Molecular Imaging Challenges With PET

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Abstract—The future trends in molecular imaging and associated challenges for in-vivo functional imaging are illustrated on the basis of a few examples, such as atherosclerosis vulnerable plaques imaging or stem cells tracking. A set of parameters are derived to define the specifications of a new generation of in-vivo imaging devices in terms of sensitivity, spatial resolution and signal-to-noise ratio. The limitations of strategies used in present PET scanners are discussed and new approaches are proposed taking advantage of recent progress on materials, photodetectors and readout electronics. A special focus is put on metamaterials, as a new approach to bring more functionality to detection devices. It is shown that the route is now open towards a fully digital detector head with very high photon counting capability over a large energy range, excellent timing precision and possibility of imaging the energy deposition process.

Index Terms—Metamaterial, molecular imaging, PET.

I. INTRODUCTION

MEDICAL imaging in the current clinical practice is aiming at in-vivo anatomic and functional visualization of organs in a non- or minimally invasive way. Isotopic imaging, in particular PET, is currently being spectacularly developed. Isotopic imaging consists in injecting into a patient a molecule involved in a specific metabolic function so that this molecule will preferentially be fixed on the organs or tumors where the function is at work. The molecule has been labeled beforehand with a radioisotope emitting gamma photons (Single Photon Emission Computed Tomography or SPECT) or with a positron emitting isotope (Positron Emission Tomography or PET). In the latter case, the positron annihilates very quickly on contact with ordinary matter, emitting two gamma photons located on the same axis called the line of response (LOR) but in opposite directions with a precise energy of 511 keV each. Analyzing enough of these gamma photons, either single for SPECT or in pairs for PET makes it possible to reconstruct the image of the areas (organs, tumors) where the tracer focused.

As an example, physicians relied for many years on the use of anatomical imaging to non-invasively detect tumors and follow up their growth. Functional imaging such as bone (^{99m}Tc methylene-diphosphonate MDP) or thyroid (^{123}I or ^{131}I) scintigraphy and more recently PET using ^{18}F 2-fluorodeoxyglucose (FDG), has provided more information for tumor diagnosis and staging [1]. Of particular interest are combined anatomic-functional devices, such as PET-CT, allowing

Fig. 1. Abdominal slice of a 78 year-old male, with biopsy-proven prostate adenocarcinoma and penile adenocarcinoma. Focal uptake in the prostate bed and in the penile shaft (full arrows). Multiple foci in the pelvis compatible with skeletal metastases (dashed arrows). (Courtesy D. Townsend).

a precise localization of metabolic hyperactivity in tumors and metastases as shown in Fig. 1.

The challenge of the future healthcare mission will be to capture enough information from each individual person to prevent disease at its earliest stage, to delineate disease parameters, such as aggressiveness or metastatic potential, to optimize the delivery of therapy based on the patient's current biologic system and to instantaneously evaluate the treatment therapeutic effectiveness.

New therapeutic strategies are entering the world of major diseases. These impose to acquire as fast as possible all the information on the pathological status of the patient in order to start adapted therapeutics and therefore to minimize the handicap. This is true for neurological and psychiatric diseases [2] but also for the treatment of inflammatory diseases [3], such as rheumatologic inflammation, and for cancer [4]. Moreover, the non-invasive determination of the molecular signature of cancers in the early stage of their development, or even before the tumor growth, will help to target therapeutic strategies and to considerably reduce the number of unnecessary biopsies.

In order to achieve this, a new revolution is being prepared in the field of imaging, which targets molecular imaging. The goal is in-vivo visual representation, characterization and quantification of biological processes at the cellular and sub-cellular level within living organisms. This is the challenge of modern biology: detect early transformations in a cell, which may lead to pathology (precancerous activity, modifications of neuronal activity as warning signs of Alzheimer or Parkinson disease). Besides early detection, assessment of prognosis and potential response to therapy will allow a better treatment selection through a precise delineation of molecular pathways from genes to disease. All aspects of gene expression will be addressed (genomics, proteomics, transcriptomics, enzymatic

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activity), but also the molecular signal transduction through cell membranes (a key to determine the efficacy of drugs) as well as the identification and quantification of specific cell receptors expression in some pathological situations. This could help solving for instance the still controversial question of dopamine receptors possibly over-expressed in the case of epilepsy [5].

