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1 Introduction

“A century ago, the living body, like most of the material world, was opaque. Then Wilhelm Roentgen captured an X-ray image of his wife’s finger – her wedding ring “floating” around a white bone – and our range of vision changed for ever”. From the words of Bettyann Holtzmann Kelves up to now, amazing progresses have been made in medical imaging. One of the most impressive achievements of the last fifteen years is probably the emergence of molecular imaging. A multidisciplinary discipline by definition, physicists, biologists, physicians, chemists and mathematicians bring their expertise to observe, characterize and quantify biological processes at the subcellular level in living organisms. Molecular imaging originates from nuclear medicine where single photon emission tomography (SPECT) and positron emission tomography (PET) imaging techniques are used to observe complex biological processes at the early stage of the disease or for therapeutic follow-ups.

The use of radioactive tracers for medical purposes began with Georges de Hevesy in the 1930s. The discovery of technetium at the Berkeley cyclotron and the announcement of the first SPECT machines in 1968 pushed the discipline forward. SPECT rapidly became the most frequently used emission-scanning technology all over the world. The detectors used in SPECT nowadays look quite similar to the ones used at the beginning of this technique. Sodium iodine inorganic crystal coupled to a matrix of photomultiplier tubes are well adapted to image 140 keV photons generated by technetium-99m. The intrinsic performance of most detectors does not impact overall image quality in SPECT, which essentially depends on the collimation stage.

PET began at the same period as SPECT and has overlapped with the other imaging modalities occasionally, but while anatomical imaging modalities such as CT and MR moved under spotlights of modern clinical practice, PET remained in the shadow, until very recently. The current success story for PET imaging as an invaluable tool in clinical routine is due to the combination of several factors, of which the improvement in detector performance played a rather minor role. The need for a “technetium”-like isotope for PET was mandatory. With a period of two hours and ideal physical properties for PET imaging, $^{18}$F rapidly became the isotope of choice. However, it requires well-established network of cyclotron facilities able of providing radiolabelled compounds at the patient bed. Finding the clinical niche in which PET does not to compete but rather complement other imaging modalities was also a determinant factor for the success of PET. The combination with CT promoted PET as a main tool in oncology. Johannes Czernin from UCLA, at the 2003 annual DGN meeting, commented that “PET/CT is a technical evolution that has led to a medical revolution.” SPECT and PET imaging techniques enter a new era where technical improvements will play an increasingly important role. As an example for SPECT, dedicated cardiac imagers already take full advantage of solid-state detectors. Time-of-flight PET and the combination with MRI will continue to challenge researchers: “PET/MRI is a medical evolution based on a technical revolution.” As mentioned by Thomas Beyer.

This chapter highlights state-of-the-art and future prospects of medical imaging mostly in the field of nuclear imaging. It focuses on new developments and innovations brought by the nuclear physics community. Different sections cover hardware and software developments in clinical and preclinical studies as well as interface applications with other chapters of this booklet.
2 From nuclear to molecular imaging

2.1 Nuclear imaging techniques

Molecular imaging using radioactive tracers makes use of 2 distinct types of “camera”. Tracers containing a radioactive isotope that decays by the emission of a positron are imaged by a positron-emission tomograph. In tomography, a 3-dimensional image of an object is obtained by combining 2-dimensional images taken at different angles around the object. Tracers emitting gamma rays are imaged by the so-called gamma camera. It is used to take 2-dimensional images and, when positioned on a rotating gantry, allows tomographic imaging (SPECT: single photon emission computed tomography).

2.1.1 Positron Emission Tomography

A typical state-of-the-art commercial clinical PET scanner contains a few ten thousand small scintillation crystals that individually detect the positron annihilation photons emitted by the radiotracers in the patient body. The detection times are measured very accurately, with a precision of about half a billionth of a second. Data rates are large: typically of the order of a million events per second. Sophisticated algorithms distil 3D images out of the huge data set thus recorded. Images with a spatial resolution of about 4 mm are obtained. A whole body scan with the $^{18}$FDG tracer, one of the most common PET procedures, takes about 15 minutes. The scanner bore of about 70 cm is determined by patient size, the axial length of 20-25 cm is a matter of limiting the costs. Nowadays, all PET scanners are combined with a CT scanner for a quick, easy and accurate determination of the attenuation correction needed for quantitative imaging. Scanners come with a collection of sophisticated data and image analysis options for specific scan procedures and clinical investigations. Ease of use and integration in the clinical workflow are well-developed important features.

2.1.2 PET combined to Magnetic Resonance Imaging

In recent years, commercial systems for clinical use combining a PET and an MRI (magnetic resonance imaging) scanner have become available. First systems allowed the integrated but sequential combination of PET and MRI. The development of silicon-based photosensors, which are insensitive to magnetic fields, have made truly integrated systems possible, first for head scans and most recently for full-body scans. These systems allow simultaneous PET and MRI without quality loss in either imaging modality.

Table 1 PET characteristics of the top-of-the-line clinical PET/CT scanners from the 3 main manufacturers, as available from their corresponding websites. The scanners are listed in alphabetical order according to their commercial name.

<table>
<thead>
<tr>
<th>Company</th>
<th>Siemens</th>
<th>GE</th>
<th>Philips</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the scanner</td>
<td>Biograph mCT TrueV</td>
<td>Discovery PET/CT 710</td>
<td>Gemini TF</td>
</tr>
<tr>
<td>Physical axial FOV</td>
<td>21.6 cm</td>
<td>15.7 cm</td>
<td>18 cm</td>
</tr>
<tr>
<td>Scintillator (dimension)</td>
<td>LSO (4x4x20 mm³)</td>
<td>LBS* (4.7x6.3x30 mm³)</td>
<td>LYSO (4x4x22 mm³)</td>
</tr>
<tr>
<td>Sensitivity for a point source at center (NEMA)</td>
<td>9.5 cps/kBq</td>
<td>7.5 cps/kBq</td>
<td>&gt; 14000 with TOF</td>
</tr>
<tr>
<td>Transverse spatial resolution 1 cm from center</td>
<td>4.4 mm</td>
<td>5.1 mm</td>
<td>4.7 mm</td>
</tr>
</tbody>
</table>

* Lutetium-based scintillator

2.1.3 Single Photon Computed Tomography

The physical characteristics of SPECT scanners have not changed much over the past

---

* Website accessed 18 October 2013

http://www.healthcare.siemens.com
http://www3.gehealthcare.com
http://www.healthcare.philips.com
few decades. The originally used scintillation material, NaI, remains adequate for the task, mainly because sensitivity and image resolution are largely determined by the collimator positioned in front of the detector. Collimators are rather simple mechanical devices that have been optimized quite a while ago. Nevertheless, SPECT scanner developers have made use of the rapid progress in electronics and computation, improving e.g. ease of use, stability and reliability.

**Table 2** SPECT characteristics of the top-of-the-line clinical SPECT/CT scanners from the 3 main manufacturers, as available from their corresponding websites. The scanners are listed in alphabetical order according to their commercial name.

<table>
<thead>
<tr>
<th>Company</th>
<th>Philips</th>
<th>GE</th>
<th>Siemens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the scanner</td>
<td>BrightView XCT</td>
<td>Discovery NM/CT 670</td>
<td>Symbia T</td>
</tr>
<tr>
<td>Detector</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>axial FOV</td>
<td>40.6 cm x 54 cm</td>
<td>40 x 54 cm</td>
<td>38.7 cm x 53.3 cm</td>
</tr>
<tr>
<td>crystal thickness</td>
<td>9.5 or 19.1 mm</td>
<td>9.5 mm</td>
<td>9.5 or 15.9 mm</td>
</tr>
<tr>
<td># of PMT</td>
<td>59</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>Intrinsic spatial resolution (FWHM in UFOV)</td>
<td>3.3 mm</td>
<td>3.3</td>
<td>≤ 3.9 mm</td>
</tr>
<tr>
<td>9.5 mm thick crystal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrinsic energy resolution (FWHM in UFOV)</td>
<td>≤ 9.6 %</td>
<td>≤ 9.8 %</td>
<td>≤ 9.9 %</td>
</tr>
<tr>
<td>9.5 mm thick crystal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>System spatial resolution (FWHM in CFOV)</td>
<td>7.4 mm</td>
<td>7.4 mm</td>
<td>7.4 mm</td>
</tr>
<tr>
<td>9.5 mm thick crystal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEHR at 10 cm, no scatter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>System sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEHR @ 10 cm</td>
<td>168 cpm/μCi</td>
<td>--</td>
<td>202 cpm/μCi</td>
</tr>
</tbody>
</table>

FOV: field of view
UFOV: useful field of view
CFOV: central field of view
LEHR: low-energy high-resolution collimator
2.2 Preclinical Imaging

During the last decade there has been a growing research interest in the field of “Molecular imaging”. The necessity of understanding the biochemical processes at molecular level have stimulated a great advance in technological instrumentation, both in the hardware and software aspects, especially as for in vivo studies on small animal, e.g. rats and mice. This field of research is often called “preclinical imaging”. Major efforts are devoted to obtain higher sensitivity, higher spatial resolution and cheaper and easy to handle instrumentation. This chapter gives a short overview of the state-of-the-art technologies for the most diffuse molecular imaging techniques, namely, positron emission tomography (PET), single photon emission computed tomography (SPECT), x-ray computed tomography (CT) and MRI (Magnetic Resonance Imaging), as applied to small animal. Finally multimodality techniques which allow the merging of molecular information with anatomical details, such as PET/CT; SPECT/CT and PET/MR will be illustrated. These are the fields where the technology is rapidly evolving these days.

2.2.1 Present Technology for Small Animal PET Imaging

Functional Molecular imaging investigations are performed on small animals, such as mice and rats, down to cellular level, so as to obtain results on simplified human models before the direct study on patients [Massoud and Ghambir, 2009]. The requirements on spatial resolution are much higher than those for clinical scanners because the dimensions of rats and even more of mice are clearly much smaller than the ones of human beings. For example, imaging of the rat brain requires a spatial resolution of less than 2 mm full width at half maximum (FWHM). A resolution better than 1 mm (FWHM) would be necessary for the brain of the mouse, whereas state of the art clinical scanner has a spatial resolution not better than 4 mm (FWHM).

In addition, the available radioactive signal is very weak. In fact, the injected activity in a mouse for brain receptor investigation is typically not greater than 5-10 MBq. Further there are limitations on the maximum volume of injected solution (~10 % of the total blood volume). As a consequence high-sensitivity instrumentation is especially required when fast dynamic processes are studied with characteristic time of the same order of the scanning time. All of the above has put stringent requirements on PET scanners for small animal and it has produced copious research in this field.

The design of most small-animal PET instruments is usually based on a miniaturized structure of a clinical scanner with small detector elements surrounding the animal in a small bore ring [Chatzioannou et al., 1999]. Other designs make use of rotating planar detector pairs [Del Guerra et al., 1998] (see Fig. 1). The latter configuration offers a better sampling and image uniformity, but it has severe limitations in terms of dynamic imaging and if very fast throughput is desired.

High-resolution multi-anodes photomultipliers tubes (MA-PMT) have been the photodetector of choice for most preclinical scanners. In most solutions the MA-PMT are coupled to pixilated matrices of scintillator. In this case, the coordinates of the photon interaction are obtained via “light-sharing” technique, i.e., by calculating the centroid of the light produced by the crystal on the high-granularity position-sensitive PMT. MA-PMTs have had a series of improvements (see Fig. 2) over the last twenty years, many of which have been partly triggered by the molecular imaging community needs: this led to the evolution from early MA-PMTs based on a typical round shape, (up to 10 cm diameter, and a crossed wire anode structure), to second generation (square-shaped metal-channel dynode structure) with a very fine anode granularity. And finally, with the third generation there has been a great improvement in the active area dimensions (up to 5 cm in side) and especially in the active-to-total area ratio (up to about 90%). These 5 cm tubes are based on the metal-channel dynode structure with an anode matrix of 16x16 elements on a 3 mm pitch.

