IMAGE REGISTRATION USING COMPUTER TECHNIQUES: APPLICATIONS ON NUCLEAR MEDICINE IMAGES

Raquel da Silva Alves

July, 2013
IMAGE REGISTRATION USING COMPUTER TECHNIQUES: IMAGE REGISTRATION USING COMPUTER TECHNIQUES: APPLICATIONS ON NUCLEAR MEDICINE IMAGES

Monograph submitted in fulfillment of the requirements of “Monographs” Course of the Master degree in Biomedical Engineering

Raquel da Silva Alves

Degree in Biomedical Engineering from the University of Trás-os-Montes and Alto Douro (2012)

Monograph prepared under the supervision of:

Professor João Manuel R. S. Tavares (supervisor)

Department of Mechanical Engineering
Faculdade de Engenharia da Universidade do Porto, Portugal

Professor Durval Campos Costa (co-supervisor)

Champalimaud Foundation, Portugal
HPP-Molecular Medicine, SA, Portugal
ABSTRACT

This essay comes in the fulfillment of “Monograph” course of the Master degree in Biomedical Engineering, from the University of Porto and its main purpose is to make a dissertation draft framework which will be held in the second academic year.

This work has as objective the identification and study of the main image alignment methods used in medical images, namely from nuclear imaging modalities. The respective computational algorithms are used as an aid to diagnosis, planning treatment and surgery such as monitoring multiple cardiac, neurologic and oncologic diseases through an automatic or semiautomatic detection and quantification, becoming the medical procedures more efficient task, once it is an important factor in the patients' life.

In summary, the work outlined in this monograph reviews the literature and study of image registration using computational techniques applied to nuclear medicine imaging.
CONTENT

1. INTRODUCTION ........................................................................................................... 1
   1.1. Introduction .................................................................................................................. 2

2. MEDICAL IMAGE REGISTRATION ............................................................................. 5
   2.1. Introduction .................................................................................................................. 6
   2.2. Registration Methods Overview .................................................................................. 7
   2.3. Registration Methods: Classification .......................................................................... 8
   2.4. Algorithms based on rigid transformations ............................................................... 11
      2.4.1. Landmark-based registration ................................................................................ 11
      2.4.2. Surface matching .................................................................................................. 11
      2.4.3. Voxel-based intensities ....................................................................................... 12
   2.5. Algorithms based on non-rigid transformations ....................................................... 12
   2.6. Optimization ............................................................................................................... 15
      2.6.1. Correlation Coefficient and Sum of Squared Intensities Differences ................. 15
      2.6.2. Information theoretic techniques ......................................................................... 16
   2.7. Interpolation ............................................................................................................... 17
   2.8. Accuracy Assessment and Validation ...................................................................... 17
   2.9. Display of registered data ......................................................................................... 19
   2.10. Clinical applications ............................................................................................... 19
      2.10.1. Radiation therapy planning ................................................................................. 20
      2.10.2. Brain .................................................................................................................. 21
      2.10.3. Cardiac applications ......................................................................................... 22
      2.10.4. Breast ............................................................................................................... 23
      2.10.5. Chest .................................................................................................................. 23
      2.10.6. Liver and Kidney ............................................................................................... 24
      2.10.7. Colon .................................................................................................................. 24
      2.10.8. Other applications ............................................................................................ 24
   2.11. Conclusions ............................................................................................................ 25

3. NUCLEAR MEDICAL IMAGING .................................................................................. 27
   3.1. Introduction ............................................................................................................... 28
   3.2. Positron Emission Tomography ................................................................................. 28
      3.2.1. Radiotracers ........................................................................................................ 29
      3.2.2. Detectors .............................................................................................................. 30
      3.2.3. Data Acquisition Modes .................................................................................... 31
      3.2.4. Image Reconstruction Algorithms ....................................................................... 33
      3.2.5. Image correction .................................................................................................. 35
      3.2.6. Noise-Equivalent Count Rate (NECR) ............................................................... 37
      3.2.7. Spatial Resolution ............................................................................................... 38
      3.2.8. PET Multimodalities ......................................................................................... 39
3.2.9. Clinical Applications ........................................................................................................ 41

3.3. Single Photon Emission Computed Tomography ................................................................. 43
  3.3.1. Radiotracers .................................................................................................................. 43
  3.3.2. Detectors ...................................................................................................................... 44
  3.3.3. Deterioration factors and corrections ......................................................................... 45
  3.3.4. Image reconstruction algorithms ............................................................................... 47
  3.3.5. Spatial Resolution ...................................................................................................... 48
  3.3.6. SPECT Multimodalities ............................................................................................ 48
  3.3.7. Pre- and Clinical Applications .................................................................................. 50

3.3.4. Conclusions .................................................................................................................. 51

4. FINAL CONCLUSIONS AND FUTURE PERSPECTIVES ..................................................... 53
  4.1. Final considerations ......................................................................................................... 54
  4.2. Futures Perspectives ....................................................................................................... 54

5. REFERENCES ....................................................................................................................... 57
LIST OF FIGURES

Fig. 1. Image registration general scheme (Adapted from Hutton et al., 2002). ..................................................8

Fig. 2. Types of transformations: (a) identity transformation (b) rigid transformation (c) affine transformation (d) and non-rigid transformation (Taken from Hajnal V.N., et al., 2001). .........................13

Fig. 3. Positron decay. A - Rich nuclei in protons emits a positron, B - The positron interacts with the surrounding tissues, losing kinetic energy, C - The positron combines with the electron and the annihilation occurs, D - Result with two 511 keV gamma rays (From Fahey, 2001). ........................................30

Fig. 4. (a) PET Scanner: collision between an electron and a positron and resulting annihilation, creating two gamma rays that move in exactly opposite directions and its detection by the scanner surrounding the patient. (b) Detection of two photon approximately at the same time and considered as coming from the same annihilation: coincidence detection. (From Fahey, H. F., 2001)......................31

Fig. 5. Resultant object and sinogram of a projection view superior to 180º turning the object (From Phelps, M.E., 2006). ..................................................................................................................................................32

Fig. 6. 2D (left) and 3D (right) acquisition. In 2D acquisition, plans crusaders whose LOR intersect with the septa are eliminated (dashed). In 3D mode, until LOR with larger axial angles are accepted (From Fahey, 2001). ..................................................................................................................33

Fig. 7. Reconstructed phantom images by FBP (top row) and OSEM (bottom row) (From Turkington, 2001). .................................................................................................................................................................34

Fig. 8. Blobs distribution represented by spherical elements (From Tarantola et al. 2003). ...............34

Fig. 9. Coincidence events occurred in a PET scanner: true (A), scatter (B) and random events (C) (From Tarantola, G., Zito, F., & Gerundini, P., 2003). ..............................................................36

Fig. 10. Image reconstruction using FBP (on the top row) and iterative algorithms (on the bottom row). Images uncorrected (on the left), transmission images (on the center) and attenuation-corrected images (on the right) (Muehllehner & Karp, 2006).........................................................37

Fig. 13. (a) Scanner PET / CT schematic. (b) Individual and simultaneous PET and CT scan images. (From Wacholtz, E. H.) ...................................................................................................................................................40

Fig 14. 18F-FDG image of a patient with colorectal cancer: CT image (left), fused PET/CT (middle) and PET image (right) (From Pimlott & Sutherland, 2011) .................................................................40

Fig. 15. Different configuration of detectors in gamma camera: single head (a), two orthogonal heads (b), two opposed heads (c), three heads (d), four heads (e) and multiple small-FOV scintillation detectors (From Spanoudaki & Ziegler, 2008). ........................................................................45

Fig. 16. Detection of liver abnormalities using CT (on the left), SPECT (on the middle) and fused SPECT/CT (on the right) (From Jacene, Goetze, Patel, Wahl, & Ziessman, 2008). .................................49
LIST OF TABLES

Table 1. Medical image registration classification criteria proposed by Maintz and Viergever (adapted from Oliveira & Tavares, 2012). ................................................................. 9

Table 2. Application of sum of absolute differences that reflects the lack of similarity: poorly aligned image result in large absolute differences (top row), contrarily to well aligned image which absolute differences are significantly reduced (bottom row) (Alves, R. & Tavares, J. M .R. S., 2013) ............... 16

Table 3. Common PET Isotopes and Properties (Adapted from Wacholtz, E. H., Online). .................... 29

Table 4. Common detector crystals and properties (Fahey, F.H., 2001) ................................................. 31

Table 5. Commonly used single photon emitting radionuclides (Adapted from Khalil et al., 2011). ...... 44
1. INTRODUCTION
2.1. Context

Nowadays, modern medicine has been widely using imaging as a fundamental tool to aid in diagnosis procedures, monitoring the development of disease and planning treatment or even surgeries. This way, it became an element key to take into account in time decision through non-invasive procedures. In the last years, a deep research and development has been increasing lead to a bigger number of information types that can be acquired from such diagnostic tool.

The enhancement of digital medical image acquisition and analysis, such as higher spatial and temporal resolutions, is the hot topic of medical imaging modalities, and it cannot be achieved appropriately without the development or better integration of different registration methods, once they enable the integration of different medical image modalities such as PET (Positron Emission Tomography), SPECT (Single Photon Emission Computed Tomography), CT (Computerized Tomography) and MRI (Magnetic Resonance Imaging) through the detection of differences between images acquired from different points of view, different time acquisition or even different subject atlas, to obtain anatomic and functional information to reflect completely the condition of the patient, providing a more complete information to the diagnosis.

2.2. Organization

This monograph is divided into the following chapters:

- **2. Medical Image Registration**
  In this chapter, medical image registration is presented through a state-of-the-art of medical image registration by the study and description of its methodologies and respective classification, such as the main types of transformations, optimization and interpolator involved in the process, describing vantages and disadvantages.

- **3. Nuclear Medicine Imaging Modalities**
  The third chapter describes nuclear medicine imaging modalities with some specifications of each modalities and current dual-modalities, referring their vantages and problems, such as clinical use.

- **4. Final Considerations and futures perspectives**
  Final considerations and futures perspectives will be referred in this last chapter.