With the development of new imaging probes and “smart probes”, imaging provides cellular protein and signal-pathway identification [6]. There is an increasing amount of molecular probes dedicated to imaging but also to tumor therapy. The molecular phenotype of cells composing the tumor can lead to tailored therapies. This tumor phenotype can be determined ex-vivo on tissue samples. Molecular imaging should allow in-vivo characterization of tumor phenotyping by a rationalized use of specific imaging probes. This molecular profiling could already be envisioned in the very near future for some specific tumors overexpressing peptide hormone receptors such as breast and prostate cancers, and should become widely developed [7].

Therefore, it represents a major breakthrough to provide the medical community with an integrated “one-stop-shop” molecular profiling imaging device, which could detect tracers dedicated to SPECT or PET, as well as Magnetic Resonance Imaging (MRI), or X-ray-Computed Tomography (CT).

Furthermore, since functional imaging allows the assessment of biochemical pathways, it will also provide accurate tools for experimental research. As an example, a large effort worldwide has recently allowed the precise mapping of the different genes in the DNA sequence but the mechanisms, by which these genes produce proteins, interact with each other, regulate their expression, are far from being understood. In other terms we can say that the genomic alphabet has been decoded but its dynamic expression, its grammar, remains to be studied and understood. In-vivo molecular imaging of gene expression is now within reach through the development of more and more elaborated molecular probes as well as of sophisticated techniques to significantly improve the performances of modern imaging devices.

Drug development can also take advantage of technical progress in imaging technologies, like quantitative positron emission tomography in small animals, to determine drug pharmacokinetics and whole body targeting to tissues of interest [8]. Moreover, the combination of functional imaging with a high resolution anatomical method such as MRI and/or X-ray CT will considerably enhance the possibility of determining the long term efficiency of a drug on basic pathological processes such as inflammation, blood flow, etc. In particular the expected progress in sensitivity, timing and spatial resolution, coupled with a true multi-modality registration, will allow to explore the activity of a drug candidate or other essential patho-physiological processes of disease models in animals, like for instance cancer or adverse inflammatory effects.

This approach will require targeting cellular activity with specific contrast agents, but also a large effort on imaging instrumentation. Developments are needed for faster exams, correction of physiological movements during acquisition time (breathing, cardiac beating, digestive bolus), access to dynamic processes, quantification, true multimodality, dose reduction to

Fig. 2. Macrophage infiltration in atherosclerotic aorta (from [9]).

the patient. This will be achievable, if significant improvements can be made on spatial resolution, timing resolution, sensitivity and signal-to-noise ratio, all parameters very familiar to particle physicists. From the technologies already available, developed for instance for the Large Hadron Collider (LHC) detectors or under development for the future linear collider, fast crystals, highly integrated fast and low noise electronics and ultrafast Geiger mode avalanche photodiodes (APDs) open the way to time of flight (TOF) PET with magnetic-compatible solid-state photodetector readout. Once these technologies can be implemented at a reasonable cost in commercial PET's, a step in timing resolution and signal-to-noise ratio will be possible, resulting immediately in a breakthrough in sensitivity. Picomolar concentrations are within reach, which correspond to the molecular activity of a few hundreds of cells only.

II. TWO EXAMPLES OF IMAGING CHALLENGES

A. Vulnerable Plaque Imaging

Atherosclerosis is responsible for the formation of vulnerable plaques, which are at the origin of artery stenosis and are the major cause of heart attack and stroke. A vulnerable plaque is an unstable collection of white blood cells (lymphocytes and macrophages) and lipids (including LDL cholesterol) attached to the wall of an artery. Plaque rupture or erosion results in exposure of thrombogenic elements to the blood flowing past the lesion and in thrombus formation.