The best readout method for modern MAPMTs would be independent single anode read-out. To this aim dedicated ASICs have been implemented and are currently used with H8500 in High Energy Physics. However, in order to limit the cost and complexity of the readout, often the simpler method of resistive chain for both X- and Y-coordinate is adopted [Popov et al., 2001; Olcott et al., 2005], so as to strongly reduce the number of output channels.
More recently, semiconductor photodetectors have become an alternative and more attractive method for the readout of matrices of scintillators. In this case, a matrix (either assembled or monolithic) of photoconductors with the same granularity as the scintillator matrix is coupled one to one to the scintillator pixel (no-coding error). Typical examples of this solution are PET inserts to MR, where matrices of small-area Avalanche Photodiodes (APDs) are used for the parallel readout of the pixilated matrices of a scintillator. [Pichler et al., 2001].

The so-called Silicon Photomultipliers (SiPM) [Golovin and Saveliev, 2004] are being characterized and studied by many groups. These photodetectors will definitely not only be used for clinical scanners, but they will replace the so-called block detector. These photodetectors could also be used to reconstruct the center of mass of the light deposited in a monolithic scintillator, by measuring, with high precision, the centroid of the light spot and also the dimension of the spot, so as to infer Depth of Interaction (DOI) information [Llosá et al., 2009].

Figure 1. Two different configurations for the construction of a small-animal PET scanner. Left: ring geometry, where the detectors are arranged in rings surrounding the animal. Right: Example of a rotating detectors configuration with four heads, where each one is in time coincidence with the opposite one.

Figure 2. Example of first (left, Hamamatsu R2486 with crossed-wire anode structure), second (center), Hamamatsu R8520 with crossed-plate anode structure), and third (right, Hamamatsu H8500 with multi-anode structure) generation of MA-PMT (images from the Hamamatsu web site: www.hamamatsu.com).

In order to maximize the efficiency of PET systems, PET heads should be positioned close to the object, and the thickness of the photon absorber should be at least one attenuation length at 511 keV. Being the detector so close to the target, there is significant contribution of the parallax error to the spatial resolution, thus many techniques have been developed to
obtain depth-of-interaction (DOI) information. [Moses and Derenzo, 1994; Balcerzyk et al., 2009; Saoudi et al., 1999].

The simultaneous improvement of spatial resolution and sensitivity is the challenge of PET imaging. However, these two figures are often in contrast, i.e., increasing one could cause the reduction of the other. Every year, new small-animal PET prototypes are produced or proposed by many research groups offering or promising even better performance. At the same time, some fully engineered scanners are released as commercial products. Nowadays, several products are present on the market. (See Table 3).

2.2.2 Present Technology for Small-Animal SPECT Systems

SPECT systems for small animal imaging are of two main types: the first one makes use of the clinical SPECT configuration, e.g. thallium-doped sodium iodide (NaI:Tl) Anger camera, equipped with a special collimator [Beekman FJ et al., 2005]; the second one consists of dedicated systems based on compact, high resolution detectors, following somehow PET scanner technology [Weisenberger et al., 2003; Furenlid et al., 2004].

In both cases the main feature is the collimator type: contrary to the clinics where regular arrays of round, square, or hexagonal holes in a high-density medium (lead or tungsten) are used, here the most widely applied collimator solution is the pinhole (or multi-pinhole) collimator. With this collimator one increases the spatial resolution of the imaging system by magnification of the object onto the detector. By using large detectors such as conventional Anger camera, a very high resolution down to a fraction of a mm is obtained. However the sensitivity could be very low because of the pinhole configuration. To overcome this problem, multi-pinhole solutions are implemented, but the large magnification produces large projections that may overlap as the number of pinholes increases. Meikle et al (2002) have solved the problem of overlapping projections by the use of iterative estimation, originally derived from the coded aperture approach [Barrett, 2001].

As for the second type of Small animal SPECT, solid-state detectors provide a promising alternative technology as compact high-resolution gamma cameras. Semiconductor detector technology is the new horizon in dedicated instruments for high-resolution nuclear imaging and such solid-state detectors with direct $\gamma$-ray conversion such as CdTe and CdZnTe have been proposed. The requirements for a good detector for SPECT, i.e., high spatial resolution, high energy resolution, and good efficiency for the detection of medium energy $\gamma$ rays, are only partially fulfilled by solutions based on scintillators / photomultipliers as in PET, especially due to the low energy resolution of scintillators and the relatively low (25-35%) quantum efficiency of the photodetector. A direct conversion solid state detector offers a much higher quantum efficiency and energy resolution and its granularity is now well in the range of the necessary high spatial resolution, whereas its intrinsic efficiency does not create severe DOI contribution, e.g. the mean free path of a 140.5 keV in CdTe is about 2.4 mm.

The major concern for the development of the next generation of PET systems for small-animal imaging is the improvement of sensitivity, always pushing the spatial resolution close to its intrinsic limit. On the other side, small-animal SPECT has almost reached its resolution limit of fractions of mm. In this case, the main challenge is to increase the sensitivity and especially the field of view in order to obtain ultrahigh-resolution systems able to visualize the entire animal in one shot.
<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Siemens</th>
<th>Philips</th>
<th>Brucker Corporation</th>
<th>Concorde Microsystems</th>
<th>Sedeal</th>
<th>Mediso</th>
<th>Inviscan</th>
<th>TriFoil Imaging</th>
<th>Sofic Bioscience</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of the scanner</strong></td>
<td>Inveon</td>
<td>Mosaic HP</td>
<td>Alibra</td>
<td>Focus 120 microPET</td>
<td>Argus (SuperArgus 2R PET/CT)</td>
<td>SuperArgus 6R PET/CT</td>
<td>NanoPET/CT</td>
<td>IRIS PET/CT</td>
<td>LabPET</td>
</tr>
<tr>
<td><strong>Axial FOV (mm)</strong></td>
<td>127</td>
<td>119</td>
<td>118</td>
<td>76</td>
<td>48</td>
<td>150</td>
<td>94.8</td>
<td>97</td>
<td>4:37</td>
</tr>
<tr>
<td><strong>Ring diameter (mm)</strong></td>
<td>161</td>
<td>197</td>
<td>190</td>
<td>147</td>
<td>118</td>
<td>160</td>
<td>181</td>
<td>110</td>
<td>156</td>
</tr>
<tr>
<td><strong>Crystal size (mm^3)</strong></td>
<td>1.51×1.51×10</td>
<td>2×2×10</td>
<td>---</td>
<td>1.51×1.51×10</td>
<td>1.5×1.5×7 (LYSO)</td>
<td>1.5×1.5×8 (GSO)</td>
<td>1.5×1.5×7 (LYSO)</td>
<td>1.5×1.5×8 (GSO)</td>
<td>1.12×1.12×13</td>
</tr>
<tr>
<td><strong>Scintillator</strong></td>
<td>LSO</td>
<td>LYSO</td>
<td>LYSO</td>
<td>LSO</td>
<td>LYSO and GSO</td>
<td>LYSO and GSO</td>
<td>LYSO</td>
<td>LYSO</td>
<td>LYSO-Ce</td>
</tr>
<tr>
<td><strong>Detector design</strong></td>
<td>Block, 20×20 array with PSPMT</td>
<td>Pixelated Arago logic, 19 mm PMTs</td>
<td>Single crystal, PSPMT</td>
<td>Block, 12×12 array with PSPMT</td>
<td>Block, 13×13 dual-layer phoswich array with PSPMT</td>
<td>Block, 13×13 dual-layer phoswich array with PSPMT</td>
<td>Block, 81×39 with Dual-MAPMT</td>
<td>Block, 26×27 with MAPMT</td>
<td>Phoswich detector, 2 crystals per APD</td>
</tr>
<tr>
<td><strong>Sensitivity for a point source at center (%)</strong></td>
<td>6.72 @ 350-625 keV</td>
<td>2.83 @ 385-665 keV</td>
<td>3.42</td>
<td>6.8 @ 100-700 keV</td>
<td>3.2 @ 250-700 keV</td>
<td>2.3 @ 400-700 keV</td>
<td>&gt; 11</td>
<td>7.7 @ 250-750 keV</td>
<td>8.7 @ 250-750 keV</td>
</tr>
<tr>
<td><strong>cFOV transaxial spatial resolution (mm)</strong></td>
<td>1.5</td>
<td>&lt; 2.3</td>
<td>3</td>
<td>&lt; 1.92</td>
<td>1.5</td>
<td>1.2 FBP</td>
<td>1.1 FBP</td>
<td>1.1 FBP</td>
<td>1.35 FBP</td>
</tr>
</tbody>
</table>

Table 3. Performances of most of the preclinical PET scanners, as available at their corresponding website. The scanner are listed in alphabetical order according to their commercial name.
2.2.3 Small-Animal CT Imaging

Computed Tomography (CT) is one of the most used techniques of noninvasive diagnosis, which provides a 3-D map of the local X-ray attenuation properties of the scanned patient. Dedicated scanners for small animal have been built in the last decades [Paulus et al., 2000; Stock, 2008], with the main goal of obtaining a very high resolution, down to tens of micron and a large field of view so that a scan of the entire animal can be performed in less than one minute. This is obtained by using x-ray tubes with very small tungsten anode focal spot (~10 micron) and low to medium x-ray energy (30-50 kVp). A large detector, such as magnified CCDs or a CMOS flat panel with a typical pixel size of 50 micron is used combined with high geometric magnification. The entire system rotates around the animal as in clinical CT in a cone-geometry configuration. Spiral CTs are also implemented. One critical issue for obtaining the design performances is that misalignments in the detectors are kept under strict control during the construction and the use of the CT. This can be done with various techniques, with and without special phantoms [Panetta et al., 2008]. A typical CT image of a mouse is presented in Fig.3.

CT for small animal can operate in step and shoot mode and in continuous mode. The standard way of reconstructing the image employs the Feldkamp algorithm [Feldkamp et al., 1984], but iterative methods are being increasingly applied. The main issue with animal CT is the high dose that is needed for obtaining the requested resolution, i.e. the quantum noise reduction. Hence dose limitation and increase speed of the exam for instance for angiography studies are the main topics of research in this field. The CT scans were mainly used in connection with PET images for providing anatomical information to be combined with functional imaging and for calculating the PET attenuation. However, they have also gained importance as mean of investigation "per se" in the field of molecular imaging.

2.2.4 MRI Small Animal Imaging

MRI (Magnetic Resonance Imaging) has become a very useful tool both in the clinical and the preclinical fields. MRI can produce images with excellent contrast between soft tissues and with a very high spatial resolution in 3-D. Like other imaging techniques, MRI uses electromagnetic radiation to study districts within the human body. Such radiation is non-ionizing, so that can be considered non-harmful for a human being. However, the interaction of the RF source to produce the MR image can increase the temperature of the body. The quantity that describes this phenomenon is the SAR (Specific Absorption Rate) measured in W/kg and defined as the RF power absorbed per unit of mass of an object. Hence, in-vivo MR imaging requires that the SAR is maintained below a safety limit. To understand the phenomenon of magnetism of the nucleus one can think of a mechanical analogy with a mass, electrically charged and rotating around its axis. If the center of gravity of the charges is not on the axis of rotation, the rotation itself generates a small magnetic field in a certain direction. This phenomenon of rotation is called "spin" and causes the nucleus to possess a magnetic moment $\mu$ which aligns along the direction of an external field (B0). An external RF pulse (the so-called B1 field) can transfer energy to the nucleus that will flip its magnetic moment according to the energy received, typically by 90 or 180 degree. Within a certain relaxation time the magnetic moment will return to its stable equilibrium position. The measurement of the relaxation times T1 and T2 gives an insight on the distribution (morphology) and behavior of the hydrogen...
The phenomenon of magnetic resonance can be investigated using different types of nuclei (1-H, 13-C, 19-F, 23-Na, and 31-P) with proper RF operating frequency to match the Larmor frequency of the nucleus under study. For small animal imaging MRI is a very versatile technique, capable of providing a very high spatial resolution (100 micron or less) for rodents. The strength of the magnetic field may vary from 0.5 to 9.4 T according to the application and of course to the cost of the apparatus. An example of a 7T system from Brucker is shown in Fig. 4. The system has a diameter of clear bore > 30 cm.