2.3. Contributions

This monograph is an introductory work to the dissertation project, presenting a deep study and bibliographic revision of relevant information in medical image registration. The main contribution is the review of the main medical image registration applications to clinical case studies.
2. MEDICAL IMAGE REGISTRATION
2.1. Introduction

Since medical imaging has been used as a common diagnostic procedure, physicians have recognized the need to correlate information from multiple images, such as from complementary imaging modalities, i.e. imaging multimodality, to build a complete description that can lead to more accurate diagnostics. In this way, due to differences in size, orientation and spatial distortions, image registration is an essential tool to establish an exact point-to-point correspondence between the elements of images; so it can be defined as the process of aligning two or more images taken at different times, from different viewpoints or by different sensors, to correspond features through a simplest way as possible.

Along the last few years, and after its use in X-ray angiography, in image-guided surgery and other interventions the correspondence obtained between images and the physical spaces of the patients during interventions have entered routine clinical in neurosurgery systems and computer-assisted orthopedic surgery. The development of registration algorithms semi- or full-automated for intra- and inter-modality registration, such as registration algorithms based on entropy and mutual information, advances in the power computer technology and in the performance of new registration algorithms and an increasing number of desktop workstations has widely contributed to a higher importance of medical image registration (Hajnal J.V., et al., 2001). Computerized approaches offer a way to accurate alignment between information from different images to provide tools for studying and visualizing the combined images.

Since medical imaging treats the establishment of shape, structure, size, and spatial relationships of anatomical structures within patients, with spatial information about function, and any pathology or other abnormality, medical image registration is fundamental to combine the information from multiple imaging modalities, such as computed tomography and magnetic resonance imaging, to monitor changes in size, shape or image intensity over time intervals, to relate preoperative image and surgical plans (Fox et al., 2005) to the physical reality of patients during intervention and to relate patient’s anatomy to a standardized atlas, which applications usually require the establishment of spatial correspondence (Ganser, Dickhaus, Metzner, & Wirtz, 2004).

Thus, medical image registration has been increasingly used in healthcare diagnosis (Ledesma-Carbayo et al., 2005; Shekhar, Zagrodsky, Garcia, & Thomas, 2004; Stewart, Tsai, & Roysam, 2003; Sun et al., 2005), planning treatments, guiding treatment (Schreibmann, Thorndyke, Li, Wang, & Xing, 2008) through the investigation of disease processes to monitoring disease progression (Irwin, Downey, Gardi, & Fenster, 2008; Niculescu, Nosher, Schneider, & Foran, 2009) and then to understand the normal development and ageing. There have been previous reviews of the medical image registration literature as Maurer and Fitzpatrick (1993), Van den Elsen et al (1993), Maintz and Viergever (1998), Pluim, Maintz, & Viergever (2001), Oliveira & Tavares (2012), Hill, Batchelor, Holden, & Hawkes, (2001), Hutton, Braun, Thurfjell, & Lau (2002), J.P.W. Pluim & Fitzpatrick (2003), Hermosillo, Hotel, Faugeras, & Antipolis (2004) and Zitová & Flusser (2003).

In this chapter, it will be referred registration methodologies from an overview point, the various classifications available in literature, image registration based on rigid
transformation and non-rigid transformation such as the optimizers and interpolators involved, accuracy assessment and validation and their main applications.

2.2. Registration Methods Overview

Image registration establishes spatial correspondence what means to align two or more images through the correspondence of points that represent a measurement localized to the same small element of tissue, from a point on one image to another particular point on the other image, with the goal of find the optimal transformation that best aligns the structures of interest in the input image (E. Lee & Gunzburger, 2009; Shafique & Shah, 2005; Shapiro & Michael Brady, 1992). This means that the minimization of error from the inaccurate measurement that must be known is the objective function (Leclerc, Luong, International, & Park, 2003). Automatic correspondence can be achieved using template-matching technique, the iterative closest points approach, by sensitivity to movement scheme and self-organizing maps algorithms (Economopoulos, Asvestas, & Matsopoulos, 2010; Ericsson & Karlsson, 2007; Xue, Shen, & Davatzikos, 2004). After the attribution of a coordinate system, the images are transformed and the alignment of information is then applied to finale the process. Most algorithms proceed by iteratively adjusting the transformations related to voxel intensity, through the similarity measure maximization, that are chosen depending on the nature of both the image modality and misalignments (Li & Hu, 2010; Liu, 2005); another approach is the cost function minimization. The use of an optimization algorithm is needed to find the most suitable transformation. An interpolator is used to resample the voxel intensity into the new coordinate system. Besides that, the likelihood of convergence must be low, so a faster convergence of the optimizer can be achieved when it is used a pre-registration transformation to become the optimizer initial solution closer to the optimal solution. Fig. 1 presents the general registration methods framework.

Depending on the registration to be a feature-based (McLaughlin et al., 2005), geometrical transformation are established, based on the matching among the features defined using criteria based on geometrical, physical or statistical properties, and the distance between the descriptors of the possible points constitute the corresponding cost, which sum will measure the similarity between the registered images. To define the matching and transformation based on the optimization of a similarity measure between the features extracted from the input images is another approach.

Segmentation is an essential task in the whole process, once it extracts the relevant information from the input images through sets of points, edges, lines, contours, surfaces, areas, volumes, medial axes or descriptors as distances, lengths, angles, moments, shape signatures and complex structures.
2.3. **Registration Methods: Classification**

Different classes of registration problems were firstly defined by Gerlot-Chiron and Bizais into four categories: (1) point methods, (2) edge methods, (3) moment methods and (4) “similarity criterion optimization” methods. Van den Elsen et al. proposed a classification based on techniques according to the number of criteria, namely (1) dimensionality (1D, 2D, 3D or 4D), (2) type of features using for registration (intrinsic or extrinsic), (3) domain of the transformation (local or global), (4) type of the transformation (rigid or non-rigid), (5) parameter determination (search or closed-form solution), and (6) interaction (interactive, semi-automatic or automatic). Maurer and Fitzpatrick divided them into (1) stereotactic frame systems, (2) point methods, (3) curve and surface methods, (4) moment and principal axes methods, (5) correlation methods, (6) interactive methods, and (7) atlas methods (Maurer & Fitzpatrick, 1993).

Classes of applications can be also distinguished as follow: intra-subject/intra-modality applications refers the images alignment of the same subject acquired using the same modality; intra-subject/inter-modality concerns the images alignment between images of the same subject but across different modalities, very useful to PET and SPECT.
multimodalities (Declerck, Feldmar, Goris, & Betting, 1997); inter-subject/intra-modality consists in align studies of different subject using the same modality; and inter-subject/inter-modality means the alignment of studies between images from different subjects across different modalities.

Table 1. shows a classical medical image registration classification criteria proposed by Maintz and Viergever that considers and explores the subdivisions of dimensionality, nature of the registration basis, domain of transformation, interaction, optimization procedures, modalities involved in the registration, subject and object, giving an overview of the registration methods and their applications.

The computation of transformations between a coordinate system of an image and another one or even a physical space requires the application of registration methods in different dimensionalities. A 2D image registration is possible when the geometry of acquisition is strongly controlled. A 3D-to-3D transformation is the more applied image transformation used to register 3D images, assuming the body as a rigid body, and a 2D-to-3D transformation is applied to aligned 3D volumes, projections or optical images. The time is also an essential factor to be taken into account since it is wanted to compare images acquired at different times (Oliveira, Sousa, Santos, & Tavares, 2011; Oliveira & Tavares, 2012).

Depending on the dimensionality of the images, a number of degrees of freedom that represents the number of parameters that are needed to describe a registration transformation can be defined, resulting in rigid and non-rigid transformations. The simplest transformation is the rigid one, which considers rotations and translations. Affine transformations consist in a straight line of an image that will transform to a straight line in the other image and parallel lines are preserved, what allows a combination of rigid body motion, scaling and skew, known as geometric distortions (Hill et al., 2001). The most complex transformation implies a great number of degrees of freedom resulting in a non-rigid transformation, which provides inter- or intra-subject registration, as Fig. 2 presents.

Table 1. Medical image registration classification criteria proposed by Maintz and Viergever (Adapted from Oliveira & Tavares, 2012).

<table>
<thead>
<tr>
<th>Classification Criteria</th>
<th>Subdivision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimensionality</td>
<td>Spatial dimension: 2D/2D, 2D/3D, 3D,3D</td>
</tr>
<tr>
<td>Temporal Series</td>
<td></td>
</tr>
<tr>
<td>Nature of the registration basis</td>
<td>Extrinsic (based on foreign objects introduced into the imaged space)</td>
</tr>
<tr>
<td></td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td>Stereotactic frame</td>
</tr>
<tr>
<td></td>
<td>Fiducial (screw markers)</td>
</tr>
<tr>
<td></td>
<td>Non-invasive</td>
</tr>
<tr>
<td></td>
<td>Mould, frame, dental adapter, etc.</td>
</tr>
<tr>
<td></td>
<td>Fiducials (skin markers)</td>
</tr>
<tr>
<td>Intrinsic (based on patient)</td>
<td>Landmark based</td>
</tr>
<tr>
<td></td>
<td>Anatomical</td>
</tr>
</tbody>
</table>
The use of feature-based methods is recommended to images that contain enough distinctive and easily detectable objects (Liao & Chung, 2010) as remote sensing and computer vision. On the other hand, area-based methods are employed in medical images that are not so rich in details. Sometimes, the lack of distinctive objects in medical images is solved by the interactive selection by an expert or by introducing extrinsic features, rigidly positioned into the patient.