Plaques can be imaged by SPECT imaging techniques using specific tracers of oxidized LDL cholesterol labeled with ^{125}I , $^{99\text{m}}\text{Tc}$ or ^{111}In , monocyte chemoattractant peptides labeled with ^{125}I and $^{99\text{m}}\text{Tc}$, or $^{99\text{m}}\text{Tc}$ labeled Annexin V as a marker of cell apoptosis (programmed cell death). But this is generally through the metabolism of inflammatory cells with PET and FDG (Fig. 2) that plaques are most frequently imaged [9].

The main challenge here is related to the small dimensions of the plaques. A typical plaque may occupy a volume of $2 \times 5 \times 0.2$ (deep) mm^3 , whereas the resolution of a whole body PET is rarely better than 4 to 5 mm. Moreover blood flow related movements impose the use of gating techniques synchronized with the cardiac beating cycle. The reduced acquisition time must be compensated by a higher sensitivity of the machine in order to maintain good image quality for a given dose injected to the patient. Finally a high background activity in the myocardium associated to the small size of the lesion require a high target to background ratio ($> 30 : 1$), which

Fig. 3. Detection limit of different imaging modalities.

can only be achieved with high PET sensitivity, electronic collimation on the region of interest (ROI), possibly using TOF techniques (see Section III.C), associated to highly specific tracers.

B. Stem Cell Imaging

There is a rapid increase of reported cases of stem cells based treatments in cardiology, oncology, immunology, neurology and transplantation [10]. Moreover there is emerging evidence in support of a stem cell based model of carcinogenesis. The need for tracking a small population of cells in-vivo is therefore increasing.

Studies with FDG on cancer cells with a standard uptake in the tumor of 50 KBq/ml suggest that the in-vivo PET detection limit is at the level of 10^6 malignant cells, which represents a tumor size of about 1 mm³ [11]. This result shows that the spatial resolution of commercial whole body PET scanners (4 to 5 mm) does not allow to localize objects at the limit of the PET sensitivity with a precision corresponding to their actual size.

Fig. 3 represents for the most frequently used imaging modalities the detection limit (expressed in number of cells) as a function of the number of molecules of contrast agent per cell. This plot has been produced in collaboration with J. Prior, CHUV Lausanne, from data collected in [12].

It clearly appears that there is a need for improving the PET limit of cell detection by a factor of at least 10^3 for imaging about 1000 cells, which is a reasonable value for tracking stem cells, or 10^6 if imaging of a single cell is desired. This can only be achieved through a combination of significant PET sensitivity improvement and multiple marking of tracer molecules or enzymatic amplification of receptor production.

III. DETECTOR CHALLENGES FOR MOLECULAR IMAGING

The spectacular development of in-vivo molecular imaging will allow in the near future bridging the gap between post-genomics research and physiology opening interesting perspectives for new diagnostics and therapeutic strategies for major diseases. Nuclear medicine and particularly PET imaging are already playing and will play an increasing role in molecular imaging [13]. Indeed PET presents a number of advantages, which lie in its specificity, its sensitivity and its ability to quantify tissue concentrations of tracer. Specificity comes from being

able to label a given molecule with radioisotopes without perturbing its biological function. Sensitivity arises from the use of coincidence, electronic collimation counting, and quantification from the ability to correct for signal loss due to tissue attenuation of emitted photons [14]. Constant progress in the medical and biological fields implies that imaging performances have to be continuously improved. To fulfill the needs of quantitative cell and molecular imaging, of dynamic studies over a certain time and of individualized therapy focusing on the patient's genotype, major technical improvements [15] will be necessary. They can take advantage of recent developments in large particle detectors, in order to deal with:

- integration of a very large number of increasingly compact measuring channels (several hundred thousands)
- data acquisition rates at the level of tens gigabytes/second
- several billions of events to reconstruct an image
- about 1000 gigabytes of data per image and commensurate computational power for the reconstruction
- integration of multiple technologies requiring pluridisciplinary competences within complex, compact and reliable systems.