The impact of MRI in molecular imaging is continuously growing: examples are translation studies for angionesis and phenotypic characterization, dynamic visualization of tissue perfusion, and many more. The step-up from MRI and MRS has been favored by high field systems which allow for a higher signal to noise ratio. The identification of different atomic nuclei provides insights to functional and biochemical information: for instance cell membrane studies, creatine and lactate quantitative studies, etc. The limit of MRI and even more so of MRS is its sensitivity, still in the micromolar range, as compared to PET and SPECT. Thus, the MRS studies with 1-H, 19-F, 31-P and 13-C MRS compounds in preclinical research are primarily confined to pharmacodynamic, but not pharmacokinetic studies. With the advent of high field (i.e., 9.4T) and the advanced shimming high-resolution proton spectra, studies of the mouse brain have been receiving a great attention especially for tumor response and fMRI.

### 2.2.5 Multimodality Approach

#### 2.2.5.1 PET/CT and SPECT/CT

Functional imaging such as PET and SPECT are intrinsically non-morphological techniques. Hence the anatomical information is often mandatory in order to localize precisely the position of the radiotracer. In addition, when quantitative information on small target sites is needed, anatomical images are needed to apply proper corrections for partial volume error. In any case, it is obvious that the information from a morphological imaging technique, such as CT or MR, is of great help for the PET or SPECT image analysis. More and more integrated systems are required in analogy to the clinical area where a PET/CT is the diagnostic instrument of choice for most investigations. Also in the field of small animal imaging, there are two types of multimodalities, the so-called “tandem configuration” where the two modalities are executed one after the other, sharing the same bed for the animal such as in PET/CT [Fontaine et al., 2005], SPECT/CT, PET/MR [Mackewn et al., 2005] and SPECT/MR, and the truly combined modality, this latter type is only implemented as of today in PET/MR.

On the shadow of the successful application of combined PET/CT scanners in the clinical environment, this technique has been recently transferred to small-animal scanners. In fact, the morphological information from CT can be used to get a finer spatial localization of the radiotracer distribution within the body as well as to obtain the attenuation coefficient map of the object under study for attenuation and scatter correction of the PET images.

CT images are mostly used to improve the emission images. In fact, the emission images are affected by a quantitative error due to the attenuation of radiation by the object under study. Even when this effect is much smaller than for humans, the magnitude of this correction in small animals is non-negligible. For example, in PET, the attenuation correction factor is 4.5 for a 40 cm diameter man, and is 1.6 for a 5 cm diameter rat, and 1.3 for a 3 cm diameter mouse. In the CT case, the
attenuation coefficients are measured with a continuous x-ray spectrum, ranging from 10 to 70 keV. Hence the CT-energy linear attenuation coefficient ($\mu_{CT, X}$) has to be scaled to the 140.5 keV value for SPECT by a linear formula and to the 511 keV for PET, by a bilinear interpolation. Figure 5 shows typical images obtained without CT (bottom) and with CT corrections and image fusion (top).

Figure 5. Typical imaging performance on one of the most recent preclinical (IRIS, raytest-IVISCAN). Top: PET/CT image obtained with the IRIS PET/CT scanner; bottom: PET image only (courtesy of Panetta D and Salvadori P, IFC-CNR, Pisa, 2013)

2.2.5.2 PET/MR

Early diagnosis and therapy are connected to molecular imaging and genetic information. As for molecular imaging, the multimodality approach is becoming more and more necessary. In fact, the combined systems PET-MR and SPECT/MR have received a great attention and developments. The advent of new solid state detector such as APD, PS-APD, MPPC and SiPM has allowed to insert a PET system within the high magnetic field of an MR. It is well known that to have quantitative PET information an attenuation correction must be performed, best made with a CT. This was the reason for introducing PET/CT systems in the clinical and also in the preclinical field. As for the MR based attenuation correction, a lot of research has been going on to find the best way to do it: segmentation, brain Atlas, and special sequences (i.e., UTE) have been proposed in combined shape. MRI and PET in the preclinical scenario are now mostly in the same system, either as a PET insert or as a combined structure from the beginning. MRI and PET offer complementary functionality and sensitivity. A simultaneous acquisition capitalizes on the strengths of each, providing a hybrid technology that has a significantly greater impact than the sum of its parts. A schematic scheme of the structure of a typical combined system is depicted in Fig. 6.

Figure 6. Cross section of the combined PET-MR system proposed for the TRIMAGE PET-MR-EEG project (courtesy of A. Del Guerra, 2013)

Among the many applications with a combined PET/MR it is worth citing: dynamic studies, MR/PET cross correlation, MR-guided motion correction of PET and PET image reconstruction.

2.2.6 Conclusions

Multimodality in small animal imaging has had a big step forward in the last decade. This was mostly driven by the introduction and widespread acceptance of PET/CT units in the clinical practice, especially in oncology, and more recently by the deployment of simultaneous PET/MRI systems. In the preclinical field the combined modalities are diffused and necessary, since the active groups are especially in academia that implement and develop the most highly sophisticated molecular imaging technologies available today. Just to address the hardware side, novel scintillators, photodetectors and DAQ systems have received a great boost from these activities, thus demonstrating the cross-fertilization between the fundamental research in detector and technology and their application in molecular imaging.
3 New challenges

Multi-modality imaging is used in order to show both the molecular processes taking place in the body and the anatomical location in which they are happening so that, for example, a tumour can be detected using PET imaging and located using CT in a PET/CT scanner. PET/CT was introduced 15 years ago and multi-modality is standard for SPECT and PET machines, which are now on sale. Commercially multi-modality means SPECT/CT or PET/CT.
The new challenge is to combine MR imaging for anatomical location with PET and SPECT. The benefits are to reduce the radiation dose by eliminating the CT scan, and the possibility to use functional MRI as well as simple anatomical MR scans (so that blood flows, for example, can be detected). However, this is technically more difficult because typical SPECT and PET scanners use scintillators which are incompatible with the intense magnetic fields in modern MR scanners. The rotating gantries used in PET and SPECT can also be affected by the MR magnetic field. Conversely the PET detectors must not affect the sensitive MR scanner operation either by perturbing the field or introducing electrical noise.

Although PET-MR multi-modal imaging has been in use for a few years it was, until very recently, done sequentially rather than simultaneously. Clearly simultaneous imaging is preferable, for example to avoid motion artefacts between scans and the first simultaneous PET/MR scanners are now coming on the market (e.g. Philips Biograph mMR). Technology from Nuclear Physics detector systems is used to overcome the magnetic incompatibility. Some pre-clinical prototypes used light guides to allow photomultipliers to be located further from the magnetic field however the more popular route seems to be to use of semiconductor light sensors (APDs or SiPMs) to replace the photomultipliers or to replace scintillators by semiconductor detectors.
The next challenges which are not yet solved in the commercial market are to integrate SPECT with MR and to integrate fast detectors for ToF PET in an MR environment for simultaneous operation (sequential ToF PET/MR exists). MR-compatible ToF modules can be made using NP detectors (fast scintillators with SiPMs) as building blocks for ToF PET/MR. SPECT/MR is far from market while research systems use semiconductor detectors to replace the scintillators either by putting CZT detectors behind the SPECT collimators or else by electronic collimation using a Compton camera made of semiconductor detectors.

These last two (SPECT/MR and ToF PET/MR) are the challenges where techniques from Nuclear Physics systems are currently making a difference and enabling the development of new multimodal imaging systems.

3.1 Detector design

Despite the excellent performance reached by PET detectors, there is room for improvements that will also allow non-standard use of PET technology, such as in-beam measurements during particle therapy sessions. Research is being carried out worldwide in order to improve all the relevant aspects that contribute to the overall performance of a PET scanner: detection efficiency, spatial resolution, depth of interaction measurement, time resolution, compactness, MR compatibility, speed, power consumption.

All the PET components reviewed in the following, as well as the strategic choices in the design of the global system are subject to continuous research and development, with the ultimate goal of providing the most accurate input information to the 3D or 4D reconstruction algorithm.

3.1.1 Scintillators

In order to be used as a primary photon converter for a PET (fixed photon energy) and a SPECT (wide photon energy range) detector, a scintillating crystal must meet the following requirements:
- high density (i.e., high conversion efficiency);
- high light yield (related to the energy and time resolution);
- short rise time to optimize the time resolution.

The figure of merit that summarizes the suitability of a crystal is usually defined as:
\[ \eta \sim \varepsilon^2 \sqrt{N/\tau} \]

with \( \varepsilon, N, \tau \) related to the crystal density, light yield and decay time, respectively.

In addition, the technology must provide uniform crystals at a low (acceptable) cost.

The state of the art for PET/SPECT scanners is a set of inorganic crystals, whose properties are summarized in Table 4. LSO and LYSO are the best choice for scanners that also aim at the Time Of Flight measurement. However, the search for new materials that would better meet the requirements for a more efficient and time performance scanner has not stopped and in recent years some candidates emerged.

As an optimal timing resolution is related to the photon counting statistics, it requires the capability to trigger at very low threshold, with the performance limit being reached when counting single photons. When these conditions are met, a high light yield and a short rise-time of the scintillating light allow the best measurement of the interaction time, with the theoretical possibility to approach a limit value of about 100 ps.

GAGG crystals have been recently studied as a possible alternative to known scintillators per PET and SPECT scanners: the density, light yield and time resolution are suitable [Iwanoqsha et al., 2013, Kamada et al., 2011], but suggest a possible marginal improvement rather than a significant step forward.

Plastic scintillators, which would provide a very short decay time, suffer from low stopping power and insufficient optical photon yield [Spanoudaki et al., 2010].

Should the scintillators be engineered with a photonic crystal pattern, the light collection at the surface would be improved. However, despite some promising preliminary results, the technology is still in an early stage.


<table>
<thead>
<tr>
<th>Light yield 10^3 ph/MeV</th>
<th>NaI</th>
<th>BGO</th>
<th>GSO</th>
<th>LSO</th>
<th>LYSO</th>
<th>LGSO</th>
<th>LuAP</th>
<th>YAP</th>
<th>LaBr₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary decay time</td>
<td>250</td>
<td>300</td>
<td>60</td>
<td>40</td>
<td>41</td>
<td>65</td>
<td>18</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>ΔE/E (%) at 662 keV</td>
<td>6</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>15</td>
<td>4.4</td>
<td>3</td>
</tr>
<tr>
<td>Density (g/cm³)</td>
<td>3.67</td>
<td>7.13</td>
<td>6.71</td>
<td>7.35</td>
<td>7.19</td>
<td>6.5</td>
<td>8.34</td>
<td>5.5</td>
<td>5.08</td>
</tr>
<tr>
<td>Effective Z_eff</td>
<td>50</td>
<td>73</td>
<td>58</td>
<td>65</td>
<td>64</td>
<td>59</td>
<td>65</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>1/μ @ 511 keV (mm)</td>
<td>25.9</td>
<td>11.2</td>
<td>15.0</td>
<td>12.3</td>
<td>12.6</td>
<td>14.3</td>
<td>11.0</td>
<td>21.3</td>
<td>22.3</td>
</tr>
<tr>
<td>PE (%) at 511 keV</td>
<td>18</td>
<td>44</td>
<td>26</td>
<td>34</td>
<td>33</td>
<td>28</td>
<td>32</td>
<td>4.4</td>
<td>14</td>
</tr>
</tbody>
</table>

3.1.2 Photon Detectors

Once the primary photon conversion efficiency and the secondary photon light yield and collection rate are optimized, a high performance photon detector is required in order to exploit the raw information at best.