<table>
<thead>
<tr>
<th>Nature of transformation</th>
<th>Geometrical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmentation based</td>
<td>Rigid models (points, curves, surfaces, volumes)</td>
</tr>
<tr>
<td></td>
<td>Deformable models (snakes, nets)</td>
</tr>
<tr>
<td>Voxel property based</td>
<td>Reduction to scalar/vectors (moments, principal axes)</td>
</tr>
<tr>
<td></td>
<td>Using full image content</td>
</tr>
<tr>
<td>Non-image based (calibrated coordinate systems)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Domain of transformation</th>
<th>Local</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interaction</th>
<th>User initializing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>User steering/correcting</td>
</tr>
<tr>
<td></td>
<td>Both</td>
</tr>
</tbody>
</table>

| Optimization procedure    | Parameter computed (the transformation parameters are computed directly) |
|---------------------------| Parameters searched for (the transformation parameters are computed using optimization algorithms) |

<table>
<thead>
<tr>
<th>Modalities involved in the registration</th>
<th>Monomodal (CT-CT, MRI-MRI, PET-PET, SPECT-SPECT, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multimodal (CT-MRI, CT-PET, CT-SPECT, PET-MRI, etc.)</td>
</tr>
<tr>
<td></td>
<td>Modality to model</td>
</tr>
<tr>
<td></td>
<td>Patient to modality (register the patient with the coordinate system of the imaging equipment)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th>Intrasubject (same subject)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intersubject (different subjects)</td>
</tr>
<tr>
<td></td>
<td>Atlas</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Object</th>
<th>Head (brain, eye, dental, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thorax (entire, cardiac, breast, etc.)</td>
</tr>
<tr>
<td></td>
<td>Abdomen (general, kidney, liver, etc.)</td>
</tr>
<tr>
<td></td>
<td>Limbs</td>
</tr>
<tr>
<td></td>
<td>Pelvis and perineum</td>
</tr>
<tr>
<td></td>
<td>Spine and vertebrae</td>
</tr>
</tbody>
</table>

10
2.4. **ALGORITHMS BASED ON RIGID TRANSFORMATIONS**

Different image registration algorithms can compute image transformations between images or within a physical space, through landmark-based registration, surface-based registration, as distance transforms and iterative closest point algorithms and voxel-based intensities, known as geometric transformations. Bartoli (2008) propose an algorithm to jointly estimate both groupwise geometric and photometric transformations while preserving the efficient precomputation-based design of the original inverse computational algorithm.

Methods for 2D-3D registration are used in image-guided interventions and endoscopic or microscopic surgeries (Yamazaki et al., 2004; Markelj, Tomaževič, Pernuš, & Likar, 2008; Ruijters, ter Haar Romeny, & Suetens, 2009; Shekhar et al., 2004) and are grouped in two classes: feature-based and direct intensity-based (Klein, Staring, Murphy, Viergever, & Pluim, 2010), which are faster but highly dependent on the integrity of the segmentation in both images (Van de Kraats, Penney, Tomazevic, Van Walsum, & Niessen, 2005). Another method is to match the pixel and voxel intensities directly, based on digital reconstruction radiographs (DDR) that are computer-integrated through the summing of intensities along the rays.

For 2D image registration, the phase correlation method is commonly used to identify displacements between multidimensional data sets due to the robust performance and computational simplicity (W Scott Hoge & Westin, 2005; William Scott Hoge, 2003).

2.4.1. **Landmark-based registration**

Landmark-based registration or point-based registration are methods based on the identification of correspondent point landmarks or fiducial markers within two images, i.e., it involves identifying correspondent 3D points in the images to be aligned, registering those points as inferring the image transformation determined from the point. Its algorithms consist of the difference of the computed average or centroid of each set of points that provides the translation that must be applied to a set of points and consider the minimization of the sum of the squared distance between each corresponding point pair (Myronenko & Song, 2010). So, it is also referred to as fiducial registration error (FRE). The point landmarks must be visible on each scan or well identified, attached to the skin or screwed into the bone such as corresponding internal anatomical landmarks manually identified.

The orthogonal Procrustes is a problem associated to this kind of registration as an error in the rigid-body point registration due to the fact that the localization of the fiducial point is never perfect, known as fiducial localization error (FLE) (Dorst, 2005; Larsen, 2008; Wiles, Likholyot, Frantz, & Peters, 2008).

2.4.2. **Surface matching**

Boundaries or surfaces are more distinct than landmarks in medical image leading to surface-based registration, which consists in the correspondence between surfaces that are delineated in the two imaging modalities and a computed transformation minimizes some measure of distance between the two surfaces (Audette, Ferrie, & Peters, 2000). It
allows a high contrast in the majority of the imaging modalities with important exception of certain tracers in nuclear medicine emission tomography.

The 'Head and Hat' algorithm, which draws contours of the surface on a series of slices from one modality and a set of points correspondent in the other modality, was based on iteration to refine the trial fits; then, it is based on the minimization of RMS. Distance transforms implies pre-computing the distance from every point in space to one of the surfaces to be registered, which values are squared and summed to calculate the cost associated with the current estimated transformation.

Iterative closest point algorithm is the most applied algorithm based on surface-based registration, once it finds the closest point on the appropriate triangular patch to each of the point that are then registered using the corresponding landmark registration. Next, it finds the least square rigid-body transformation relating those point sets and repeats the two stages until it find the local minimum match between the two surfaces.

When using differential geometry tools, two principal curvatures can be defined at each point on a surface and crest lines are obtained, i.e., the loci of the surface where the curvature is maximal on its principal direction that can be obtained directly from the image voxel arrays. It is useful in medical images once it determines isosurfaces that delineate structures of interest, enabling image registration through the alignment of those crest lines (Hill et al., 2001).

Hybrid registration using surface registration such as combined with volumetric registration is also available in scientific literature (Postelnicu, Zollei, & Fischl, 2009).

2.4.3. Voxel-based intensities

Algorithms using the intensities (Jia & Tang, 2005) of the two images separately, without any requirement to segment or delineate the corresponding structures (Prieto & Allen, 2003) such as voxel similarity-based registration, results in a robust and accurate computation, through joining the histograms (Yang & Wu, 2004). They tend to average error caused by the noise or random fluctuations. Some problems can be minimized using Branch-and-bound methods, as described by Olsson, Kahl, & Oskarsson (2009).

The determination of the center of mass and the orientation of the images to be registered enable a direct transformation. The alignment is achieved by aligning both centers of mass and orientation, called principal axes, which is fast but tends to lack of accuracy.

2.5. Algorithms based on non-rigid transformations

This type of algorithms is required when it is needed to establish correspondence between images of one individual and atlas (Hurvitz & Joskowicz, 2008) or computer models (McInerney & Terzopoulos, 1996), in inter-subject registration, or to accommodate the substantial anatomical variability across individuals, such as between images of tissues deformed or grown over time, in intra-subject registration (Crum, 2004; Holden, 2008; Wu, Murtha, & Jaramaz, 2009; Zagorchev & Goshtasby, 2006).

Any non-rigid registration technique can be described by a transformation, which relates the target and source images, a similarity measure (Bronstein, Bronstein, & Kimmel, 2008;
Budd, Huang, Klaudiny, & Hilton, 2012), which measures the similarity between the target and source images, and an optimization, which determines the optimal transformation parameters as a function of the similarity measure to achieve the goal of finding the six degrees of freedom of the transformation \( T: (x, y, z) \mapsto (x', y', z') \) to map any point in the source image into the corresponding point in the target image.

Since affine transformations are an extension of these models that has twelve degrees of freedom allowing scaling and shearing and are frequently used for image registration when some image acquisition parameters are not known (Kadyrov & Petrou, 2006) or to accommodate a limited amount of shape variability, non-affine registration algorithms include an initial rigid body or affine transformation that provides an estimated starting. It is regarded as a deformation field (Rao et al., 2004) that records the displacement vector at each voxel in an image to align it with the corresponding location in the other.

Adding more additional degrees of freedom, as a linear transformation, models can be extended to non-linear transformation models, but they can introduce artifacts like oscillations, so they are rarely used for non-rigid registration.

Fig. 2. Types of transformations: (a) identity transformation (b) rigid transformation (c) affine transformation (d) and non-rigid transformation (Taken from Hajnal V.N., et al., 2001).

Registration using non-rigid transformation can be done using basis functions as a set of Fourier basis function (Andreetto, M., Cortelazzo, G. M., & Lucchese, L., 2004; Larrey-Ruiz, Verdú-Monedero, & Morales-Sánchez, 2008; Lucchese, Doretto, Member, Cortelazzo, & Member, 2002; Oliveira, Pataky, & Tavares, 2010; Pan, Qin, & Chen, 2009), describing the frequency of the deformation, or Wavelet basis function (Gefen, Tretiak, Bertrand, Rosen, & Nissanov, 2004), which as frequency-based methodologies can directly evaluate the SSD and CCD similarity measures of a shift in a faster way compared to iterative optimization (Delon, 2004). The correlation technique is also used to estimate the optimal optimization.

Registration using splines consists of techniques are based on the assumption that a set of corresponding points or landmarks, called control points, can be identified in the source and target images. Then, the spline-based transformations either interpolate or approximate the displacements at control points that are needed to map the location of the control point in the target image into its corresponding counterpart in the source image, providing a smoothly varying displacement field (Fields, Karaçalı, & Davatzikos, 2004) between the landmarks (Marsland & Twining, 2004). The location of these points can be update through the optimization of a voxel similarity measure or mutual information, but pseudo- or quasi-landmarks are used as a parameterization of the transformation not corresponding to anatomical or geometrical landmarks.
Thin-plate splines (TPS) are based on radial basis functions, as multiquadrics and Gaussians, and used in surface interpolation of scattered data. However, each basis functions contributes to the transformation and each control point has a global influence on the transformation what can become modeling local deformations more difficult, requiring the use of freeform deformations based on locally controlled functions (Rogers & Graham, 2007). Serifović-Trbalić, et al., (2009) propose a TPS approximation method that incorporates anisotropic landmarks errors and rotational information, integrating it into a hierarchical elastic registration framework. B-splines are part of TPS registration algorithms, since they deform an object through the manipulation of an underlying mesh of control points what control the 3D object’s shapes and produce a smooth continuous transformation (Noblet, Heinrich, Heitz, & Armspach, 2005; Xia & Liu, 2004; Xie & Farin, 2004); this requires a regular mesh of control points with uniform spacing. Thin-Plate Spline Robust Point Matching (TPS-RMS) algorithm is also used as a final application of geometric algebra, useful to surgical procedures (Bayro-Corrochano & Rivera-Rovel, 2008), as well Reyes-Lozano, Medioni, & Bayro-Corrochano (2010). Sorzano, Thévenaz, & Unser (2005) applied vector-spline to biological deformable images.