The challenge for molecular imaging lays in its capacity to identify the specific molecular pathways in action in a metabolic process and to quantitatively measure their relative metabolic activity. To achieve this it is necessary to improve both the imaging system spatial resolution, that is, its capacity to discriminate two separate objects, and the image signal-to-noise ratio, that is, how precisely a metabolic agent concentration in a body area can be determined. The precision of the concentration's measurement depends mainly, but not only, on the imaging system sensitivity, and therefore its capacity to accumulate the statistics needed to tomographically reconstruct the radiopharmaceutical tracer distribution. Moreover the location of this metabolic activity must be precisely associated to the organs or parts of the organs under examination. This is why there is an increasing demand for combining functional and anatomical imaging devices.

Thus, the perspectives to develop isotopic imaging for the purpose of molecular imaging with multimodality and multifunctional capability revolve around three goals:

- improving sensitivity and specificity
- improving spatial resolution
- improving temporal resolution.

A. Improving Sensitivity and Specificity

Sensitivity is defined as the ratio between the detected number of radioactive disintegrations and the radioactivity, which was injected to the patient and fixed on the organ under study. It reaches at best a few % in the case of PET scans on small animals, and 0.1% in the case of whole body PET [16]. Moreover whole body PET scanners visualize only the patient's thorax in one acquisition run, which is sometimes a limiting factor, for instance in oncological studies of bone metastases in limbs. In the medium term, the use of faster scintillating crystals and electronics as well as a better geometrical acceptance will allow to reach a sensitivity of several % for whole body scanners on a large volume of interest and largely in excess of 10% for small animals devices.

Sensitivity has to be improved for many reasons. First, examination durations have to be shortened. Today, a whole body scan lasts about 30 minutes, but it should be possible to reduce this time to a few minutes. Thus, patients' comfort should be significantly improved. Increasing the productivity of costly equipment and infrastructures would obviously have a significant impact on the cost of examinations. Shorter acquisition times would also improve the image quality because the impact of the patient's natural movements – breathing and cardiac activity, digestive bolus, etc. – would be significantly reduced. Quicker metabolic processes could be followed, which is crucial for pharmacokinetic studies.

Looking for increasingly specific molecular signatures for the main diseases so as to devise individually targeted therapies adapted to the patient's genotype makes increasingly sensitive equipment and protocols more and more on demand. Indeed it is highly desirable to study different molecular pathways simultaneously and to record the amplitude, the range, the localization and the development over time of various biochemical processes in their natural environment in the human body. In this way, the nature of the pathology could be established, at least partially, through molecular imaging, using an array of radiopharmaceuticals giving information on cell proliferation (FLT) [17], on energetic metabolism (FDG) [15] or on aminoacid synthesis (methionine) [18] in the various tissues. In order to achieve multitracers analysis of various biochemical or pathophysiological processes, several radioactive tracers have to be administered. In order to keep the doses tolerable for the patient high-sensitivity PET scanners have to be developed, which would also open new prospects for young or pregnant women and for children.

There is a strong interplay between sensitivity and spatial resolution, since the signal-to-noise ratio per voxel is the relevant image quality factor. To double linear spatial resolution, a 16 time improvement in noise equivalent rate is necessary if the statistical quality of the image is to be maintained. The acquisition time of an image depends on many factors, which simultaneously influence the noise-equivalent measurement of the imaging system and of the radioactivity administered to the patient. To quote only a few we can mention:

- the imaging system's geometrical acceptance,
- the detection efficiency and energy resolution – thanks to which the energy selection of events can be improved and diffused events can be discriminated more easily–,
- the time resolution – thanks to which, in a coincidence system, the width of the coincidence window can be reduced and random coincidences can be rejected more efficiently –,
- the dead time of the detectors.

The sensitivity of a PET detector is given by:

$$S \approx \Omega \cdot \eta_{\gamma}^2$$

where Ω is the detector geometrical acceptance and η_{γ} is the single γ -ray detection efficiency.

The angular acceptance of commercial PET scanners rarely exceeds a few percents. In some cases, building dedicated equipment might be the right solution to study an organ (brain, breast,

TABLE I
SCINTILLATORS ALREADY USED OR IN DEVELOPMENT FOR MEDICAL IMAGING.
PARTICULARLY ATTRACTIVE PARAMETERS ARE MARKED IN BOLD.