Clinical PET and SPECT scanners are typically based on photomultipliers (PMTs), which, despite the high gain, do not meet two important requirements: compactness and magnetic field compatibility.

In recent years, research projects focused on solid-state detectors, such as Avalanche Photo Diodes (APDs), Silicon PhotoMultipliers (SiPMs), which are APDs operated in Geiger mode, and Digital Silicon PhotoMultipliers (dSiPMs) which directly provide a digital output.
APDs, that are insensitive to magnetic fields, were used for the first commercial PET/MR scanner [Schmand et al., 2007]; however their drawbacks (low gain and long rise time), make them unsuitable for high performance TOF-PET.

SiPMs, on the other hand, besides meeting the requirements of compactness and magnetic filed insensitivity, present very interesting advantages: low bias voltage makes them even more attractive than APDs for hybrid PET/MR imaging, while high gain and short rise time make them the best candidates for TOF-PET. The short rise-time and the high level of homogeneity of SiPM matrix components should be compatible with a time resolution that could approach the lower limit of 100 ps. In addition, the high gain could allow single photon counting, which, if the dark count rate is kept under control with active cooling, would make it possible to design a detector that couples continuous crystals to segmented SiPM matrices.

dSiPMs, developed by Philips [Degenhardt et al., 2009], [Degenhardt et al., 2010] [Frach et al., 2009], are based on the integration within the SiPM sensitive area of basic processing electronics and eliminate the need for external processing [Philips, 2010]. Each micro-cell of the array is connected to an integrated counter and an integrated TDC that provide the energy and time information, respectively. dSiPM coupled to LYSO crystals reach time resolutions as low as 150 ps (FWHM). The different performances are summarized in Table 5.

Table 5. The most important parameters of (secondary) photon detectors.

<table>
<thead>
<tr>
<th>Detector</th>
<th>PMT</th>
<th>APD</th>
<th>(d)SiPM</th>
<th>UFSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain</td>
<td>10^5</td>
<td>50-1000</td>
<td>~ 10^6</td>
<td>5-15</td>
</tr>
<tr>
<td>Rise Time (ns)</td>
<td>~ 1</td>
<td>~ 5</td>
<td>~ 1</td>
<td>~ 0.1</td>
</tr>
<tr>
<td>QE @ 420 nm (%)</td>
<td>~ 25</td>
<td>~ 70</td>
<td>~ 25-75 (PDE)</td>
<td>~ 75</td>
</tr>
<tr>
<td>Bias (V)</td>
<td>&gt; 1000</td>
<td>300-1000</td>
<td>30-80</td>
<td>100</td>
</tr>
<tr>
<td>Temperature sensitivity (%/K)</td>
<td>&lt; 1</td>
<td>~ 3</td>
<td>1-8</td>
<td>Negligible</td>
</tr>
<tr>
<td>Magnetic filed sensitivity</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Ultra Fast Silicon Detectors (UFSD) are a new promising technology for the improvement of the spatial resolution, while keeping a time resolution of the order of 100 ps [Sadrozinski 2013]. Their possible performance limit, however, lays in the low gain (5-15), which could deteriorate both the signal to noise ratio and the related time resolution with respect to the nominal expected values. The construction and characterization of the first prototypes will require a special attention to the capability of detecting the first secondary photons emitted in the crystal de-excitation process, which are key to an excellent time resolution. Should this limitation be overcome, UFSD would be an excellent candidate for hybrid PET systems, thanks to their compactness and intrinsic insensitivity to temperature and magnetic fields.

Semiconductor detectors based on CdTe or CdZnTe [Schlesinger & James 1995, Schlesinger 2001] are solid-state devices that allow the direct conversion of gamma rays to electrical charges. The conversion yield is large with respect to scintillation devices: typically 30000 charges for a 140 keV energy release. As a consequence, the energy resolution is not limited by charge generation...
statistics but by other phenomena like electrical noise or material uniformity. While the best devices achieve less than 2% of resolution at 140 keV thanks to an optimized design, typical resolution values by standard systems are close to 5% at 140 keV [Eisen 2004, Verger 2004, Meng 2009] a value that can help the development of dual-isotope imaging protocols [Ben-Haim 2010]. The spatial resolution of these semiconductor detectors can be extremely good as it is not limited by light spreading and photon statistics but rather by the readout circuitry. A typical device resolution is of the order of 2.5 mm, but the use of high density readout [Meng 2009] or sub-pixel positioning electronics [Montemont 2012] allows to obtain an intrinsic resolution of few hundreds of micrometers (200-400µm).

CdTe or CdZnTe-based detectors are integrated in small modules that couple the semiconductor crystals and the readout electronics on the same substrate. System designers have taken profit of the compactness of such modules to build innovative SPECT tomographs [Bocher 2010, Erlandsson 2009, Ben-Haim 2010] that exploit the modularity to enhance sensitivity and resolution by focusing of a given region of interest. Additionally, these systems also avoid the motion of the camera head around the patient.

3.1.3 Front-End Electronics
Front-end electronics is becoming a key enabling technology (KET) for detectors due to the increasing number of channels and the high level of integration that allows to reduce cost and dimensions. A general trend is to integrate more and more functions in ASICs (amplification, filtering, digitization, signal processing) making them Systems on Chip (SoC). These multi-channel ASICs also tend to move closer or even onto the detectors, minimizing the connections and improving both performance and reliability. This localization coupled to the increasing number of channels requires in turn low-power design so that the performance and compactness obtained are not spoiled by large cooling systems. The evolution of microelectronics technologies allows this increase of performance together with power reduction and higher operating speeds, an important feature for reducing the patients exposure while maintaining high quality resolution. Such a design is also useful from the point of view of the system performance, since it allows more accurate timing measurements that improve the noise and background reduction and therefore provide better quality images with lower doses delivered to patients.

![Figure 7. Example of compact front-en electronics to read-out a SiPM matrix.](image)

3.1.4 Module Layout
State-of-the-art scanners are based on segmented crystals that collect most of the secondary photons on a single channel, then detected by PMTs, APDs or SiPMs, whose signals are processed by dedicated ASICs and FPGAs.

Any change in the detector design is related to the possible improvements of the key parameters that describe the overall system performance: Efficiency, 3D Spatial resolution, Time resolution, MR compatibility, Compactness, Speed, Power Consumption.

The scintillator, selected according to the figure of merit already discussed, is usually segmented. However, the availability of highly performant segmented SiPM matrices, with a high gain and the possibility to detect single photons, prompted some projects based on continuous scintillator blocks read by segmented matrices [Llosa et al., 2010, Pennazio et al., 2011]. The continuous crystal would allow a cluster reconstruction, with the double advantage of using the cluster size for the DOI measurement [Maas et al., 2009; Zhi et al., 2010; Morrocchi et al., 2013] and of a multi-sampling of the secondary photon time distribution, which would help improve the TOF measurement. Such an approach strictly depends on the capability to control the SiPM dark count rate, so as to limit the trigger rate and to distinguish contributions to the cluster reconstruction from channels triggered by dark counts. This result can only be achieved with a cooling system that allows a temperature stability within about 1°C.
SiPMs (analog or digital) are the photon detector of choice for almost every ongoing research project: they are efficient, with very high gain, single photon counting capabilities, very high spatial resolution, excellent time resolution (with intrinsic resolution among the different cell contributions to a matrix element quite close to 100 ps). They are also compact, compatible with operations in a magnetic field and acceptably priced.

Custom front-end electronics developments mostly focus on optimizing the TOF measurement, so as to reach an overall resolution below 200 ps. If the scintillator rise-time and the photon detector signal formation time are short enough and the detector uniformity in the time response is good (as it is for the latest SiPM matrices available on the market), the front-end electronics contribution can become the main source that contributes to the system time resolution. Whether the crystal is segmented or continuous, the key to optimize the time resolution is the capability to identify the first photon(s) from the crystal deexcitation and to distinguish them from the spurious dark count signals. With a segmented crystal, the analysis of the rising signal shape is the clue, while in the case of a continuous crystal, where the threshold must be as low as required to detect single photons, the cluster analysis algorithm must be able to distinguish true signals from dark count background events.

The need of precise temperature control and uniformity is also being addressed by designing active cooling systems that are very important to keep the system performance constant.

System compactness and MR design compatibility are also provided by the choice of solid-state photon detectors such as SiPMs.
3.2 Simulation and reconstruction

Contrary to planar imaging, which includes scintigraphy, or radiography, tomographic images are not directly obtained from the measurements, but are the result of the so-called tomographic or image reconstruction process. Classically, the goal of tomographic reconstruction is to obtain the image of an “object” from its “projections”, where the object might be an attenuating medium (CT) or a radioisotope distribution (PET, SPECT or Compton cameras). Tomographic image reconstruction is a process based on mathematical algorithms which are implemented in computers. Although a mathematical solution for the problem of tomographic reconstruction was first proposed in 1917, the advent of modern computers made CT a reality. Computers are also essential to simulate the complex physical phenomena which underlie the image formation process, such as the behaviour of optical photons within scintillation materials, the radioisotope decay and subsequent radiation emission, etc. The continuously increasing computing power has allowed for the development of more sophisticated image reconstruction algorithms, and more detailed and accurate simulations of tomographic systems. In this section, we will present state-of-the-art research and most recent advances in image reconstruction and simulations.

3.2.1 Image Reconstruction

Traditionally, a tomographic image corresponds to a plane section (2D image) of the object under inspection. A volume (3D image) was thus constructed by aligning several reconstructed sections. Nowadays, modern reconstruction techniques can directly provide 3D images (fully 3D reconstruction) and 4D images if time is also taken into account. 4D image reconstruction is particularly useful in cardiac PET and SPECT, or to image regions affected by respiratory motion, and it is essential in dynamic emission tomography, whose goal is to study the concentration of the injected tracer over time. At present, there are several image reconstruction algorithms, which can be grossly divided into two categories: analytic and iterative reconstruction methods. Analytic reconstruction methods are based on a direct mathematical solution, and are still widely used for CT reconstruction. However, the assumptions on which analytical methods are based on, usually do not hold in emission tomography.

Compared to analytical reconstruction, the main advantage of iterative methods is their ability to include a more accurate description of the imaging process, which in turn, usually leads to better images. This is specially the case when the measurements are noisy, or when the imaging device cannot provide uniform or complete sampling (see Fig. 8). Therefore, iterative reconstruction methods are the preferred ones in Emission Tomography, although analytical methods, such as Filtered Backprojection (FBP) are still used for quantitative image analysis in spite of their limitations.

The goal of iterative reconstruction techniques is to find an image estimate by successive steps. In the last decades, a wide variety of algorithms have been presented. We refer the interested reader to some excellent reviews [Qi & Leahy 1998; Bruyant 2002; Lewitt & Matej 2003; Defrise & Gullberg 2006]. Most iterative reconstruction techniques share the same “ingredients”: models for the image, the data and the imaging system, an objective function, and an optimization algorithm. The underlying physics of the image formation and degradation phenomena can be taken into account in the choice and description of the models, as well as in the design of the cost function, as will be described in the following paragraphs.

3.2.1.1 Physics & Iterative Image Reconstruction in Emission Tomography

One of the main strengths of iterative algorithms relies on their ability to include accurate models of the underlying physics, which include the statistical nature of radioactive decay or radiation detection, and the interaction of radiation in matter. The statistical nature is contemplated within the data model. Most commonly used reconstruction techniques are based on a Poisson model; this model naturally leads to the Maximum-Likelihood (ML) criterion to determine which image is the best estimate of the true object.