Elastic registration, also known as deformable or curved registration, represented in a Lagrangian frame, enables modeling the deformation of the source image into the target image as a physical process, resampling the stretch of an elastic material. But its limitation due to the highly localized deformations that cannot be modeled because of the deformation energy from stress that increases proportionally with the strength of the deformation. However, Fischer & Modersitzki (2004) present a unified approach to a faster image registration such as Kybic & Unser (2003) and Grosland, Bafna, & Magnotta (2009) describe its use to an automated hexahedral meshing. Fluid registration, represented in an Eulerian reference frame, provides a modeling of those deformations, what is really useful for inter-subject registration. Registration using optical flow is a technique that is equivalent to the equation of motion for incompressible flow.

Kullback-Leiber Divergence and SVM (Support Vector Machine) are examples of registration methods that incorporates joint intensity distribution as non-rigid transformations (Fung & Stoeckel, 2006; Guetter, Xu, Sauer, & Hornegger, 2005), as well as Brownian Warps, a diffeomorphism registration algorithm (Nielsen, Johansen, Jackson, Lautrup, & Hauberg, 2008). A symmetric non-rigid registration is proposed by Tagare, Groisser, & Skrinjar (2009) using exactly symmetric registration algorithms.

Respecting to their applications, inter-subject registration implies the alignment of images with changes in size and topology, which approaches include extending the rigid-body method to incorporate deformations that follow quadratic and higher polynomial curves order or even more complicated functions as Fourier or wavelet basis function and splines. The optimization process, fundamental in all non-rigid algorithms, is based in the fact that the goodness of match is balanced against some constraint prohibiting implausible deformations that maybe provided by some estimate of the energy required to physically induce the deformation or couched in probabilistic terms.

There are approaches basis in rigid-body transformations for blurred images followed by multiple rigid-body transformation for arrays of volume through iteration with interpolation between elements or even modeling the deformation on the physical process.
of diffusion, known as Demons algorithm. In intra-subject registration, deformations are due to natural involuntary or voluntary motion or by an intervention. The problem of poor constraints can be minimized using known information about tissue as volume preservation or local rigidity. The algorithms can be divided in those based on modeling, where some physical proceed are used, as viscous fluid flow or elastic deformation (Auer, Regitnig, & Holzapfel, 2005), or based on interpolation or approximating functions. It is used also to the reconstruction of deformed images (Docef & Murphy, 2008).

2.6. **Optimization**

This process consists of taking a series of guesses from an initial starting position within its capture range, that must be closed enough to the algorithm converge to the correct answer. It is always needed but using Procrustes technique. The algorithm optimization computes a cost function or similarity function, as correlated coefficient, sum-of-squared-intensities differences and mutual information, to relate the goodness of the two registered images, guessing subsequent alignment transformations that will stop when an optimal registration is achieved by seeking transformation that increase or decrease the cost function until a maximum or minimum is found.

One of the difficulties is that they can converge to an incorrect local optimum, because there are multiple optima within the parameter space and registration can fail if the optimization algorithm converges to the wrong optimum (Klein, Staring, & Pluim, 2007; Marques & Abrantes, 1997; Nguyen & Torre, 2009). The small optima caused by interpolation artifact or local good match between features or intensities can be removed by blurring the images, so the images are first registered at low resolution and then the transformation resolution obtained is used as the starting estimate for registration at higher resolution (Marai, Laidlaw, & Crisco, 2006; Telenczuk, B., et al., 2006).

To surface-matching algorithms, the optimization algorithm starts in an estimated initial point, resulting in multiple solutions. To choose the solution that has the best value of the similarity measure is the called multi-start optimization, an approach to get the global optimal solution (Oliveira, Tavares, & Pataký, 2009; Oliveira & Tavares, 2008, 2009). However, in voxel-based intensity measures, it is desired to obtain the local optima, what implies to start the algorithm within the capture range of the correct optimum that is already close to the correct solution. Adaptive stochastic gradient descent are an alternative (Klein, Pluim, Staring, & Viergever, 2008).

2.6.1. **Correlation Coefficient and Sum of Squared Intensities Differences**

In the case of register intra-subject/intra-modality, the correlation coefficient (CC) is good to measure the alignment, since it involves the multiplication of the corresponding image intensities assuming that there is a linear relationship at registration between the intensity values. It is possible to subtract (Zubal, Spencer, Smith, & Hoffer, 1994) them instead of multiply, as Table 2 shows, allowing the adjustment of the alignment by the smallest sum of squared intensity differences (SSD). This way, it assumes implicitly that after the registration the images differ only by a Gaussian noise, so it is very sensitive to a small number of voxels that have a very large intensity differences between images.
Table 2. Application of sum of absolute differences that reflects the lack of similarity: poorly aligned image result in large absolute differences (on the top row), contrarily to well aligned image which absolute differences are significantly reduced (on the bottom row) (Alves, R. & Tavares, J. M. R. S., 2013)

<table>
<thead>
<tr>
<th>Fixed Image</th>
<th>Moving Image</th>
<th>Difference Image Before Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Fixed Image" /></td>
<td><img src="image2.png" alt="Moving Image" /></td>
<td><img src="image3.png" alt="Difference Image Before Registration" /></td>
</tr>
</tbody>
</table>

Ratio image uniformity (RIU), variance of intensity ratios (VIR) and partitioned intensity uniformity (PIU), used to register inter-modalities images, are examples of these algorithms, but there are recent algorithms demonstrating applicable techniques to both inter-and intra-modality registration, based on information theory.

2.6.2. Information theoretic techniques

Image registration can be described as trying to maximize the amount of shared information in two images which means that a measure of information can be used as a registration metric (Karaçali, 2006). The joint entropy measures the amount of information existing in combined images, resulting in a method that can be used to rigid and non-rigid image registration (Loeckx, Slagmolen, Maes, Vandermeulen, & Suetens, 2010; Josien P W Pluim, Maintz, & Viergever, 2004).

Mutual information, given by the difference between the sum of entropies of the individual images and the information in the corresponding volumes of the original image, a measure of how one image explains the other, makes no assumptions about the functional form or relationship between image intensities (Maes, Collignon, Vandermeulen, Marchal, & Suetens, 1997; Maes, Vandermeulen, & Suetens, 2003; Josien P W Pluim et al., 2003; Seppa, 2008). Changes in overlap of very low intensity regions, such as noise around the patient, can disproportionally contribute to the mutual information, so it is commonly associated with results normalization in a very robust algorithm and in a fully automated 3D-to-3D rigid-body registration algorithms (Collignon, A., et al, 1995).
2.7. **Interpolation**  

When it is needed to transform an image into the space of the other, a process of interpolation is applied, which goal is to estimate the intensity at the new position, and depends on the motivation for registering the images. The accuracy and speed of the registration process can be improved by the interpolation solution, as the linear and nearest neighbor interpolation.

Trilinear interpolation method consists of a voxel value in the transformed coordinates that is estimated by taking a weighted average or the nearest eight neighbors in the original data set; the weightings are inversely proportional to the distance of each neighbor from the sample point. This interpolation applies a low-pass filter to the image and introduces aliasing, and in the case of rotations, the amount of filters varies with position (Kazhdan, 2007; Keller, Shkolnisky, & Averbuch, 2005).

Methods to interpolate between neighboring slices in a greyscale, which registration can be achieve by B-splines (G P Penney, Schnabel, Rueckert, Viergever, & Niessen, 2004), geometric multi-grid (Keeling, 2007) using a modified control grid interpolation algorithm (Frakes et al., 2008) or adaptive 2-D autoregressive modeling and soft-decision estimation (Zhang & Wu, 2008) are recent developments.

When transformations involve pure translation of datasets with equal sample spacing, where the period of the modulation is the same as the sample spacing, the interpolation error can introduce modulation in the similarity measure. Interpolation methods must be used with a practicable computational cost, firstly using a low cost interpolation as trilinear or nearest neighbor, and a more expensive interpolation in the final few iterations or even take advantage of the spatial-frequency dependence of interpolation error, such as cubic B-splines or windowed sinc interpolators, except when the smoothness and robustness of the similarity measure is affected by imperfections, requiring a superior interpolation solution during the optimization step (Oliveira & Tavares, 2012a).

2.8. **Accuracy Assessment and Validation**

The algorithms used in the entire image registration process must be validated, especially in medical applications, through a process of verification. The software industry has already developed standards, protocols and quality procedures, which available software indicates what is specified to do, with accuracy and other performance criteria, resulting in a correct validation (Lee, J.S., et al., 2005; Loi et al., 2008). Validation usually follows a sequence of measurement using computer-generated models, known as software phantoms, consisting of physical phantoms images of accurately known construction and dimension, and images of patient or volunteers which must demonstrate robustness, that implies a very low failure rate, and high accuracy, through the knowledge of a ground truth registration (Moisan & Stival, 2004).

Considering three-dimensional views, that accommodates intra- and inter-modalities registration, it is possible to define several measures of error including target registration error (TRE) that consist of the disparity in the position of two corresponding points after
registration that must be as the quantity of choice to be reported in the validation process. It can be expected to vary with the registration situation, since it comprises the image modalities, anatomy and pathology, and also with position within a view. This way, experimental validation of a registration system must be extended to a clinical situation to extent if the clinical situation matches the experimental one, whose degree of matching will vary with the registration system, as referred by Docquier et al. (2009), Willendrup et al. (2004) and Woods et al. (1998).