Crystal	Density g/cm ³	Light Yield (PMT) Ph/MeV	Emission wavelength nm	Decay time ns	Hygro scopic
BGO	7.13	9000	480	300	No
GSO:Ce	6.7	12500	440	60	No
LGSO:Ce 20% Lu	6.5	16000	415	65-75	No
LSO:Ce	7.4	27000	420	40	No
LYSO:Ce 95% Lu	7.2	31000	420	40	No
LuAP:Ce	8.34	10000	365	17	No
LuAG:Ce	6.7	25000*	535	70	No
LaBr ₃ :Ce	5.29	61000	358	35	Yes

* from recent measurements at CERN on samples produced in Yerevan (A. Petrosyan). Usually quoted at 20'000ph/MeV.

prostate) in a more efficient and optimized way. Being closer to the organ under study automatically increases the angular acceptance of the scanner. The inter-crystal gaps and the dead space between crystal matrices reduces also the geometrical acceptance by a factor, which can be as large as two. Interesting strategies based on trapezoidal block detectors are being developed allowing a much more compact detector design [19].

In order to increase the γ -ray detection efficiency η_{γ} the scintillating crystals used in PET scanners have to be dense, with a high atomic number, so as to increase the photo-conversion efficiency, and fast, in order to reduce dead time. The ideal crystal still has to be developed and the choice of a material generally results from a trade-off between several practical considerations. The most largely used or interesting candidates for PET are listed in Table I.

B. Improving Spatial Resolution

Spatial resolution reaches 1.2 mm to 2 mm at the centre of the field of view of small animal PET scanners, but worsens off-axis. In whole body PET devices it is at best 4 to 5 mm. In both cases, temporal resolution is about 5 nanoseconds. Modern technologies should make it possible to reach a 1 mm resolution on a large field of view for small animal PET scanners or for scanners dedicated to specific organs, and a 2 mm resolution for whole body scanners. Similarly, temporal resolution should be reduced to a few hundred picoseconds.

Good spatial resolution is obviously of value for the study of small animals, but also human beings: increasingly smaller structures, which are involved in specific metabolic processes can thus be visualized. Anatomical localization can also be more precise and combining CT or MRI information can be improved. But it is in the field of quantification that the improvement potential is likely to be the most significant. By reducing the blur caused by insufficient spatial resolution (also called partial

volume effect), the dynamic sensitivity of the radiotracer's concentration measurement, related to the Standard Uptake Value (SUV), can be significantly improved [20].

There are four factors, which limit a PET camera's spatial resolution:

- the positron's mean free path: once the ligand has fixed itself on the organ or tumor under study which is to be studied, the radioisotope used to label it emits positrons with a kinetic energy, which depends on the isotope. As the annihilation probability of this positron is maximum when the positron has sufficiently slowed down, there is a difference between the positron emission point and its annihilation point. This difference is about 0.5 mm in the case of ^{18}F , but it can reach several mm for other isotopes – 4.5 mm for ^{82}Rb , for instance. This blurring is considered as an intrinsic limitation to the PET spatial resolution, even if it can be theoretically attenuated thanks to various electromagnetic artifices. For instance, the positron's trajectory usually revolves around the lines of a magnetic field – which is naturally present in the case of a combined PET-MRI camera –, which therefore reduces its conversion distance. This is however only effective in the plane perpendicular to the magnetic field and for new generation of MRI devices with high field (7T or more). It has to be noted also that positron annihilation probability as a function of its speed is a well-known function but it is not exploited today in image reconstruction algorithms.
- non-collinearity of the two gamma photons deriving from positron annihilation: according to the laws of kinetics the two gamma rays resulting from the annihilation of a motionless positron have to be emitted on the same line of response (LOR) in opposite directions. In practice the positron is not at rest when it is annihilated, which causes an average acollinearity of the two gamma photons of about 0.25° . The error in the reconstruction of the emission point varies linearly with the scanner's radius. This error is reduced in equipment dedicated to the study of specific organs whose detectors can come close to the areas to be studied.
- size of the detection crystal (or pixel): it is the limiting factor in spatial resolution of commercially available scanners. Typically, the reconstruction error of each LOR is given by half the width of the pixel. The use of higher-density crystals and highly segmented photodetectors improve the spatial resolution. A significant increase in the number of channels, resulting from finer detector segmentation, implies that important efforts have to be made to develop cheap solutions for photodetectors and readout electronics. Difficult engineering problems have to be solved in order to integrate all the channels in a small volume and to keep the electronic equipment's thermal dissipation at an acceptable level.
- parallax effect: good spatial resolution has to be obtained not only on the axis, but also on the whole field of view (FOV). The depth of detecting crystals is limited by the density of the crystals and it cannot be reduced without altering the detector's sensitivity. If the conversion point of the gamma photon in the crystal is not known, spatial res-