The behaviour of the imaging device is described within the so-called system response model or system response matrix (SRM). In
PET or SPECT, the elements of the SRM correspond to the detection probability of gamma rays originating from a certain location. In the first place, the effects of the geometry and arrangement of the detector elements on the detection (and the collimator in SPECT) should be modeled. The system model can also include a description of crystal penetration effects, cross-talk, inter-crystal scatter, etc. In principle, the more effects are correctly modelled and included within the SRM, the better the reconstructed image. However, computing the SRM for a certain device can be very challenging given the dimensions of the matrix, which corresponds to N\times M, being N and M the number of data and image elements, respectively. For a conventional clinical PET scanner, N can be larger than 10^8, and the image might be composed by several millions of voxels. The more physical effects are contemplated, the less sparse the SRM becomes. Several techniques have been proposed to compute and handle the SRM. The factorization of the SRM in several components makes it easier to calculate and store the SRM, and to handle it during the reconstruction [Qi & Leahy 1998]. Monte-Carlo simulations have been proved to be a very useful tool to compute the whole SRM or several of its components for PET [Rafecas et al. 2004] and SPECT [Lazaro et al. 2005]. Approaches based on measurements can provide very realistic models for the Point Spread Function [Panin, et al. 2006]. Analytical models usually allow for faster but less accurate alternatives [Aguiar et al. 2010]; Analytical comprehensive models have been also proposed but its computational cost can be prohibitive. In any case, since the factorisation of the system matrix allows the contribution of the various physical phenomena to be calculated separately, different approaches can be combined to calculate the various components of the system response model. Finding a balance between computation cost and model accuracy is currently a very active field of research.

Patient-dependent effects such as attenuation or scatter can be also included within the reconstruction process. Attenuation factors, previously obtained from CT, MRI or additional measurements, are built within the SRM. Some attempts have been done to include object scatter within the SRM, for example using Monte-Carlo simulations [Rehfeld & Alber 2007]; however, the most common approach is to use the scatter estimate within the comparison step of the iterative algorithm. In this step, the measured data are compared to the ideal data which would have been measured for an object being described by the last image estimate. For PET, the contribution of accidental coincidences can be also taken into account in the comparison step. As mentioned above, the increasing number of detection channels, and the subsequent need of smaller image elements poses several challenges in the computation and handling of the SRM. Many efforts have been put in the last years to optimise the balance between accurate models and computational efficiency. A way to avoid the storage of the SRM is to calculate the system model on-the-fly. This approach is usually the one chosen when dealing with “list-mode data”, i.e., the measured data are not compressed into histograms (such as sinograms), but are stored according to the registration time. List-mode reconstruction [Barret et al. 1997] makes it possible that the whole information contained in the data is preserved and exploited. This is done usually at the cost of simplified system models, since the latter are calculated on the fly; however, fast but accurate system models for list-mode reconstruction, usually based on analytical approaches, have been proposed lately [Prax & Levin 2011].

Time information is the key in Time-of-Flight (ToF) PET, which requires dedicated algorithms to exploit the location constraint for the positron-electron annihilation provided by the time difference in the arrival of the two annihilation photons. This technology, already proposed in the eighties has been recently translated into clinical PET. In combination with TOF dedicated algorithms, TOF PET allows image quality (in terms of SNR and lesion detectability) to be improved [Conti et al. 2009].

Concerning the image model, rectangular voxels are the preferred options. In the last years, spherical based functions (“blobs”) [Lewitt 1992] have deserved renewed attention given their ability to reduce image noise, but usually at the cost of higher computational cost. Other potentially interesting alternatives are polar pixels, which allow the symmetries of the imaging device to be exploited [Israel-Jost, et al. 2006] or those based on irregular grids [Boutchko et al. 2013].
The cost function and its optimization are the “core” of a reconstruction algorithm. Most widely used techniques are based on the optimization of the aforementioned ML criterion, being the Maximum-Likelihood-Expectation-Maximization algorithm (MLEM) and its accelerated version Ordered-Subsets-Expectation-Maximization algorithm (OSEM) the most popular ones. However, the ML estimation problem is ill-conditioned, which translates that the unavoidable noise in the data causes noisy images. Noise regularization is thus needed, which can be achieved through early stopping (before convergence), post-reconstruction smoothing, or by adding a penalty function in the objective function. The latter approach can also be derived if the problem is formulated in a Bayesian framework (Maximum-A-Priori algorithm, MAP). The penalty function (or prior) might also include some anatomical information of the patient obtained from a CT or MRI [Gindi et al. 1993]. Compressed sensing (CS) reconstruction approaches and CS-based Total-variation (TV) regularization are earning much interest in the community, especially for CT [Tang et al. 2009]. TV priors offer a promising alternative to compensate for missing data, as those arising from gaps between detectors or partial PET ring configurations.

3.2.1.2 Accelerating Iterative Image Reconstruction

One of the main drawbacks of iterative image reconstruction is its computational cost. Not only the calculation of the system response matrix might be computer expensive, but also the image reconstruction process as such. Therefore, much effort has been devoted to accelerate the reconstruction process, which remains an active field of research. Some of the proposed approaches rely on parallel computing using clusters, or multicore architectures; the use of Graphical Processor Units (GPUs) has earned much attention in the last years, as a cost-effective alternative [Pratx, & Xing 2011] especially useful for TOF PET.

A completely different approach is to implement the reconstruction within a Field Programmable Gate Array (FPGA).

3.2.1.3 Image quality, quantification and compensation of degradation phenomena in ET

Tomographic images can be employed for different purposes. PET and SPECT are commonly used for diagnostics and therapy follow-up in clinical routine. More recently, PET images are also used for tumour delineation in radiotherapy planning. At the same time, emission tomography of rodents and larger animals (such as monkeys for neurosciences and pigs for cardiology) is a common tool in biomedical research, or pharmacology. It is obvious that, for any of these applications, the quality of the image should be “as good as possible”. On the other hand, the kind of information to be extracted from a reconstructed image depends on the final purpose: visual inspection, lesion detection, quantification of certain physiological parameters, etc. [Kupinski 2012]. In the end, this purpose will determine which are the main properties or characteristics that a “good image” should exhibit and which, in turn, the reconstruction algorithms of choice should be able to provide.

Quantitative image analysis (quantification) consists in extracting certain parameters of interest from an image, for example tracer uptake. To obtain quantitative information, a linear relationship is required between image voxel values and activity concentration. For this purpose, several effects need to be accounted for; some of these effects are related to the underlying physics and image formation processes and are thus unavoidable, but can be compensated for. This is the case of attenuation and Compton scattering in the patient, Compton scattering in the detectors, partial volume effects, variable spatial resolution across the Field-of-View. In PET, also accidental coincidences might be a source of inaccuracy. Truncation artefacts due to limited-angle geometries, or ring artefacts also hinder quantification. Motivated by the advancement of novel technologies such as TOF-PET or PET/MR, novel methods able to compensate for attenuation by simultaneously estimating the activity distribution and the attenuation have been proposed [Salomon 2011].

One main source of image degradation is patient and organ motion. Specially cardiac and respiratory motion (in thorax or abdominal examinations), and involuntary head motion in brain studies might strongly distort the
information content of the images. Several strategies to deal with motion have been proposed (see reviews in [Rahmim et al. 2007]), which can be grouped into two categories: gating and non-gating methods. In gating-methods, the acquired data are split in frames based on an external motion detection system. Assuming that there is little or no motion in the single frame, the frames are reconstructed individually with a standard algorithm. The external signal could be a respiratory belt for respiratory motion or an electrocardiography for a cardiac motion (or both, named “dual-gating” [Martínez-Möller 2007]. This simple method allows the motion effects on the image to be reduced but at the cost of increased noise levels (i.e. worsening the signal-to-noise ratio). To overcome these limitations, many research efforts are being currently dedicated to the development of sophisticated non-gating methods, which do not rely on any external signal and, in general, make use of all the acquired data at the same time. The later fact leads to improving the signal-to-noise ratio, as it is shown in Figure 9. Among these approaches, there are strategies that assess separately motion and image, and other methods that jointly estimate motion and the activity distribution (image). Regardless of the motion correction method, accurate quantification requires that the CT map and the PET images are acquired in the same respiratory conditions. In some cases, this is done by acquiring a 4D-CT that entails an increase of dose not justifiable for all the patients. In [Fayad et al. 2013] a method to generate dynamic CT images combining a reference CT image and the motion estimation of the 4D PET is presented as an interesting solution to solve the dose burden of the 4D-CT.

3.2.2 Simulations
Monte-Carlo (MC) Simulations have always been a fundamental tool in nuclear and particle physics, and have also become essential for the advancement of emission tomography [Ljungberg, Strand & King 1998; Buvat & Castiglioni 2002; Harrison 2012]. MC simulations are often used to optimize the design of novel imaging systems or their components. Simulations are especially useful to examine the effect of a single physical phenomenon or a certain parameter, since the physics in real experiments is very complex and the effects of the underlying physical phenomena cannot be easily isolated. Simulated data are also cardinal to test and optimize new techniques for data correction, image reconstruction, reconstruction of the interaction position within a detector, etc. Additionally, as mentioned in the former section, Monte-Carlo simulations are also used to calculate the system response model for image reconstruction. Several multi-purpose packages for photon and particle tracking are being currently employed in Emission Tomography. Especially relevant ones are Geant4, EGS, MCNP, FLUKA, and Penelope. These packages can provide accurate simulations of the interaction of particles in matter, usually at the expense of large computing times, that might be prohibitive in case of complex imaging devices. For these cases, dedicated simulation software, specially conceived for photon-tracking in emission tomography, is usually preferred. Several packages have been developed for both PET and SPECT, such as GATE, SimSET, GRAY, or GAMOS, being GATE and GAMOS based on a GEANT4 framework. Some packages are PET specific (PETSIM, PET-EGS, PenelopePET, PET-SORTEO, or EIDOLON), whereas SiMIND was originally developed for SPECT. (Please, see [Ljungberg, et al. 1998; Buvat & Castiglioni 2002; Harrison 2012; Ljungberg, et al. 2012] for an overview and the corresponding references to each single package.) These dedicated packages are usually faster but less flexible than general-purpose ones. Simulating unconventional imaging devices might be difficult or even impossible without modifying the source code; however, for standard devices, they provide a number of interesting features such as detector electronics modeling, complex source and phantom description, or modelling of time-dependent phenomena.

As for image reconstruction, one main issue is to find a trade-off between accuracy and computing time. When speed is the main issue, analytical simulation packages, such as ASIM, might provide the desired performance. On the other hand, several efforts have been put in accelerating simulations by parallelizing the software or adapting it for distributed computing environments. A very promising alternative is the use of GPUs, which remains an active field of research.
Figure 8. Reconstructed images from a clinical scanner. The data were reconstructed using analytical (left) and iterative (right) reconstruction algorithms.

Figure 9. The effect of motion and its correction. Left column: no correction applied. Middle: A gate-based correction is applied. Right: Motion compensation is performed through simultaneous reconstruction of motion and image [Blume et al. 2012]. The two rows correspond to different gates of very low statistics.
3.3 Photon counting: towards spectral CT

Hybrid pixel arrays applied to X-ray detection might provide a new generation of digital X-ray photon counting cameras that can replace conventional “charge integration” CMOS and CCD cameras used in X-ray Computerized Tomography (CT). Applied to the detection of X-rays, this technological breakthrough, which was originally developed for the construction of vertex detectors used in high energy physics experiments, can provide spectral information on the X-rays transmitted through an object. Thus, the current advent of X-ray photon counting cameras enables the development of spectral CT: a novel intrinsic anatomical and functional imaging modality that will hopefully open a new door in the field in molecular imaging.

3.3.1 Photon counting with hybrid pixels

Hybrid pixel detectors [Wermes 2005] form a new generation of digital X-ray cameras working in photon counting mode that can replace conventional “charge integration” CMOS and CCD cameras used in X-ray Computerized Tomography (CT). This novel approach involves several advantages [Yorkston 2007], such as the absence of dark noise, a high dynamic range and photon energy discrimination.

The development of hybrid pixels was initiated for the construction of vertex detectors used in particle physics experiments to observe charged particle pathways with high timing and spatial accuracies. Hybrid pixels detectors have fulfilled these requirements quite successfully in the experiments ATLAS [Cristinziani et al 2007] and CMS [Kästli et al 2007] on the CERN Large Hadron Collider (LHC) and brought decisive contributions to the discovery of the Higgs boson.

