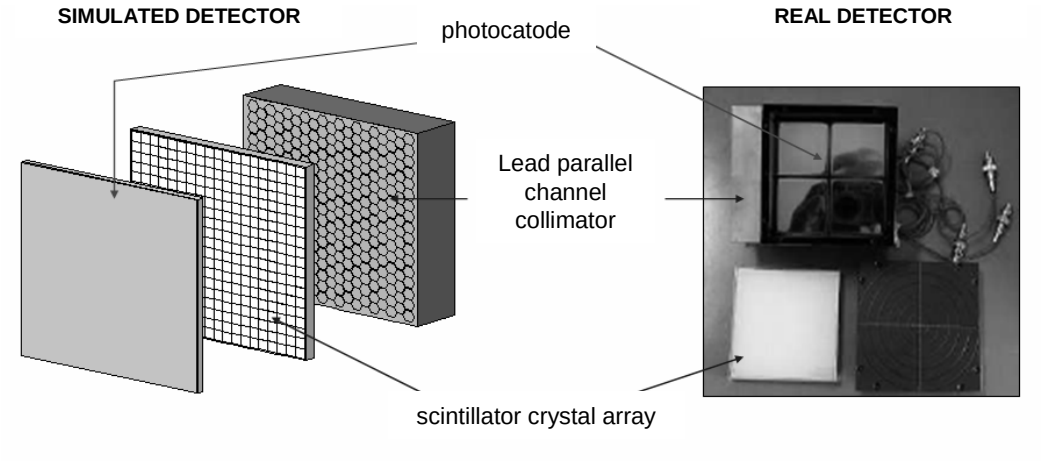

Figure 1. Basic components of simulated gamma camera and real detector

Images are obtained cutting out the events with number of detected photons less than 700 in order to consider primary 140 keV gamma only (Figure 2).

Collimator hole size, scintillating crystal size, PMT anode size, tumor diameter and T/B ratio are free parameters of the simulation. In particular we considered, some combinations of:

- collimator hole size of 1.5 and 1.9 mm, (High resolution, HR, and High Efficiency, HE, respectively);
- crystal pixel size of 1.0×1.0 and 1.3×1.3 mm^2, pixels are spaced by epoxy glue of 0.2 mm in both configuration;
- PMT anode size of 6 and 3 mm (simulated model H8500 and H9500 from Hamamatsu) (5, 6);
- Tumor diameter of 6, 8, 10 mm;
- T/B values of 6, 10, 12.

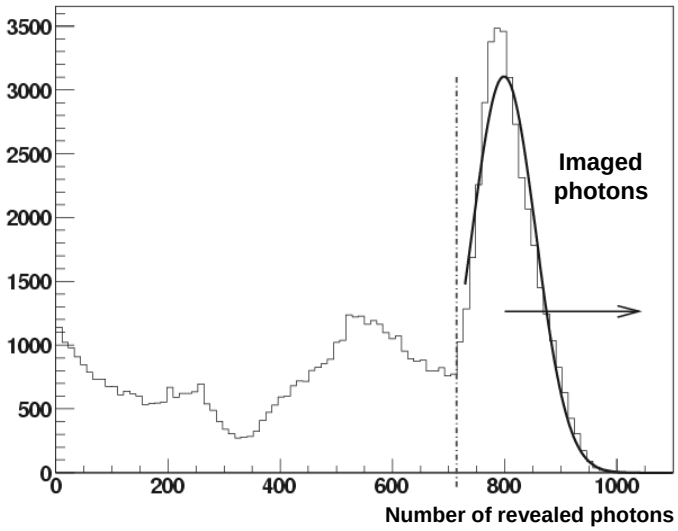

Figure 2. Distribution of the detected optical photons. The gaussian fit represents the photoelectric peak of the 140 keV emitted gamma

SNR and detector configuration

In order to compare tumor images from different scans we use the Signal to Noise Ratio (SNR) operatively defined as the maximum - respect to regions of interest (ROI) surrounding the tumor - of "the background subtracted counts in the ROI" over "the ROI total counts squared". The ROIs are square boxes centered on the tumor maximum intensity pixel.