olution deteriorates with distance from the scanner axis. This effect, which is known as parallax error, is becoming important as the scanner's radius decreases. To limit this effect, one solution is to use several crystals in depth in a so-called phoswich configuration. If appropriate emission wavelength and decay time parameters are chosen for the crystals, the readout electronics can differentiate a conversion occurring in the front part or in the back part of the phoswich. This scheme has been adopted in the ClearPET[®] small animal PET scanner with a combination of two 10 mm long LYSO and LuYAP crystals [21]. Another solution is to determine the γ conversion point in the crystal by means of a light-sharing scheme with readout at both ends of the crystal. This solution has been chosen for 20 mm long LYSO crystals in the ClearPEM[®], a dedicated PET scanner for breast imaging [22] and provides a depth of interaction (DOI) resolution of better than 2 mm.

C. Improving Timing Resolution

To improve timing resolution scintillating crystals with short decay time and fast photodetector and acquisition electronics are needed. This has a double impact on image quality:

- as the width of the coincidence window is reduced, the number of isolated events decreases linearly. The proportion of random coincidences, which increase the detector's dead time and introduce noise into the image, is therefore reduced as the square of the single event rate. Images are less noisy and require less filtering, increasing spatial resolution and contrast.
- Time of flight reconstruction can also significantly contribute to signal-to-noise ratio improvement in PET scanners [23], by constraining the annihilation point to a shorter segment on each LOR, with an uncertainty given by:

$$\Delta x = \frac{c}{2} \Delta t$$

where Δx is the position error, c is the speed of light, and Δt is the error in the timing measurement. Sub-centimeter position resolution would require a timing resolution of less than 50 ps, which is presently impossible to obtain. However the achievable timing resolution of $\Delta t \approx 500$ ps constrains the positron position to a line segment of approximately 7.5 cm, which allows reduce the noise variance by a factor f if the segment length is smaller than the image source D :

$$f = \frac{D}{\Delta x} = \frac{2D}{c\Delta t}.$$

For instance for whole body imaging, where $D \approx 35$ cm noise reduction can be expected if the timing resolution is better than 2.3 ns. For $\Delta t \approx 500$ ps the gain in noise variance would be 4.6. The resulting improvement in image quality is illustrated in Fig. 4.

A good timing resolution requires a crystal with a high light yield and a short decay time. Indeed the rate of photoelectrons, after photon conversion in the photodetector, determines the photostatistics and therefore the timing resolution. There is

Fig. 4. Image of a 116 kg patient, 2 hours after ^{14}mCi FDG injection obtained on the Philips TruFlightTM scanner, showing a lymphoma within the right iliopectas muscle with central area of necrosis. The TOF information brings a significant improvement in image quality. (Courtesy of Philips).

however a strong limitation related to the crystal geometry and high index of refraction of the majority of crystals used in PET scanners. Simulations have shown that for standard crystal geometry used in PET not more than 24% (LuAP:Ce) or 34% (LSO:Ce) of the photons generated in the crystals are actually extracted to the photodetector [24].

In recent years however, micro- and nanostructurization of materials has found widespread interest as a tool to overcome the problem of total internal reflection, which is a major source of losses in light-emitting and -transmitting media with high refractive index. A rather novel technique is the use of thin photonic crystal (PhC) slabs – media with a periodic modulation of the dielectric constant to guide incident photons into or out of the substrate. Our ongoing R&D effort along this line brings promising results [25].