Comparing the system to be validated against a gold standard (system with high accuracy) is the most popular strategy for validation. Gold standards can be based in computer solutions, by acquiring one image and generating a second with a known geometrical transformation, i.e., phantom images such as cadavers or patient images, which provide arbitrarily accurate geometrical transformations. A novel method of validation of non-rigid medical image registration is based on the simulation of physically plausible, biomechanical tissue deformations using finite-element methods, allowing the simulation of gold standard deformations (Schnabel et al., 2003). Those simulations are also important in non-rigid validations due to the bias of such validations on favor of registration methods that employ similar non-rigid transformations, whether they are meaningful at a physical way or not. These are based on pairs of acquired patient images that represent the most desirable class of standard, because the inclusion of all the patients physical effects, but suffer from the difficulty of establishing the true transformation between the acquired images (Tsai, Yang, Tsai, & Kao, 2004).

The target feature is any object that can be localized independently at each view which is used to establish each transformation between the acquired images, effective phantoms and patients. This way, the RMS disparity in the two localizations of the target feature after registration provides an upper bound on the RMS of TRE at the location of the feature. Several fiducial features can be employed as registration cues as a more desirable method for rigid-body registration, constituting a validation standard accurate that can be determined without reference to other standard and can be accomplished by the exploitation of establishing statistical relationships among FLE, a poor measure of registration error but with an important role in this translation, and TRE to translate self-consistency into accuracy.

Visual assessment is also used as a standard and recently subjected to validation with a self-consistency method that is considered based on the registration circuit in which a set of three or more images are registered in pairs and the intra-patient, inter-modality, rigid-body registration of the head for tomography and emission tomography image involvement based on a gold standard which employs bone-implanted fiducial markers are efforts in this type of validation methods.

However, the rigid registration validation is which have been strongly studied due to its importance in medical image registration, but greatest challenges in assessing the success of registration systems won’t be equal to non-rigid regime.

Summarizing, in medicine technologies, it is fundamental to evaluate whether there is a clear benefit to the patient and how to achieve it in a cost-effective manner, so improving registration accuracy is an important goal, but without a means of validation no
Registration method can be accepted as a clinical tool. New methods for assessing accuracy must be developed to accelerate progress towards improved registration systems and make existing methods accessible to physicians, surgeons and their patients.

2.9. Display of Registered Data

Registration image sets can be displayed through different approaches depending on the type of applications, but in nuclear medicine applications, dual cursor and fused image display are the most commonly used.

Dual cursor consist in displaying the aligned images set side by side, generally with three orthogonal views per data through a selected point, using the position of the cursor to appreciate the exact correspondence between the two image sets. This method can provide sufficient information to physician can make the diagnostic.

A single combined image where the information from the aligned images set is already combined constitute the fused image display, through the alternation of the display between the two registered image sets from one pixel to the next, producing a checkerboard pattern, where two colors or a combination of greyscale and a color is used to display the two data sets. The adjustment of the greyscale or color for each image independently is an advantage but is difficult with some alternative fusion schemes, due to the generation of values based on combinations of the two data sets as hue and brightness encoding or frequency encoding. It is very useful to demonstrate 3D location of some focal uptake but both image sets are in some way compromised by the combined display.

Surface displays or cut surface displays are alternative methods to display an image superimposed either on a cut surface generate through the second image volume or superimposed on a volumetric surface generated from the second image. Providing means of removing surface detail to expose information from the registered data sets at some internal location is another alternative. Due to the limited values in primary diagnosis using nuclear medicine data, they are useful to complement the conventional display, namely to demonstrate 3D location.

2.10. Clinical Applications

The clinical applications of medical image registration are applied to the organs that are computer-assisted diagnosed, namely brain, breast, chest, liver, kidneys and colon, concerning static images, or even applied to tracking motion of organs, as well as heart, to study the behavior of cardiac diseases. This way, inflammatory diseases localized at each organ are also included in the studies involving medical image registration. Some reviews are available in literature (Gholipour, Kehtarnavaz, Member, Briggs, & Devous, 2007; Mclnerney & Terzopoulos, 1996; Rueckert et al., 1999; Toga & Thompson, 2001), as well as the quantitative comparison and evaluation of intra- and inter-modality brain image registration techniques (Erika et al., 1999; Stephen, Jon, & David, 1994).

Among model-based techniques, deformable models are a powerful approach to image analysis that combines geometry, physics and approximation theory, proving to be effective in segmenting, matching, and tracking anatomic structures. They are capable of accommodating the significant variability of biological structures over time and across
different individuals, exploiting constraints derived from the image data together with a priori knowledge about the location, size and shape of those structures (McInerney & Terzopoulos, 1996; Schnabel et al., 2001). Based on multi-organ deformable image registration, various finite element models are becoming more used (Brock, Sharpe, Dawson, Kim & Jaffray, 2004) due to its accuracy and non-necessity of some assumptions. Normalized entropy measure for automated 3D multimodality medical image alignment provides a significant improved behavior over a range of image fields of view (Studholme, Hill, & Hawkes, 1999; Holden et al., 2000).

Besides the non-rigid image registration being the most used in medical image registration, they have a high computational cost that can be solved using a parallel implementation, taking advantage of shared-memory multiprocessor computer architecture. It is possible using multithreaded programming by both portioning of data and tasks (Rohlfing, T., Maurer, C.R., 2003). Dedicated hybrid imaging systems and software image co-registration techniques are available (Slomka & Baum, 2009), performing multimodality image integration of functional and anatomical data. However, their utilization in clinical environments is hindered by the lack of appropriate picture archiving and communication systems infrastructures.

2.10.1. Radiation therapy planning

The radiation therapy planning is the widest area of clinical applications since it considers all the organs referred above. Several studies have been developed to validate different image registration approaches, aiming the calculation of localized dose distributions to allow higher doses to be delivery to cancerous tissue without harming nearby normal tissue. A 3D registration of diagnostic imaging data with CT offers a substantial improvement in tumor target identification for many radiation patients, so multimodality or sequential imaging can substantially aid in better tumor definition undergoing 3D treatment planning (Rosenman, J.G. et al., 1998). A phantom-based quality assurance of the image registration and fusion process can be used in a routine clinical setting or for providing a working image set for development of the image registration and fusion process (Mutic et al., 2001).

The assessment of a model-based deformable image registration approach through the development of a surface-based deformable image registration strategy assessing the accuracy of the system for the integration of multimodality imaging, image-guided radiation therapy and the geometrical changes during and after therapy is described by Kaus et al., (2007). It enables quantitative description of geometrical change in normal tissue and tumor with acceptable accuracy and speed, where a volumetric deformation field is derived using different volumetric elasticity models as alternatives to finite-element modeling. Note that where a physical process is affecting image contrast in a series of images, modeling the effect of that process on the appearance of image structure is a powerful approach.

Biomechanical-based deformable image registration techniques also incorporates classification, targeting and monitoring of tumor and normal tissue using a multi-organ technique based on finite element modeling and surface projection alignment of selected
regions of interest with biomechanical material and interface models (Brock, Dawson, Sharpe, Moseley, & Jaffray, 2006).

2.10.2. **Brain**

The brain is the most representative human organ concerning image registration applications. In order to define the location of brain activity or to produce functional/parametric maps with respect to the brain structure or anatomy that are not clear in functional brain images, various techniques are introduced in literature. Cortical surface registration and automatic brain labeling are some of the tools established to get a fully automatic functional localization procedure. Brain atlases and brain templates provide a standard basis for activation labeling and, in group studies analysis, the functional images of different subjects can only be compared and analyzed if the anatomical variations are compensated via appropriated mapping (Gholipour et al., 2007).

The subject head movements are one of the main practical difficulties with functional MRI, and then the motion correction is a common application of image registration. Cox & Jesmanowicz (1999) described 3D image realignment for small movements through a fast accurate method for rotating and shifting 3D image using a shear factorization of the rotation matrix. However, motion correction algorithms may create spurious brain activation on the absence of subject motion, a problem that can be overcome by methods based on a robust similarity measure like mutual information (Freire & Mangin, 2001). Despite that, the commonly used multiresolution local optimization methods can get trapped in local minima, so to apodize the cost function or to employ a novel hybrid global-local optimization method can solve this problem, reducing the likelihood of producing misregistrations (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001).

Spatial transformations are a key issue in computer-aided surgery, functional image analysis and morphometrics. Deformable surface algorithms are used to find a parametric representation of the outer cortical surface and then to define a map between corresponding cortical regions in two brain images, and a consequent three-dimensional elastic warping transformation is determined bringing two images into register. It can be used to model structural irregularities as ventricular expansion occurring with aging or diseases and growth of tumors (Davatzikos, 1997).

Monitoring change in the individual by acquiring serial scans is a common practice since it is particularly useful in dementia where fluid registration is a cue to visualize patterns of regional atrophies (Crum, 2004). Concerning detailed characterization of neurodegeneration, symmetric diffeomorphic image registration with cross-correlation, i.e. symmetric normalization method for maximizing the cross-correlation within the space of diffeomorphic maps and providing Euler-Lagrange equations, to evaluate automated labeling of elderly and neurodegenerative brain was developed through the quantification of spatial and longitudinal atrophy applied to MR images (Avants, 2008).

As said above, a generic application of non-rigid registration is in segmentation or labeling through the labeling of structures or tissue classes, achieving good correspondences between structurally equivalent regions on the two images. Fully automatic multimodality image registration algorithms, namely CT-PET, MR-CT, MR-PET and MR-SPECT
registrations requiring no user interaction, are already available through the detection of the head contour on MR or CT images using a gradient threshold method, followed by segmentation into a set of connected components using clustering algorithms, that will consequently segment the nuclear images, being the best registration the one that optimizes the segmentation introduced on the nuclear image (Ardekani et al., 1995; Davatzikos et al., 1996).

Finite element computation of the deformation field within the brain is a strong tool concerning the use of non-linear biomechanical models to complement medical image processing techniques when conducting non-rigid registration, since they do not require unrealistic assumptions that brain deformations are infinitesimally small and brain stress-strain relationship is linear (Wittek, Miller, Kikinis, & Warfield, 2007).

2.10.3. Cardiac applications

Registration of cardiac images is a more complex tasks than brain image registration since it is non-rigid moving organ inside a moving body, exhibits fewer accurate landmarks. Real-time 3D ultrasound is a flexible, inexpensive, non-invasive tool that provides important information of cardiac function. Due to its low signal-to-noise ratio and limited field of view, multi-model dynamic cardiac image registration compensates these problems (Huang, Hill, Ren, & Guiraudon, 2005).