Hybrid pixels consist in the association of pixelized sensor and readout electronics connected together using bump bonds (Fig. 10). Usually, the sensor consists in N-type high resistivity silicon of a few hundreds nanometers thick with P⁺ pixel implants, but it can also be from different materials of higher effective atomic numbers such as cadmium telluride (CdTe), cadmium-zinc telluride (CZT) or gallium arsenide (GaAs) in order to provide better photon interaction efficiencies at X-ray energies up to 120 keV. The readout electronics chip (ASIC), which is pixelized at the same pitch as the sensor, is designed using standard CMOS processes.

![Figure 10. Schematic view of a hybrid pixel detector.](image)

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The charges generated by photon interaction in the pixel sensor are collected on the ASIC via the bump bond connection and converted after an amplification stage in either a current or a voltage signal that is compared with one or several adjustable detection thresholds. Signals overcoming the threshold(s) are then stored in a local memory acting as a counter. Several ASIC designs have already been developed so far, most of which with only one threshold yet, for the detection of X-rays using hybrid pixels (Tab. 6).

X-ray cameras consisting in an assembly of one or several modules of pixelized sensors bump bonded with hybrid pixel detector circuits have been built (see e.g. Fig. 11) and are used to pioneer spectral X-ray imaging.
3.3.2 Spectral X-ray imaging

In X-ray CT, the amount of X-ray absorption that induces a useful contrast for imaging depends on the energy of X-rays and the density and atomic composition of the matter they penetrate. In the past, several authors have pointed out the benefits of X-ray spectral information in computed tomography (see e.g. [Alvarez and Macovsky 1976], [Riederer and Mistretta 1977], [Tapiovaara and Wagner 1985]). Energy resolving detectors, with two or more energy bins, permit material decomposition thanks to the dependency of the attenuation coefficient on the X-ray energy, which is specific of each element. The increase of contrast-to-noise ratio for a given material can be maximized by choosing the optimal energy bins and/or by performing a proper image weighting, either at the projection [Shikhaliev 2008] or at the reconstruction image level [Schmidt 2009]. Moreover, when the energy of X-rays reaches the K-shell binding energy of atoms that compose the traversed matter, photoelectric absorption probability of X-rays increases sharply. This phenomenon is referred to as the K-edge. It is then possible to get to the atomic composition of matter by analysing these sudden absorption changes with energy. Subtractive analysis of X-ray absorption above and below the K-edge values of selected contrast agents such as yttrium (17 keV), silver (25.5 keV), iodine (33 keV), gadolinium (50 keV) or gold (80 keV) permits to identify these contrast agents in a CT image.

<table>
<thead>
<tr>
<th>Table 6 Technical specification of some hybrid pixel detector circuits.</th>
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<tr>
<td>Number of pixels</td>
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<td>-------------------</td>
</tr>
<tr>
<td>Pilatus II</td>
</tr>
<tr>
<td>[Broennimann et al 2009], [Henrich et al 2009]</td>
</tr>
<tr>
<td>Eiger</td>
</tr>
<tr>
<td>[Dinapoli et al 2011], [Radicci et al 2012]</td>
</tr>
<tr>
<td>Medipix2 (256 × 256)</td>
</tr>
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<td>[Llopart et al 2002]</td>
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<tr>
<td>Medipix3 (SPM)</td>
</tr>
<tr>
<td>XPAD3</td>
</tr>
<tr>
<td>[Delpierre et al 2007], [Pangaud et al 2007], [Pangaud et al 2008]</td>
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<td>PIXIRAD</td>
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pixel threshold around the K-shell binding energy $E_K$ of the selected contrast agent. In case of detector pixels with only one energy threshold, images are acquired with three different thresholds: $E_1 = (E_K - DE_1)$, $E_2 = E_K$ and $E_3 = (E_K + DE_3)$ with $DE_1$ and $DE_3$ equivalent to a few keV. Thanks to the increase in absorption associated to its K-shell binding energy (Fig. 12), subtraction of images reconstructed within energy windows ($E_2 - E_3$) and ($E_1 - E_2$) permits to discriminate the selected contrast agent. If more than two materials have to be quantified, more energy bins must be taken into consideration [Riederer and Mistretta 1977], [Roessl and Proksa 2007], [Schlomka et al 2008].

K-edge imaging has been demonstrated using small size (typically built using a single chip or a pair of chips) hybrid pixel detectors [Butler et al 2008], [Firshing et al 2009], [Tlustos 2010], [Anderson et al 2010], [Ronaldson et al 2011], as well as with the larger size XPAD3 camera (Fig. 11) that permits to scan a mouse without detector translation [Cassol Brunner et al 2012]. As an example, Figure 13 shows the result of iodine and silver K-edge imaging of a phantom made of three twisted rubber pipes filled with silver, copper and iodine solutions.

**Figure 11.** Picture of the XPAD3 camera composed of XPAD3-S ASIC bump bonded to 500 µm thick silicon sensors to form horizontal modules. 8 modules of 7 chips are tiled vertically to form a detector of 11 × 8 cm² composed of more than 500,000 pixels of 130 × 130 µm².

**Figure 12.** Principle of K-edge imaging of iodine ($E_K = 33$ keV).

**Figure 13.** Transverse slice (a) and 3D volume rendering (b) of a phantom made of three twisted rubber pipes filled with Ag, Cu and I solutions. Data presented in (a) and (b) are acquired with a threshold of 25.5 keV and reconstructed using the FDK algorithm. 3D volume rendering of data obtained after subtractive analysis of X-ray absorption above and below the K-edge values of Ag (25.5 KeV) and I (33 keV) are shown in (c) and (d), respectively [Cassol Brunner et al 2012].

**Figure 14.** Presents maximum intensity projections (MIP) of standard absorption CT and K-edge scans of a mouse injected with 200 µL Iomeron®. We used a 50 kV, 600 µA X-ray spectrum generated by a molybden anode tube filtered by 100 µm copper. 360 projections of 5 s were reconstructed with the FDK algorithm. K-edge imaging of the mouse suppresses bone structures that do not uptake iodine, while it reveals clearly the mouse...
3.3.3 Prospects

In a photon counting camera, every pixel can select X-ray photons above an energy threshold, or within energy windows when pixels have several thresholds, and count every photon individually without adding dark noise. Indeed, this feature cannot be achieved using conventional “charge integration” CMOS detectors, because it necessitates to settling quite a large amount of functions in a small surface that has to be smaller or equal to the pixel sensor surface. This makes a hybrid pixel detector ASIC quite a complex integrated circuit with several millions of transistor elements. Despite this difficulty, the technology of hybrid pixel detectors with silicon sensors is now rather well mastered and their performance correctly understood and modelled [Cassol Brunner et al. 2009], [Ponchut 2008], [Cassol Brunner et al. 2011], [Marchal and Medjoubi 2012], which makes it possible to develop spectral CT for various applications.

As an example of a prospective application of spectral CT, let us consider glioblastoma that are aggressive brain tumours with currently no treatments. Vascularisation and inflammation are two possible therapeutic targets whose relative contributions to tumour growth have to be characterized dynamically in vivo. Being able to image longitudinally both the tumour vascularisation and the inflammation would represent an invaluable tool to assess their effects on tumour growth. Markers of tumour vascularisation and inflammation can be labelled with gadolinium and iodine contrast agents used for magnetic resonance imaging (MRI) and CT, or gold nano-particles, which all have K-edges within the energy range of soft X-rays ($E_K = 33, 50$ and $80$ keV for iodine, gadolinium and gold, respectively). K-edge imaging of gadolinium, gold and iodine is thus possible by processing subtractive analysis of X-ray absorption above and below their K-edges using X-ray photon counting detectors to select detected X-rays by their energies. As another example, it has been demonstrated that imaging of gold nano-particles can be used to study arterial inflammation and bring information on the composition of atherosclerotic plaque [Cormode et al. 2010], [Roessl et al. 2011]. Nevertheless, X-ray absorption efficiency above $35$ keV in silicon is only of a few percents, whereas more than $80\%$ X-rays interact in cadmium telluride above this energy. Thus the development CdTe or GaAs hybrid pixel cameras is of uppermost importance to address K-edge imaging above iodine K-edge ($E_K = 33$ keV). At present, the

Figure 14. (top) MIP of standard absorption CT images. (bottom) MIP of K-edge images.
relatively small diameters of CdTe or GaAs wafers do not permit to hybridize large modules [Basolo et al 2008], [Steadman et al 2010], [Steadman et al 2011], [Koenig et al 2012], [Tlutos et al 2011], [Hamann et al 2013]. Furthermore, CdTe wafers are quite brittle and can barely sustain mechanical stress, e.g. due to different dilatation coefficients of the CdTe sensor and the Si integrated circuit. However, given the energy range that is targeted by this new technology, the methodology developed on preclinical models, even using small size detectors, would be easily if not directly transferable to human clinics [Herrmann et al 2010], [Barber et al 2011].

3.3.4 Conclusion

The advent of X-ray spectral CT as a novel intrinsic hybrid imaging modality able to superimpose anatomy and function will hopefully open a new door in molecular imaging. Potentially, photon counting will impact positively “black and white” or grey-scale CT accuracy by improving image contrast and signal-to-noise ratio [Shikhaliev and Fritz 2011]. Indeed, with “charge integration” X-ray cameras, the higher is the energy of the detected X-ray, the more it will contribute to the formation of the detected signal, whereas with photon counting cameras, every detected photon contributes evenly to the Poisson statistics of the photon count. Hence, image contrast, which results predominantly from the detection of soft X-rays, tends to be better with photon counting CT than with “charge integration” CT [Ouamara et al 2012]. Furthermore, the rejection of low energy X-rays by photon counting detectors suppresses X-rays that are scattered with large angles and thus also tends to improve image signal-to-noise ratio.

More importantly, it is the ability of photon counting detectors to get spectral information on the detected X-rays that will bring a paradigm shift from “black and white” to “colour” CT. This will permit to identify and/or discriminate multiple contrast agents simultaneously, some of which being nanoparticles labelled with metallic elements identified from by their K-edge signature, and locate those within the anatomic grey-scale CT image, thus providing as many different functional information in vivo [Jorgensen et al 2011].
4 Interfaces

4.1 Quality control in hadrontherapy

Tumour treatment by means of charged hadrons (i.e. protons or light ions) offers great therapeutic potential in terms of improved conformation of the dose to the tumour in combination with dose reduction to normal tissue due to the favourable physical and biological properties of the impinging ions. Primary particles are completely stopped in the irradiated tissue and deliver most of their energy at the end of their path. Thus, a steep distal dose gradient can be achieved and organs at risk distal to the tumour can be spared. However, in order to fully profit from the advantages of ion beams a monitoring of the dose delivery is required. Since the range of the particles and, thus, the spatial position of the maximum dose delivery is very sensitive to modifications in the irradiated tissue, already minor changes in the tissue density as well as inaccuracies in patient positioning can lead to substantial deviations in dose distribution.

Several methods of medical imaging in ion beam therapy are under investigation in order to measure the range of the particles in the tissue or even directly measure the applied dose in vivo. Positron emission tomography (PET) is currently the only clinically investigated method for in vivo range verification during or shortly after irradiation, and its potential benefit for ion tumour therapy has been proven [Enghardt 2004, Nishio 2010, Parodi 2008, Bauer 2013]. Further treatment verification methods based on the detection of secondary nuclear reaction products are prompt gamma imaging and charged particle imaging, which are currently under investigation. Another promising imaging tool in particle therapy is ion radiography and tomography, which is intended to be primarily used for position verification and treatment planning, but also can serve as a range verification method [Schulte 2004]. In the following, all of these imaging techniques are presented. They require deep knowledge on nuclear processes as well as substantial abilities in detector design. Apart from challenging reconstruction tasks, the development of such imaging techniques also requires the simulation of the expected distributions. Therefore, extensive modelling of nuclear and electromagnetic interactions is necessary.