IV. FUTURE TRENDS

In the last few years, there have been noticeable improvements in commercial imaging equipment, with increased level of pixellization, better angular coverage, faster crystals, higher degree of electronics integration of electronics with increased built-in functionality, more efficient reconstruction algorithms [26]. New scintillator production processes, novel photodetector approaches putting single photon detection and digital counting within reach, as well as recent advances in nanotechnologies, in particular in the domain of photonics crystals and nanocrystals, open interesting perspectives to develop new detector concepts capable of delivering much richer information about X- or Gamma-ray energy deposition. They are based on metamaterials to simultaneously record with high precision the maximum of information of the cascade conversion process such as its direction and the spatial distribution of the energy deposition.

As an example we are developing a detector head for a PET scanner on the basis of photonic crystals and quantum dots. The spatial encoding is provided by the emission wavelength of these quantum dots. The principle is to organize the readout through two different channels, one dedicated to energy deposit measurement with the best possible resolution and the second one optimized for three-dimensional spatial resolution of the different components of the conversion cascade.

The detector block is made of a matrix of heavy scintillating fibers. The scintillating material is selected as a function of its intrinsic light yield, which has to be high enough to allow splitting of the light through different readout channels and minimizing the photostatistics contribution to energy resolution. Moreover a good linearity of the response is requested

Fig. 5. Concept of a metacable for low energy X- and gamma-rays detection.

to achieve good energy resolution. We are presently exploring different materials, among which LuAG is a good candidate with a light yield recently measured of 25'000 ph/MeV (similar to LSO:Ce), a decay time of 70 ns or 20 ns whether it is Cerium or Praseodymium doped and a reasonable response linearity. The technology to grow such fibers by the micro-pulling-down technology is also well mastered and fibers of several meters in length and a diameter ranging between 300 μm and 3 mm can be grown with consistent quality. The diameter of the fibers is defined as a function of the desired spatial resolution.

If the scintillating fibers have a cylindrical shape the tiny gaps between them can be filled with a few hundred microns diameter photonic crystal fibers. Photonic crystal fibers transmit light through a regular lattice of holes arranged in a material of higher dielectric constant than air. This supporting material can be loaded with quantum dots with a different diameter range from fiber to fiber and distributed with a gradient of their diameter along each individual fiber. A conversion event, photoelectric or Compton in a scintillating fiber will produce an isotropic emission of scintillating photons. The photons emitted in the forward or backward direction will propagate along the scintillating fiber and be eventually collected at both ends and summed on a sufficient large number of fibers to measure the total energy deposited in the cascade of primary and secondary events produced by the conversion of the incident X- or γ -ray. On the other hand some of the photons emitted laterally will escape the scintillating fiber and excite the quantum dots of the photonic crystal fiber, allowing identify the fiber hit and determine the depth of interaction with high precision by measuring the spectrum of the light collected on miniaturized spectrophotometers or diffractive optics components with a high chromatic aberration. A possible scheme of this low energy detector block is shown on Fig. 5.

V. CONCLUSION

This paper describes the trends of modern medical imaging in the context of the spectacular development of *in-vivo* molecular imaging, which will soon allow to bridge post-genomics research activities with new diagnostics and therapeutic strategies for major diseases. In particular the molecular profiling of tumors and gene expression open the way to tailored therapies and therapeutic monitoring of major diseases like cancer, degenerative and genetic disorders. Moreover, the repeatability of non-invasive approaches allows an evaluation of drug targeting

and pharmacokinetics studies on small animals, as well as a precise screening and treatment follow-up of patients. The technical requirements on imaging devices are very challenging but are rather similar in many respects to the ones of modern particle detectors on high luminosity accelerators. Moreover new scintillator production methods and recent advances in nanotechnologies, in particular in the domain of photonics crystals and nanocrystals, open the way for new detector concepts capable of delivering much richer information about X- or Gamma-ray energy deposition.

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