Non-rigid registration is a key requirement for the application of biomechanical models of cardiac function through the creation of a generic cardiac model that is instantiated by linear elastic registration with cardiac images of a subject acquired in different modalities (Crum, 2004), which the mechanical parameters obtained from each image allow the creation of a model used to track heart motion in time-series. Atlas-based segmentation and tracking (Lorenzo-Valdés, Sanchez-Ortiz, Mohiaddin, & Rueckert, 2002) organs positions and shape, such as lungs during breathing is an issue with growing interest (Makela et al., 2003).

Ultrasound calibration using rigid intensity-based image registration for application in cardiac catheterization procedures constitute a method of optically tracking calibrated 3D probes to produce extended fields of view, enabling the registration of ultrasound images (Ma et al., 2008). Mutual-information-based rigid and non-rigid registration (Ledesma-Carbayo et al., 2005) of ultrasound volumes requires a smooth (Ledesma-carbayo, Kybic, Desco, & Unser, 2001), quasi-convex mutual information surface with an unambiguous maximum (Shekhar & Zagrodsky, 2002; Shekhar, Zagrodsky, & Castro-pareja, 2003), meaning that its application to cardiac cases studies is possible using progressively generalized transformations, as well as to other abdominal and thoracic organs.

Cardiac 4D image analysis (McInerney & Terzopoulos, 1995; Shen, Sundar, Xue, Fan, & Litt, 2005) allows anatomical surface segmentation, reconstruction and tracking in multidimensional medical images using a dynamic finite element surface model or a deformable biomechanical model (Sermesant, Forest, Pennec, Delingette, & Ayache, 2004).
2.10.4. **Breast**

Sivaramakrishna (2005) and Suri et al. (2006) present a survey of breast image registration techniques since it is the most common cancer in women and image registration plays an important role in its detection. Then, intra-modality breast image registration, as registration of X-ray and MR mammograms and registration of ultrasound breast images, and inter-modality breast image registration are crucial tasks to an effective detection of breast tumors.

Image registration techniques considering boundaries are also available to applications to mammogram registration. A model focused on the matching of regions of interest, combining region matching and segmentation by formulation of the energy minimization problem with free boundary conditions presents itself more robust to initialization inaccuracies than another one with fixed boundaries conditions (Richard & Cohen, 2003). Free-form deformations with a local rigidity constraint (Loeckx, Maes, Vandermeulen, & Suetsens, 2004) or incompressibility constraint (Rohlfing et al., 2003) have demonstrated local shape preservation, such as the reduction of both shrinkage of contrast-enhancing structures and motion artifacts.

As brain applications, the reduction of the effect of movement artifacts present in the acquired breast images can be realized using rigid, affine or non-rigid registration. In fact, non-rigid registration significantly reduces those effects in subtracted contrast-enhanced breast MRI, enabling a better visualization of small tumors (Denton et al., 1999). Deformable registration techniques combined with segmentation methods (Hayton, Brady, Smith, & Moore, 1999) by mapping the whole breast clinical target volume from a template case to a new patient allowed autosegmented contours (Reed et al., 2009), which can be applied to patients with different body mass indexes aiming motion correction and autodetection, such as models based on a curvature type smoother (Fischer & Modersitzki, 2004) or subvolume-based algorithms (Krucker et al., 2002).

Even less used due to its non-general application, registration using models of compressible viscous fluids have the ability to model large diffeomorphic deformations (Crum, Tanner & Hawkes, 2005). Also biomechanical models of the breast are gaining more interest and can be achieved using a finite element formulation, which requires noded elements with well-defined properties due to its tissue constitution (Samani et al., 2001).

2.10.5. **Chest**

Diagnosis and prognosis of cancer depend upon growth of pulmonary nodules, being the imaging modalities a well-established means of diagnosing pulmonary metastases of oncology patients and evaluating response to treatment planning. The landmark detection in the chest and consequent registration of lung surfaces initially segmented, through an iterative closest-point process, constitute a valid method to register lung nodules present in CT scans of the same patient (Betke, Hong, Thomas, Prince, & Ko, 2003). As in the applications referred above, free-form deformations with mutual information as a similarity criterion, and a rigid body deformation combined with localized cubic B-splines allows image registration between functional and anatomical images (Mattes et al., 2003).
2.10.6. Liver and Kidney

Cancer is one of the most common diseases that affect an increasing number of people. Its detection and treatment in the liver and kidney requires the analysis of images that are frequently corrupted by noise, motion artifacts and tissue deformation that need to be align with dissimilar images acquired with different MRI techniques, CT, laser range scanner (Cash et al., 2003) or freehand 3D ultrasound (Bao, Warmath, Galloway, & Herline, 2005; Leroy, Mozer, Payan, & Troccaz, 2004; G.P. Penney et al., 2004; Wein, Brunke, Khamene, Callstrom, & Navab, 2008; Wein, Khamene, Clevert, Kutter, & Navab, 2007). The image registration applied to these cases, considering 3D images, can be manual, semiautomatic or automatic, but generally based on non-rigid transformations.

Image registration liver applications allow the transference of information from preoperative modalities to intraoperative ultrasound images to aid needle placement during thermal ablation of liver metastases (Lange et al., 2003; Graeme P Penney et al., 2001), as well as model liver motion using intensity-based free-form registration of gated MR images (Rohlfing, Maurer, O’Dell & Zhong, 2001) and 3D ultrasound images (Blackall, Penney, King, & Hawkes, 2005). Once again, mutual information has demonstrated more accurate and robust, giving better results than other similarity measures (Carrilo, Duark, Lewin & Wilson, 2000).

Similarly to the other organs, 3D models of the liver, reconstructed from anatomical images, are useful for planning treatment and hepatic surgery guidance when compared with external video images of the patient. However, the absence of visible anatomical landmarks and the shape of the upper abdomen requires the use of fiducials, to able a registration criterion for liver radio-frequencies ablations (Archip et al., 2007) guided by augmented reality (Lange et al., 2009; Pennec, Soler, & Ayache, 2004) or surface registration using salient anatomical features (Clements et al., 2008; Herline et al., 2000).

2.10.7. Colon

Colon clinical applications are generally related with images from computed tomography colonoscopy, since it is minimally invasive and allows the evaluation of the colon wall with consequent detection and identification of abnormalities as polyps, precursors to colorectal cancer. However, those images have too much artifacts due to some collapsed walls covered with water or retained stool that might be improved using image registration. Li et al. (2003) described an algorithm based on the registration of the colonic central paths and then matches polyps candidates. The path length and curvature, as well as descriptors of the shape and size of the colon near the path are information that might be included in automated methods (Nain et al., 2002), used to produce synchronized fly-through or slice views.

2.10.8. Other applications

Respecting to inflammatory diseases that can affect several organs, the main applications were already described, since they can be detected through the current imaging modalities. However, image registration can be applied to extraction of characteristic structures through endoscope navigation, where camera motion tracking is a fundamental task required for image-guided treatment or therapy system. As the position of the
sensors are difficult to be equipped, image registration between the real and virtual endoscope images is needed (Deguchi et al., 2009). Inflammation and cerebral atrophy are related; aiming to understand the temporal relationship between them, image registration over temporal spaced acquired images was applied (Richert et al., 2006).

The therapeutic response of radiofrequency therapies to carcinomas can be evaluated by automatic image registration and segmentation of preoperative and postoperative CT images (Fujioka et al., 2006), enabling to understand the relationship between tumors and the ablation zone.

Due to the increasing number of patient with hip replacements, pelvic radiotherapy is also an interest application of image registration. This kind of therapy is usually planned using CT images that can contain artifacts caused by the presence of metallic implants and make images useless for target definition (Charnley, Morgan, Thomas, Wilson, & Bacon, 2005). Then, the registration of CT and MR images is needed to compensate the problem.

2.11. CONCLUSIONS

The last few years have been an important role to the development of new image registration methods, which research provides the overcoming of many obstacles. Besides that, the more accessible data from different imaging modalities due to its digital format enables the expansion of registration methods to hospitals and private clinics, becoming an essential aid in computer-assisted diagnosis tool inherent to imaging systems.

However, it is fundamental to be aware of the limitations concerning available software that makes the image registration valid and consequently image interpretation realistic, such as flexible software capable of providing registration accuracy between anatomical and functional modalities.

Moreover, further works needs to be done to demonstrate the validity of non-rigid registration techniques in nuclear medicine applications, there being a need for additional demonstrations of the applicability of those registration methods, due to its direct benefits.
3. NUCLEAR MEDICAL IMAGING
3.1. Introduction

Nuclear image modalities have been widely used in healthcare diagnostic since it provide a physiological diagnose through the use of radiotracers to map the metabolism and fluid flow on tissues, organs or human systems.

Positron emission tomography and single photon emission computed tomography are nuclear image modalities, currently three dimensional that use radioactive tracers but different principles of detection, to measure and evaluate the metabolic processes of the individual or object under study. Thus, the PET scanner or SPECT Anger camera are based on electronic detection of positrons and photons, respectively, which can be produced by a cyclotron, generating three-dimensional images of the radiopharmaceutical distribution administered by intravenous injection into the human body.

Unlike other imaging techniques such as X-rays, computerized tomography or magnetic resonance imaging that aims the detection of anatomical structures, those modalities assess the perfusion and metabolic activity, even if there are no changes from the structural point view, commonly used as a diagnose complement in oncology, cardiology and neuropsychiatric disorders.

In this chapter, it will be referred radiotracers, detectors, image data acquisition, image reconstruction and algorithms in 2D and 3D, such as the common sources of degradation factors that minimize the quality of the images acquired and its corrections concerning PET and SPECT, nuclear imaging modalities where image reconstruction is an essential task to get a more accurate diagnose. Multimodalities commercially used and common applications are also reviewed.