4.1.1 Positron Emission Tomography in Particle Therapy

Particles impinging on tissue induce among others positron emitters due to nuclear reactions with the atoms of the irradiated tissue. These positron emitters undergo radioactive decay according to their respective half-life, and positrons are released. These positrons annihilate with electrons of the tissue under emission of two annihilation photons with an energy of 511 keV each and an emission angle of approximately 180° (Fig. 15). By means of a PET scanner these annihilation photons can be detected in coincidence. Reconstruction of the measured events results in a 3D $\beta^+$-activity distribution.
The measured activity distribution cannot be compared directly to the applied dose distribution, since $\beta^+$-activity and dose origin from completely different physical processes. Thus, a simulation of the expected $\beta^+$-activity distribution has to be performed on the basis of the treatment plan, under consideration of the time course of the irradiation and imaging. This calculated $\beta^+$-activity can be then compared with the measured distribution. The simulation has to model all physical processes from the electromagnetic slowing down and the nuclear interactions of the impinging ions and further secondary particles with the atoms of the tissue, the induction of positron emitters, the $\beta^+$-disintegration and formation of positrons, the thermalization of positrons and annihilation with electrons, the transport and attenuation of the annihilation photons in the tissue until detection. All these processes require extensive knowledge of electromagnetic and nuclear processes, as for example double differential reaction cross sections.

For PET imaging three implementations are investigated, which are described in detail in Shakirin 2011. The first one is in-beam PET, which allows the measurement of $\beta^+$-activity during irradiation and requires a dedicated PET scanner integrated into the treatment site. The first in-beam PET scanner in clinical use was operated from 1997 to 2008 at GSI, Darmstadt, Germany [Enghardt 1999, 2004]. Another PET scanner directly integrated into the treatment gantry is located at NCCHE, Kashiwa, Japan [Nishio 2010], and is meanwhile commercially available. Furthermore, small prototypes of in-beam PET scanners for research purposes are installed, e.g., at HIMAC, Chiba, Japan [Iseki 2004, Tashima et al 2012] and at CATANA, Catania, Italy [Attanasi 2010]. The second modality is in-room PET. Here the PET scanner is located in the treatment room and imaging of the $\beta^+$-distribution takes place shortly after irradiation. An in-room PET scanner is investigated at MGH, Boston, USA [Zhu 2011, Min 2013]. The third modality is off-line PET where no dedicated PET scanner is required but conventional diagnostic devices, typically combined with CT scanners, can be used. After treatment the patient is transported to a PET system and the measurement of $\beta^+$-activity starts with time delays of several minutes, depending on the location of the scanner. This offline implementation is in clinical use e.g. at HIT, Heidelberg, Germany [Bauer 2013], and HIBMC, Tatsuno, Japan [Abe 2007].

Figure 15. Principle of PET imaging in particle therapy for a $^{12}$C ion (projectile) colliding with an $^{16}$O atom of the irradiated tissue. Both nuclei may e.g. lose a neutron, resulting in the positron emitters $^{11}$C and $^{15}$O, respectively. They disintegrate under emission of a positron $e^+$, which annihilates with an electron $e^-$ of the tissue. Annihilation photons with an energy of 511 keV each are emitted.
Although being already implemented in clinics, Positron Emission Tomography in particle therapy requires more technological and methodological developments. A major issue in future detector developments and a research field of several groups is the use of ultra-fast time of flight (TOF) information for PET monitoring in order to improve image quality (Crespo 2007). Further investigations are dealing with improvements on the knowledge of reaction cross sections [e.g., Bauer 2013b], feasibility of PET for moving targets [Stützer 2013], application of PET for various other ions interesting for therapy [Priegnitz 2012], automatic evaluation of PET measurements [Unholtz et al 2011, Helmbrrecht 2012, Kuess 2012] as well as application of PET in unconventional high energy photon therapy [Kunath 2009].

4.1.2 Prompt Gamma Ray Imaging

During tumour irradiation with particles a large variety of prompt gamma emission occurs. These prompt gamma arise from nuclear de-excitation in an energy range of a few MeV. However, besides prompt gamma rays from the excited nuclei also a substantial amount of background arises from other secondary particles, e.g. neutrons, light charged fragments as well as Compton scattered photons (Fig. 16). Thus, several imaging modalities are being investigated to shield the background and selectively acquire information from prompt gamma emission [Dauvergne 2009].

A first approach is a collimated gamma camera, i.e. a collimator with a hole [Min 2006] or a slit [Bom 2012, Smeets 2012] in front of a position sensitive detector. A more advanced system thereof is a multi slit camera [Roellinghoff 2012] with a collimator with multiple slits in front of the detector. For those kinds of imaging systems 3D information requires the synchronization with an upstream beam positioning device such as an hodoscope. Another possibility of prompt gamma ray imaging entirely independent from the treatment device is a Compton camera which uses two or more energy and position sensitive detectors [Kormoll 2011, Lang 2012] and, thus, no mechanical collimator is necessary.

![Figure 16 Principle of prompt gamma imaging using the example of a projectile ion colliding with an $^{16}$O atom of the irradiated tissue. The target nucleus is excited and de-excites under emission of prompt gamma radiation.](image)

Improving detection efficiency and background rejection by means of a TOF gamma is also under investigation [Testa 2009]. It is supposed that discrimination between photons and hadrons becomes possible by using the time of flight information, although the time microstructure of the beam can be critical in this respect [Biegun 2012].

4.1.3 Charged particle imaging

During irradiation with primary ions heavier than protons lighter projectile fragments are produced in collisions of the incident ions with nuclei of the irradiated tissue (Fig. 17). Some
of these light fragments have enough energy to leave the patient and can be easily detected. A reconstruction of the trajectory of the emerging charged particles and the intersection with the impinging ion path gives the point of ion-nucleus interaction. By means of a comparison between simulated and measured vertices distributions the range of impinging ions can be verified. For this method, also known as interaction vertex imaging [Dauvergne 2009, Amaldi 2010], a feasibility simulation study has been reported [Henriquet 2012] and first promising measurements on homogeneous targets have been recently performed [Agodi 2012, Gwosch 2013].

4.1.4 Ion radiography and tomography

Ion radiography enables the direct measurement of the residual range of high-energy low-intensity ions traversing the patient [Schulte 2004]. It may replace X-ray radiography to produce low dose, high density resolution images of the patient at the treatment place. In terms of pre-treatment verification, the method can be also used to validate in-vivo the treatment planning range calibration curve deduced from the X-ray CT, which currently introduces the larger source of range uncertainties due to different physical processes of ion and photon interaction [Schneider 2005]. Tomographic extension of radiographic imaging can enable volumetric images providing a direct measurement of the ion stopping power ratio relative to water. Due to the weak energy dependence of the stopping power ratio, these images obtained at higher energies than for therapy can be used as patient model in treatment planning, again eliminating the range uncertainties connected to the usage of calibrated X-ray CT images. Spatial resolution of the method is limited by multiple Coulomb scattering in the patient, which is more pronounced for protons than for heavier ions. However, 1 mm is anticipated to be reachable, even for the more scattering protons [Schulte 2004]. New prototypes are currently under development both for protons [e.g., Sadrozinski 2013] and carbon ion beams [e.g., Rinaldi 2013].

![Figure 17. Principle of interaction vertex imaging shown for the collision of a $^{12}$C ion with a target nucleus. The projectile ion loses a proton which leaves the irradiated tissue and is used for imaging.](image)
4.2 Mass spectrometry

Mass spectrometry is a technique, which was developed more than hundred years ago and lead to many discoveries, which laid many foundations of what is now called nuclear and particle physics. At that time it was a key technology to explore atomic and subatomic particles, and exactly 100 years ago the discovery of isotopes was made: the chemical elements have constituents of different mass number. Since that time the building blocks of matter were discovered and analysed in great detail, and mass spectrometry found its application as an analytical tool in many directions of science, not only in physics but also chemistry, biology, geology, space science and many other fields. Besides these natural sciences, where the analytical aspects dominate, there are a lot of applications where mass spectrometry fulfills qualitative and quantitative purposes. These are e.g. environment, health, nutrition, security, explosives etc. Here, we concentrate on health and medicine, with some emphasis on “in-situ” applications.

4.2.1 Basic concept

Mass spectrometry separates and analyses the chemical composition of a substance according to its’ mass-to-charge (m/e) ratio. Two methods by which this may be achieved include time separation and geometric separation based approaches. The three principal elements of a mass spectrometer are depicted in figure 18: ion source (where the sample is transformed from its original form to ionized atoms, molecules or clusters), analyzer (in this case a dipole magnet, which spatially disperses the ions according to their mass) and detectors (including data acquisition, storage, graphical display and quantitative analysis systems). There are many other forms of mass spectrometers including, for example: quadrupole, ion trap, time-of-flight (TOF) and tandem based techniques (MS/MS).

Figure 18. Left: schematic view of a magnetic mass spectrometer and the components characteristic for every mass spectrometer: ion source, mass analyzer (here: magnetic dipole) and detectors to analyze the spatially separated components according to their mass. Right: a typical mass spectrum of residual air in a vacuum vessel, including components outgassing from the walls, like water.

The performance of a mass spectrometer is characterized by several parameters, the most characteristic ones are mass range (the range from the lightest to the heaviest mass which can be analyzed, typically this ranges from 1 [for hydrogen, which is the lightest chemical element] to a few 10,000 [which is typical for fragments of complex biomolecules]), mass resolving power (the ability to distinguish adjacent masses, this number should be high and typically ranges from ~1,000 to 10,000,000), resolution (the smallest gap of adjacent masses which can be separated from each other, this number should be small and ranges down to 1E-7) and the accuracy (which is the ability to measure the true value of a certain species). Besides these, other properties like the sensitivity of an instrument (the ability to investigate small amounts of sample material) or scanning or non-scanning operation (the former samples the mass range stepwise, while the latter covers the whole range overall) determine the potential for certain applications. Most specific however is the sample preparation, ionization and inlet techniques. Here, an almost infinite variety of
concepts and techniques exist, tailored for the specific physical and chemical properties of the sample and the purpose of the analysis. The goal of all these techniques is to destruct the sample by the impact of photons (e.g. laser light) or energetic particles (e.g. swift ions) such that it releases microscopic fragments from its surface (atoms, ions and molecules), which can be analysed by the mass spectrometer. For biological substances are often processed at ambient air pressure, while the mass spectrometer itself operates in a vacuum vessel; they are connected by an atmospheric pressure interface and the sample fragments are introduced by various transport mechanisms, which are simultaneously used to improve the selectivity towards the material of interest, but also to remove the necessity for pre-concentration of samples before analysis.

4.2.2 Present techniques for bio-chemical and medical applications

The growing number of applications and the analytical potential of mass spectrometry has stimulated the development of many different techniques including miniaturized and portable apparatus for field deployment and use in many daily circumstances. It is the goal of this section to introduce the reader to modern sample preparation and mass spectrometric techniques, which are presently used for tissue imaging, medical analyses and applications in safety, nutrition and environment.

Sample preparation and ion formation

Two widely used ambient ionization methods for mass spectrometry are desorption electrospray ionization (DESI) and paper spray (PS). DESI, illustrated in figure 19, is an ambient ionization method that can be performed on untreated histological sections of biological tissue to image lipids, fatty acids, hormones and other compounds. PS is used for biofluid analysis and involves electrospraying dry blood spots or biofluid deposits from a porous medium. It is characterized by extreme simplicity and speed: a spot of whole blood or other biofluid is analyzed directly from paper, simply by applying a high voltage to the moist paper.

![Figure 19. Illustration of desorption electrospray ionization (DESI), a widely used method to evaporate and ionize samples for tissue imaging applications.](image)

Many other methods exist, which cannot be described here. They all have specific strengths and characteristic applicability to individual problems, depending on the sample, environment and purpose. Common to all is the generation of charged sample fragments, which can be analyzed by the mass analyzer.