Figure 3 shows the SNR *vs* both uptake (T/B) for tumor sizes of 6 and 10 mm and tumor sizes for T/B of 6 and 10.

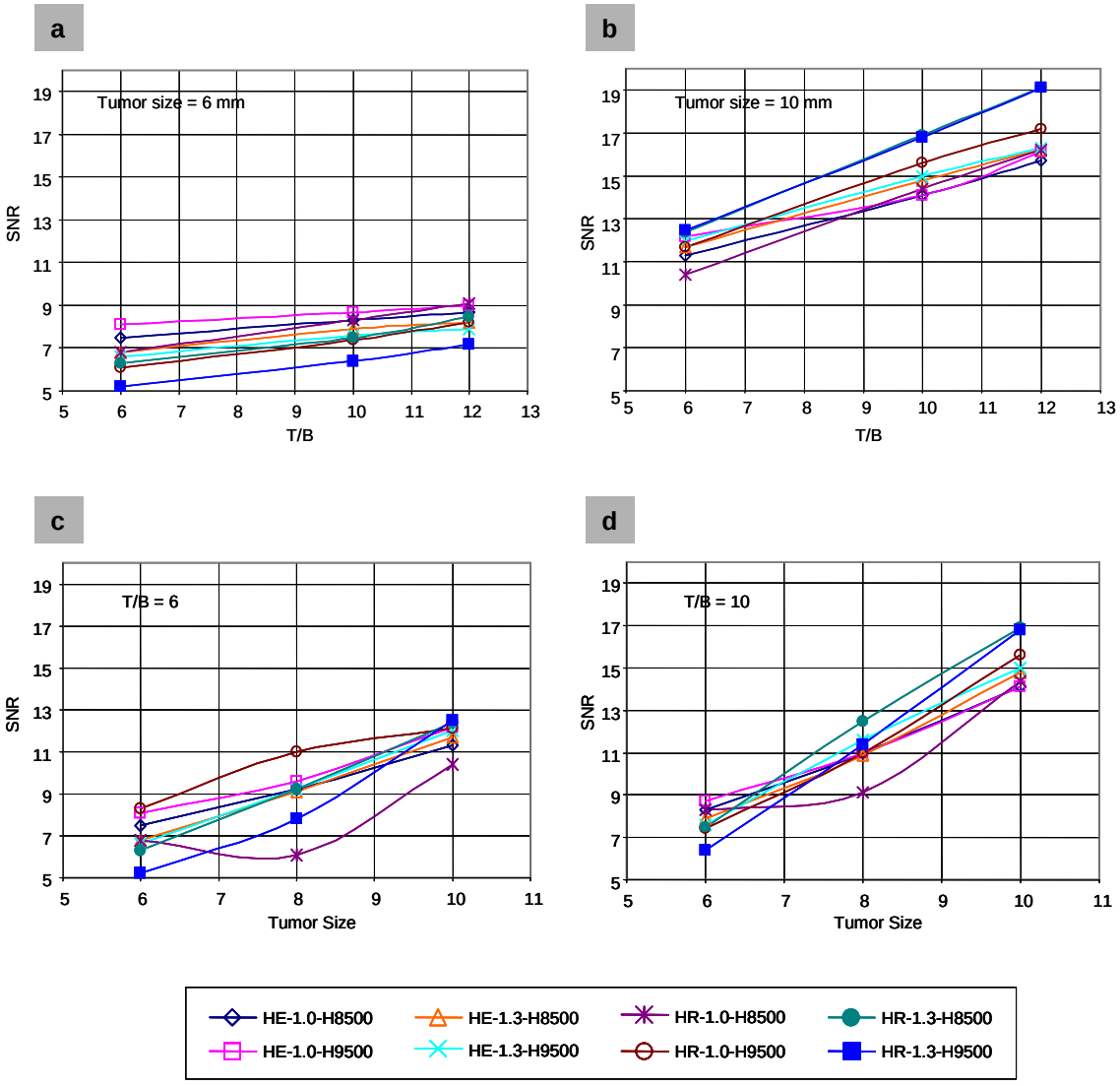

Figure 3. SNR *vs* both uptake (T/B) for tumor sizes of 6 and 10 mm (*a* and *b*) and tumor sizes for T/B of 6 and 10 (*c* and *d*)

Spatial sampling

In order to evaluate the optimal spatial sampling, the influence of different PMT anode sizes on the centroid reconstruction has been investigated. Figure 4 summarizes the results in terms of the FWHM of the photon shower emitted by the different NaI scintillator pixel sizes.