3.2. Positron Emission Tomography

Despite the pioneering ideas for positron emission tomography have been developed more markedly in the 50’s, it should be noted that computed tomography (CT), also a diagnostic imaging procedure, was created first and had already been made studies on groups of radioisotopes with half-life times, short decay positron emission schemes, the gamma camera or scanner, as well as the creation and development of cyclotrons for E. O. Lawrence, thereby producing and identifying radioisotopes with short life time (Wachtoltz, E. H., Online).

The nuclear reactor development, the rectilinear scanner and gamma camera were important for the emergence of imaging in nuclear medicine, and built the first device (Brownell, Gordon L., 1999) capable of detecting and recording the existing annihilation of positrons when electrons collide in the human body to obtain information through the translation of two opposite detectors using coincident detection with mechanical movements to form a two-dimensional image of the positron source (Muehllehner & Karp, 2006).

Using advanced algorithms for three-dimensional images computation, the perception of high accuracy of brain mapping through blood flow, measured with short half-life radiopharmaceuticals, with a quickly, safely and effectively measurement, making PET a new modality to understand the human physiology and diseases, despite the costs
involved in this equipment (Augusto & Pilgrim, 2004). It requires human resources highly qualified able to make the cyclotron operations and maintenance for the manufacture of radioisotopes, scanner, gamma-ray imaging, radiopharmaceutical synthesizing using a synthesizing unit and image analysis task. The reduction and automation of procedures, the development of a detector block and smaller, cheaper and more efficient cyclotrons, and then synthesize radiopharmaceuticals capable of emitting positrons with low energy, made possible its installation in a large number of health units settings (Garcia, Faber, Galt, Cooke & Folks, 2000).

More recently, in 2000, it was produced and marketed the scanner PET / CT which combines the anatomic information from CT with functional PET images providing improved images with CT attenuation correction of PET emission data, eliminating the need for separation and long scanning transmission and also reduces 40 % the whole body scan time (Pomper, MG, et al, 2004; Cherry, SR, 2009).

3.2.1. Radiotracer

The PET images are based on the detection of an injected tracer into the body. Comparing the tracer distribution in a patient with normal data, the physicists are able to evaluate the anatomic and physiologic status of the patient.

The tracer consists in a pharmaceutical component and a radioactive marker, administered in very low concentrations in the nano or picomolar order, with no pharmacological effects, causing the tracer do not alter the physiological component assessed. The pharmaceutical component determines where and how the tracer will behave, since the drug is chosen in function of the organ which is intended to study through the metabolism of such drug. Consequently, due to the marker's radioactive activity, the metabolic processes mapping can be obtained (Hoffman, J. M., 2002). Table 3 indicates the most used radiotracers according their biomedical application.

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Radioisotope</th>
<th>Physical Half-life (min)</th>
<th>Mean Positron Range (mm)</th>
<th>Production</th>
<th>Biomedical Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorodeoxyglucose (FDG)</td>
<td>Fluorine-18</td>
<td>109.8</td>
<td>2.5</td>
<td>Cyclotron</td>
<td>Glucose metabolism</td>
</tr>
<tr>
<td>O-15 Water</td>
<td>Oxygen-15</td>
<td>2.03</td>
<td>1.5</td>
<td>Cyclotron</td>
<td>Blood flow, brain studies</td>
</tr>
<tr>
<td>N-13 Ammonia</td>
<td>Nitrogen-13</td>
<td>9.96</td>
<td>1.1</td>
<td>Cyclotron</td>
<td>Blood flow, brain studies</td>
</tr>
<tr>
<td>C-11 SCH23390 C-11Flumazenil</td>
<td>Carbon-11</td>
<td>20.3</td>
<td>Carbon-13</td>
<td>Cyclotron</td>
<td>Mapping serotonin and GABA receptors</td>
</tr>
<tr>
<td>Rubidium</td>
<td>Rubidium-82</td>
<td>1.25</td>
<td>5.9</td>
<td>Generator</td>
<td>Myocardial perfusion studies</td>
</tr>
</tbody>
</table>

The signal measured by PET is generated when the radioactive tracer attached to the drug decays and emits a positron, which consist in an elementary particle and antimatter, with the same properties as an electron, elementary particle and matter, but its charge is positive. The positrons, such as other forms of antimatter that have short life times and react violently, interact with the tissues of the patient, losing kinetic energy gradually until its speed is low enough to be captured by an electron. When matter (electron) collides with the corresponding antimatter (positron), i.e., electron-positron pair is combined, forms a molecule called positronium transient, very unstable for about 10-20 seconds.
until the positron and electron annihilate, causing its mass becomes two gamma rays of 511keV, as Fig. 3 shows. The two photons move in exactly opposite directions, that is, spaced 180°, forming the so-called coincident line, an indicator that the annihilation occurred somewhere in that path and it is a vital component in the detection scheme whereby the PET image is created (Wu, J., et al, 1998; Pomper, MG, et al, 2004; Ollinger, JM, et al. 1997; Franquiz & Ph, nd). The positron band, i.e., the distance traveled by the positron before it annihilates with the electron, depends on its kinetic energy, in the case of a statistical measure of the distance traveled by the positrons emitted by a particular isotope and revised on lower spatial resolution (Fahey, 2001).

![Positron decay diagram](image)

Fig. 3. Positron decay. A - Rich nuclei in protons emits a positron, B - The positron interacts with the surrounding tissues, losing kinetic energy, C - The positron combines with the electron and the annihilation occurs, D - Result with two 511 keV gamma rays (From Fahey, 2001).

The types of events are classified as single, prompt and true, which means that two photons have moved from a single point of annihilation straight in opposite directions, resulting in a line or coincidence line of response (LOR).

### 3.2.2. Detectors

The two gamma rays, which are dispersed in exactly opposite directions, are detected on opposite sides of the patient's body. The PET camera then records the decay positron events detecting the two photons annihilations that are emitted, through coincidence detection and must be detected before any event to be recorded, as can be observed in Fig. 4. The detectors are arranged in a ring configuration around the scanner's inside, where each detector has an associated detector on the opposite site, existing detectors comprising a scintillation crystal and a photomultiplier tube recently combined in arrays, known as detectors block.
Fig. 4. (a) PET Scanner: collision between an electron and a positron and resulting annihilation, creating two gamma rays that move in exactly opposite directions and its detection by the scanner surrounding the patient. (b) Detection of two photon approximately at the same time and considered as coming from the same annihilation: coincidence detection. (From Fahey, H. F., 2001)

The annihilation photons are detected using scintillation crystals, indicated in Table 4. 511keV gamma-rays interact with the crystal, exciting many of the electrons to a higher energy level. As the electrons return to the ground state, it emits a photon of visible light or near ultraviolet light. Since there are many electrons excited by each gamma ray, each one generates a shower of photons that is detected by a multiplier tube (PTM), which converts light into electric signal and amplifies it. At this point, the amplified electrical signal can then be processed and registered in a computer. So, the PET detector camera is constituted by a large number of small crystals that are coupled into a PTM matrix which amplifies the signal from the crystals.

Table 4. Common detector crystals and properties (Adapted from Fahey, F.H., 2001)

<table>
<thead>
<tr>
<th>Crystal Name</th>
<th>Density (g/cm$^3$)</th>
<th>Linear coefficient attenuation at 511keV (cm$^{-1}$)</th>
<th>Decay time (ns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaI Sodium iodide</td>
<td>3.67</td>
<td>0.34</td>
<td>230</td>
</tr>
<tr>
<td>BGO Bismuth germanate</td>
<td>7.13</td>
<td>0.95</td>
<td>300</td>
</tr>
<tr>
<td>LSO Lutetium oxyorthosilicate</td>
<td>7.4</td>
<td>0.88</td>
<td>40</td>
</tr>
<tr>
<td>LYSO Lutetium yttrium oxyorthosilicate</td>
<td>7.1</td>
<td>0.83</td>
<td>41</td>
</tr>
<tr>
<td>GSO Gadolinium oxyorthosilicate</td>
<td>6.71</td>
<td>0.70</td>
<td>60</td>
</tr>
</tbody>
</table>

3.2.3. Data Acquisition Modes

PET has various data acquisition modes, which may be implemented by reprogrammable architectures (Sportelli et al. May 2011). Temporal acquisition uses sonograms, exemplified in Fig. 5, that allow obtaining PET images built over time with the records of the number of events occurred in each LOR, where a larger number means less noise in the data. Depending on the type of data that is desired, it may be used different signal temporal acquisition modes.
The static mode allows to obtain a static picture, which can provide information about the radiotracer relative positions and hence its relative distribution, by storing data on a single occasion, forming a sinogram for each trans-axial plane.

The closed acquisition allows more functional information, using a periodic impulse signal (physiological signal as the electrocardiographic signal) so that the data recorded by the scanner are converted into sinograms based on the elapsed time since the last impulse and added to each period to reduce noise. The images are then reconstructed and displayed in cine-loop for medical analysis. This type of acquisition allows the study of contractile activity of the heart and surrounding processes.

Once the PET scanner ring has geometrical shape consisting in a ring of detectors, it is possible to record all LOR simultaneously, making possible image reconstruction in a short period of time - temporal dynamic acquisition. It starts with very short images which tend to increase its length as the radiotracer stabilizes. Thus, by acquiring a series of images over time, it is possible to follow the radiotracer movement immediately after injection. This analysis allows us to measure quantitative physiological parameters accurately.

The listmode records each event individually, including information such as its location, detection energy and time, generating a list of events. Although require more storage space data, it provides great flexibility in processing data and its analysis (Fahey, 2001).

In 2D and 3D acquisition, the approach uses single-slice rebinning (SSRB) (Turkington, 2001), with an introduction of absorbent materials septa such as tungsten between plans for the acquisition of 2D crystals, which requires methods of static image reconstruction. Without these materials, a 3D acquisition is obtained, as Fig. 6 shows, requiring image reconstruction methods assuming deterministic data (Ollinger & Fessler, 1997). Although it requires a greater storage capacity in terms of hardware, it provides a greater flexibility in the post-processing and image reconstruction (Phelps, ME, 2006; Boellaard, 2009).
3.2.4. Image Reconstruction Algorithms

The crystal size, positron range, photon acollinearity, intercrystal interaction and scatter, such as depth of interaction and reconstruction algorithms are fundamentals factors in the reconstructed image of the data acquired from PET scanners (Khalil, Tremoleda, Bayomy, & Gsell, 2011).