Ion mobility mass spectrometry

Ion mobility spectrometry (IMS) is one of the most widely used detection techniques in routine use due to its ability to characterize the sample both qualitatively and quantitatively as well as the very low detection limits that are often attainable. IMS characterizes a sample through the mobility of ions within the gas-phase of the instrument whilst an electric field is applied (see figure 20). The sample vapors are ionized at atmospheric pressure before introduction into the drift tube. The drift times are related to the dimension (collision cross section), and the additional mass information allows to identify the components and composition of large biomolecules.
**Imaging mass spectrometry**

Mass spectrometry imaging, where high spatial resolution of the sample is combined with mass spectrometric analysis of the sample material, is a versatile method to analyze the spatial distribution of analytes in tissue sections. It provides unique features for the analysis of drug compounds in pharmacokinetic studies such as label-free detection and differentiation of compounds and metabolites.

In the following figure 21 the spatial distribution of the anti-cancer drugs imatinib and ifosfamide in individual mouse organs is shown. For instance, the whole kidney of an animal dosed can be measured with typically 10...30 μm spatial resolution and mass resolving power of typical 30,000, thus giving highly specific information. Such methods represent a major improvement in terms of spatial resolution and specificity for the analysis of drug compounds in tissue sections and support tailored drug development and analyze the effect in organs.

![Figure 21](image-url) Top: optical image of the investigated mouse kidney section; H&E stained after mass spectrometry imaging measurement. Bottom: single-pixel FTMS spectrum of the outer stripe outer medulla of the mouse kidney section.

### 4.2.3 Applications

Mass spectrometers and related techniques are presently used mainly in the laboratory by specialists in natural or technical sciences. However, the fact that basically every organic or inorganic material can be “dissolved” to microscopic material fragments and ionized, an infinite wide range of applications emerges.

**Analysis of blood and body fluids**

This is a wide field with manifold applications from trace detection in urine (e.g. drug abuse),
to measure large proteins (>1E4 Da), to therapeutic drug monitoring and dried blood analysis. Since the measurements are done in biological matrices, they require sensitive, high resolving mass spectrometer with high dynamic range to be able to handle the complex mass spectra. A high throughput is mandatory for clinical studies of drugs, because in many cases large amount of samples from many patients (hundreds to thousands) need to be analyzed to have sufficient statistics for significant results.

**Tissue recognition**
Very appealing is the potential of mass spectrometry for histology. Histological analysis take several hours, for intra-operative case there exist faster (~30 minutes) but less reliable techniques. Here, fast and precise identification by means of mass spectrometry can be a solution. The tissue sample needs to be ionized and brought into the mass spectrometer for mass analysis. In case of surgery with an electro-scalpel this can be done by attaching a tube to the electro-scalpel, which can suck in the tissue vapour to the inlet of a mass spectrometer, where it is ionized by rapid evaporation. With this method, first measurements to identify cancerous tissue in-situ and in-vivo, i.e. during patient surgery, have shown spectacular results. With this method automated fast (<1 second) recognition of different body tissues becomes possible, with a reliability that is even higher than for histological methods.

The obtained mass spectra of the tissue exhibit different lipid profiles, which are analyzed by a principal component analysis. This is used to distinguish diseased and healthy tissue types “in-situ”, i.e. during the ongoing surgery. This new development suggests a potential role in guiding therapy in parallel with standard histochemical and immuno-histological methods.

**Wastewater monitoring**
The contamination of pharmaceuticals and personal care products (PPCP) in environment waters are becoming more and more concerning. They are a threat to wildlife and humans. To monitor and ensure good wastewater quality a fast and reliable detection method is needed. Such a method has been currently developed and is based on thin film microextraction and desorption electrospray ionization mass spectrometry. This method allows fast measurements without much need for sample preparation. The analysis method is faster and has higher throughput than conventional liquid chromatography mass spectrometry methods. It is not only able to qualify PPCP, but also quantified them with an accuracy comparable to "standard" methods (solid-phase extraction coupled to liquid chromatographic tandem mass spectrometry). The method relies on high resolving mass spectrometers and therefore was tested so far with a stationary high performance mass spectrometer. When combined with a mobile, high throughput and high resolving mass spectrometer, this method is readily applicable to ensure water quality at "hot-spots", e.g. wastewater plants.

**Biodefence and homeland security**
The possibility of deployment of biological weapons by terrorists is an existing threat and effective detection and countermeasures are necessary. Mass spectrometry can help in detection, remediation, forensics and developments of new drugs and vaccines. Modern mass spectrometry based proteomics can rapidly and sensitively identify peptides and proteins and thus detect lowest levels of biological weapons in complex mixtures.

**In-situ analysis of contaminants in food**
A main source for the intake of environmental toxins is contaminated food. The kind of contaminations can be numerous, e.g. pesticides, natural toxins, veterinary drugs, food additives, adulterations or food-packaging migrants. To identify and qualify the contaminations fast, sensitive methods that do not require sample preparation are needed. Here, mobile mass spectrometers with ambient pressure ionization capability are the ideal tool. The major obstacle with currently existing mass spectrometers is the low mass resolving power and consequently the high risk of false-positive and false-negative findings.
Figure 22. Top left: principle of an electro-scalpel in combination with an Venturi-pump inlet system for mass spectrometric analysis of vaporized tissue. Bottom left: the device in operation during surgery. Right: mass spectra of cancerous (top) and healthy (bottom) tissue show different characteristic patterns.
4.3 Nuclear Medical Imaging using $\beta^+\gamma$ Coincidences: $\gamma$-PET

So far a whole class of potential PET isotopes, where in addition to the two back-to-back emitted 511 keV $\beta^+$ annihilation photons a third, higher-energy $\gamma$ ray will be emitted from an excited state in the daughter nucleus, has been excluded from medical application. The resulting extra dose delivered to the patient, as well as the expected increase of background from Compton scattering or even pair creation, prevented the use of isotopes such as $^{44}$mSc, $^{86}$Y, $^{94}$Tc, $^{94m}$Tc, $^{152}$Tb, or $^{34}$mCl. However, provided the availability of customized gamma cameras, this alleged disadvantage could be turned into a promising benefit, offering a higher sensitivity for the reconstruction of the radioactivity distribution in PET examinations. Presently two approaches are pursued towards the realization of a medical imaging system based on $\beta^+\gamma$ coincidences. Both of them draw on the imaging properties of a Compton camera, where the registration of the Compton scatter and absorption kinematics of an incident photon in a suitable detection system (i.e. inelastic scattering of a photon with a (quasi-free) electron) is exploited to reconstruct the source position, within one event restricted to the surface of a cone (see Fig. 23 and 24). Determining the intersection of this Compton cone with the line-of-response (LOR) as defined by the positron annihilation allows for a sensitive reconstruction of the decay position of the PET isotope.

In 2004, a project was started in France, aiming at realizing $\gamma\gamma$ imaging by combining a PET scanner with a Compton camera based on a cryogenic Time Projection Chamber (TPC) filled with liquid xenon (LXe), acting simultaneously as scatter, absorption and scintillation medium for the additional 3rd photon [Grignon et al, 2007]. A small LXe-TPC prototype already reached promising results [Oger et al, 2012].

Figure 23. Schematic drawing of the $\gamma\gamma$ imaging principle based on the detection of a line-of-response (LOR) from two positron annihilation photons and a prompt third photon emitted from the excited PET isotope daughter nucleus. In this approach the additional photon is detected in a Compton camera formed by a cryogenic time-projection chamber filled with liquid xenon. (from [Oger et al, 2012])

A second, more conventional, experimental approach pursued in several European laboratories utilizes solid-state detectors to set up the Compton camera system [Donnard et al, 2012, Kormoll et al 2011, Roellinghoff et al 2011]. Here, double-sided Silicon strip detectors serve as Compton scattering unit, while scintillation crystals (either from well-established materials like BGO or LSO, or from novel scintillators like LaBr$_3$, see Fig. 24) act as photon energy absorber. Such modules could be combined with a ring of PET detectors (similar to the concept illustrated in Fig. 23), alternatively a set of several Compton camera modules (as shown in Fig. 24) could be arranged to detect either the $\beta^+$ annihilation photons or the additional $\gamma$ photon in coincidence.

The concept of $\gamma\gamma$ coincidence imaging ($\gamma$-PET) may open up the perspective to exploit a whole class of new PET isotopes, offering a highly sensitive and highly resolving...
localization of the photon source position. The high sensitivity of $\gamma$-PET can be illustrated by the setup shown in Fig. 24, where already a few ten reconstructed intersections between the LOR and the direction towards the 3rd photon are sufficient to localize the activity contained in a voxel size of 2x2x2 mm$^3$ [Lang et al, 2013]. In order to achieve the same with a conventional PET-based analysis, a few thousand LOR’s would be needed to be reconstructed. Outside Europe, also in the US the topic of ‘unconventional’ PET isotopes is studied [Gonzales et al 2011, Chinn et al 2011], however, so far no dedicated project to develop a ‘$\gamma$-PET’ detection system has been reported.

![Diagram](image)

**Figure 24.** Arrangement of 3 Compton camera modules to define the LOR from $\beta^+$ annihilation in coincidence with the detection of the 3rd photon. Each module consists of a double-sided silicon strip detector (DSSSD) a scatterer and a LaBr$_3$ scintillator as absorber.
Medical imaging in general and nuclear medicine in particular, for which detection of radiation emitted by the atomic nucleus is involved, has experienced and continues to exhibit evolution at exponential speeds. In the past, this evolution has largely benefited from technologies developed and tested in the experimental nuclear physics battleground and it seems that will do so even more in the future. The maturity of the nuclear imaging sector can be seen in the fact that, while in the past most nuclear detector technologies employed in the medical field, such as PMT and scintillators, were borrowed from the experimental nuclear physics knowledge base, nowadays new technologies are being pursued by the demanding medical industry, where the rate of technological evolution has never been so fast and new techniques are translated into biomedical research and clinical use within the year.

Nuclear physics groups were always aware that their work in radiation detector, simulations, electronics, and data processing, may find application in nuclear medicine. But today we realize that our activities in these two fields are not only complementary and synergetic, but that their pace of development is very different. Nuclear physics experiments may take several years to design, raise funding, setup, run and analyze data. In the nuclear imaging arena, though, trends and technologies are being introduced, tested and dismissed at high speeds. One can assess this by attending the leading conferences in the nuclear imaging instrumentation sector, such as the IEEE Medical Imaging Conference, celebrated on a yearly basis, and witnessing how the trends of previous year have been given up an new ones are on the spot.

The urge to evolve nuclear imaging detectors is dynamizing the activity of nuclear physics groups, while on the other hand, mid-term stability in the scientific goals needed to face multi-national nuclear physics experiments makes it possible to train and shape the best technicians, doctors, researchers and in general experts in technology for nuclear detection. There are many examples of researchers trained in nuclear physics groups doing basic research that have later pursued successful careers in the medical imaging industry.

This chapter provided a glimpse on how nuclear physics research has been involved in the medical imaging advance and, more interestingly, how our current efforts are paving the way for the imaging technologies of tomorrow. Spectral CT, PET/MRI scanners, devices for quality control of hadrontherapy, to name a few, will be commonplace in the most up to date clinical practice in a few years. We feel more than ever that it is our duty to help and promote the translation of developments from our nuclear physics labs and basic nuclear science experiments into practical tools for the clinical and preclinical environments. This chapter reflects the fact that inside the nuclear physics community, research and development activities in medical imaging detector development coexist, at times even in the same group, with the preparation of nuclear physics experiments. This makes it possible that, even when from the outside basic nuclear physics efforts look far from real world application, actually it will continue to provide the best ground field to test new technologies in detector, electronics and processing and to help obtaining critical mass to interface with the medical imaging industry.
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Three gammas section


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