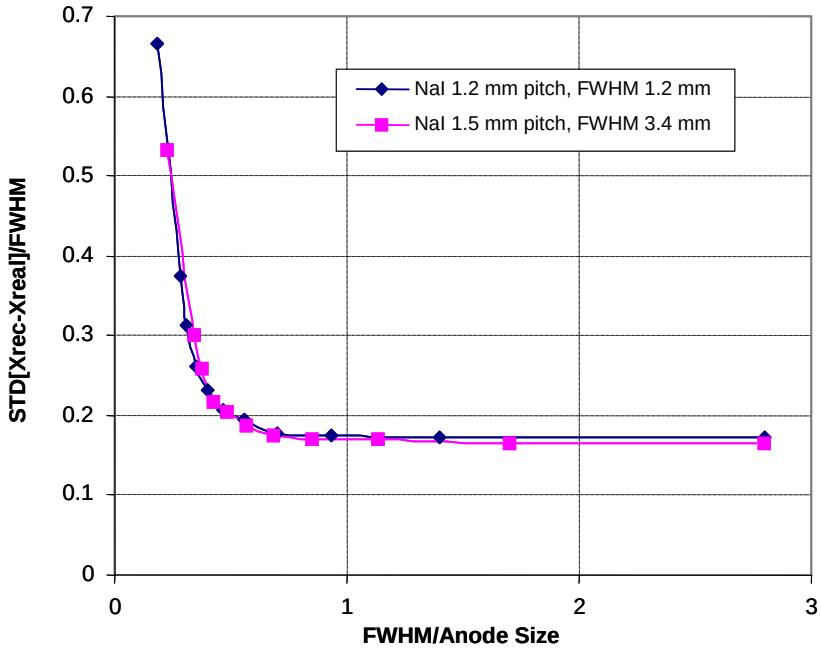

Figure 4. Estimated Centroid Standard Deviation (STD[Xrec-Xreal]) *vs* width of the photon shower emitted by the NaI scintillator crystal. The optimal anode size (minimum degradation at maximum pixel size) is ~0.5 × [FWHM Optical Distribution]

The estimated Centroid Standard Deviation (STD[Xrec-Xreal]) is an index of the spatial resolution degradation induced by the sampling; smaller values correspond to smaller degradation.

Conclusions

The above investigation is still underway; more configurations and different tumor depths will be simulated and compared to real measurements. The very preliminary results show that the High Efficiency, 1.3 mm scintillator pixel combined to the H9500 PMT seems to represent the optimal configuration in terms of SNR, in most of the simulated cases. The use of H9500 PMT (when coupled to a 1.3-1.5 mm crystal pixel) is also confirmed by the spatial resolution analysis.

References

1. Garibaldi F, *et al*. Small animal imaging by single photon emission using pinhole and coded aperture collimation. *IEEE Tran Nucl Sci* 2005;52(3 Pt1):573-9.
2. Cusanno F, *et al.* Molecular imaging by single photon emission. *Nucl Instr and Meth* 2004;A527:140-4.
3. Agostinelli S, *et al*. GEANT4: a simulation toolkit. *Nucl Instr Meth Phys Res* 2003;A506:250-303.
4. Gruber GJ, *et al.* Monte Carlo Simulation of breast tumor imaging properties with compact, discrete gamma cameras. *IEEE Trans Nucl Sci* 1999;46(6):2119-23.
5. Hamamatsu Photonics KK. *H8500 specifications*. Hamamatsu City (Japan): Hamamatsu Photonics KK; 2003. Available from: http://sales.hamamatsu.com/assets/pdf/parts_H/H8500.pdf; last visited 10/4/06.
6. Hamamatsu Photonics KK. *H9500 specifications*. Hamamatsu City (Japan): Hamamatsu Photonics KK; 2004. Available from: http://sales.hamamatsu.com/assets/pdf/parts_H/H9500.pdf; last visited 10/4/06.

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