The PET reconstruction can be performed in 2D, where each data plane is treated independently and trans-axial plane is reconstructed one at a time, i.e., image reconstruction estimates the radiotracer density distribution through LOR data acquisition, plane by plane, matching reconstructed plans sequentially. The acquisition is then a uniform angular sampling, where the elements of each individual projection angle represent the full line of LOR issued, registering a sinogram array whose rows and columns represent the angular and radial samples.

In fact, the filtered backprojection (FBP) algorithm was the first to be used (Tarantola, Zito, & Gerundini, 2003; Muehllehner & Karp, 2006) because 2D provides an accurate radiotracer distribution using the Fourier transform of positions angle, and a simple and easy way to implement. The use of a ramp filter also amplifies noise, so the solution is to apply a smoothing filter. However, this leads to obtaining images with less spatial resolution and consequently blurred.

The iterative algorithms are based on an attempt to maximize and minimize a target function determined by an algorithm and obtained by iteration. Note that a high number of iterations leads to increased noise and image deterioration as well as the relaxing factor, which is why there needs to be a compromise between image quality and these factors (Muehllehner & Karp, 2006). Although requiring greater computational complexity hence the processing time, it can incorporate a lot of different information, such as noise, attenuation or non-uniformity characteristics of the detectors for a more accurate image. The maximum likelihood maximization (MLEM) and ordered subsets expected maximization (OSEM) are examples of such algorithms (Tarantola et al. 2003).

Depending on the algorithm chosen, the results are quite different, as Fig. 7 shows, comparing a FBP reconstruction against a OSEM algorithm.
In image reconstruction considering 3D algorithms, each LOR axial angle must be taken into account along with the geometric limitations of the scanner, and the whole volume of data is used to reconstruct the image. Due to the scanner finite axial extent, sampling is often incomplete.

To compensate these problems, it is used a set of 2D sinograms applying the SSRB method through the definition of LOR axially inclined to trans-axial planes intersecting them at the midpoints and has the advantage of using more sophisticated algorithms which allow to reconstruct the image with sharper distinctness as the FORE (Fahey, 2001).

The construction of 3D PET scanners allowed the improvement of image quality, but the algorithms have high computational complexity. The 3D-RAMLA is implemented in some commercial systems, based on substitution of voxels by volume elements spherically symmetrical, blobs, placed in a 3D grid, shown in Fig. 8, thus having the possibility of controlling the quality of the reconstructed image with a priori setting of amplitude and shape.

Other algorithms have been described in the literature, as well as weighted least-squares (Anderson, Mair, Rao & Wu, 1997; Markovsky & Mahmoodi, 2009), automatic segmentation algorithms that combine the input images in areas of interest (Cizek et al., 2004), nonlinear algorithms based on free-form deformation (Camara, Colliot, Delso, & Bloch, nd; Mattes, Haynor, Vesselle, Lewellen, & Eubank, 2003) and wavelet transforms (Unser & Aldroubi, 1996). Their appropriate choice is fundamental, since they are an influencing factor in the three-dimensional segmentation of PET volumes (Daisne et al., 2003).
However, the literature on optimal alignment is relatively limited due to the specifications of each manufacturer and type of scanner, making it not easy to generalize. Furthermore, depending on the capabilities of certain place, different levels of accreditation must be defined, which means that the PET centers should be encouraged to high quality workable standards (Boellaard, 2009).

3.2.5. Image correction

The magnitude of the signal measured by the scanner depends on factors such as the interaction of annihilation photons with the patient and the response of the components and configuration of detectors, always demanding the application of corrections.

The block of uniformity correction compensates the differences in sensitivity of the detector block, element by element, i.e. as the sensitivity of PTM varies in its front face and the sensitivity is reduced in the spacing between the elements they do not respond by the same way to incident radiation. It obtains a block detector uniform map, thereby correcting the variation of sensitivity. Similarly, differences in gain between the detector blocks are also normalized using a normalization source.

Respecting problems of geometry and sensitivity, the number of different LOR accepted causes variation in sensitivity of the scanner, plane by plane, along the field of view and can be corrected by measuring a uniform cylindrical source or line, which is then used to calculate the relative sensitivity of each plan and its appropriate resize - geometric correction (Levin, 2008).

As the activity in the scanner view field increases, the rate of incident photons on the detector increases linearly and thus the number of events that must be processed. At the start of scan, activity levels are high and need to be measured accurately to trace acceptable time-activity curves. However, during the time that the crystals are slow to return to the ground state after absorption of the crystals, the detection system is unable to detect new photons, resulting in dead time, which translate into lost event count. By early measuring, the camera response for activities is increasingly high; so it is possible to determine the dead time losses, which in turn compensates this effect.

Random events cannot be avoided, but they can be compensated using a measuring delayed window or second coincidence window, similar to the first one in width, with an offset time fairly large. The photons that are registered in this window does not belong to the same annihilation of the previous window and therefore allow random coincidences rate directly measured, which is then subtracted from the measured signal in the first coincidence window to compensate random events. Another solution is to calculate the random rate: the number of random events detected by a pair of crystals is related to the detection of single events rate. The random rate is given by equation (1), where $R$ is the random rate, $r$ is the temporal resolution, and $S_1$ and $S_2$ are the only event rates of the two elements detectors.

$$R_{12} = 2rS_1S_2$$

(1)

The scattering events, shown in Fig. 9, are recorded by dispersion rates which indicate the respective number of occurrences divided by the sum of true and scatter events. The
techniques for correcting these events consist in a way of estimate the dispersion and then remove it. The estimation can be done by methods based on energy windows from sinograms or based in the activity distribution estimation while the removal is done by subtracting the estimated dispersion sinogram, reconstructing the data as image dispersion and finally including that rate at the reconstruction algorithm.

Fig. 9. Coincidence events occurred in a PET scanner: true (A), scatter (B) and random events (C) (From Tarantola, G., Zito, F., & Gerundini, P., 2003).

Attenuation is the loss of true events due to scattering and absorption: once two photons must be detected to define an event as true coincidence, there is much greater chance of this being attenuated, there is thus an excessive loss event count, which results in an increased noise and not exact quantification of the radiation distribution. Another effect of attenuation is to introduce non-uniformities in the reconstructed image, since the radiation is strongly attenuated within the body, but not on the surface. Two approaches can be taken for its correction: the correction calculated assumes that the outer contour of the body can be known and that within this attenuation is constant and so the outer contour is determined automatically from the data set or through an operator using an image without attenuation correction; measuring the attenuation is carried out with an additional scan, whose transmission uses a radioactive source and detectors of the PET scanner to measure the attenuation of the body along the LOR. The attenuation correction is essential, and without this the variation of the reconstructed image density is significant and there is less intensity in the center of the image (Crepaldi & De Pierro, 2007). The effect of this correction applied to different image reconstruction can be observed in Fig. 10.
In the case of dynamic images, it is also necessary to count the radioisotopes decay. Since each image is acquired at different instants, the sign of radioisotopes with short half-lives decay significantly altering the appearance of images and distorting physiological changes, which, after reconstruction, is typically compensated through a decay correction in image values backing to the acquisition start instant.

The absolute calibration should also be made to translate the number of counts observed in the view field when large existing activity is carried out through the image acquisition of a water cylinder with a quantity of known activity and uniformity in its interior, obtaining then the derivation of an appropriate scale factor.

As the resolution of PET increases, the image degradation increases due to patient movement, which requires alignment algorithms of reconstructed images to reduce their effects, by rebinning techniques about sinograms acquired in listmode along the head position or by using a look-up table to select the location sinogram to the appropriate head position in real time. Picard & Thompson (1997) developed a new method based on the acquisition of multiple frames. Also the analysis of dynamic PET is possible using Sparse Bayesian Learning (Peng, Aston, Gunn, Liou, & Ashburner, 2008) or compensation intrinsic movements methods on the measured data, using deformable alignment or optical flow techniques, and yet problems related to motion estimation, which is based on noise frames of motion (Blume, Martinez-Möller, Keil, Navab, & Rafecas, 2010).

### 3.2.6. Noise-Equivalent Count Rate (NECR)

Despite the various possible corrections, it is necessary to remove the noise associated with the measured signal, i.e., random variations in the intensity of pixels, shown in Fig. 11.

The sound is an expression of count rate required to achieve a given level of noise (uncertainty) in the correction of the data given by equation (2) where \( T \) is the true event rate, \( S \) is the scattering events rate, \( R \) is the random events rate, \( f \) is the view field occupied by the patient or object containing radioactive sources and \( k \) is equal to 1 or 2 depending on the random events correction method (Herraiz, España, Udias, Vaquero, & Desco, 2005).

\[
\text{NECR} = \frac{T^2}{(T + S + kfR)} \tag{2}
\]
Fig. 11. NECR: Contribution of total prompt events detected in a PET scanner as activity increases (Fahey, 2001).

3.2.7. Spatial Resolution

The resolution of PET is determined by a combination of factors. The point of interaction of the gamma ray is located within a crystal element and the accuracy of that location depends on the dimensions thereof. The resolution loss caused by crystal size is smaller in the center and falls as the point of annihilation becomes closer to the face of the crystal, where the uncertainty becomes equal to the size of the crystal. Thus, a crystal of 4mm introduces an error of 2mm at the center of the scanner. Therefore, these crystals are not the same size in both axial and trans-axial directions, leading to different resolutions on the plane and off.

An additional factor which significantly degrades the resolution is called the effect of depth of interaction (DOI), shown in Fig. 12. When an event is detected in a crystal, the DOI is unknown; then it is assumed that the photon detector entered the ring on the same crystal which was detected (knowing that the photons do not reach the crystals always perpendicular). The point of interaction is then placed on the surface of the incorrect crystal, leading to a wrong positioning of LOR. This effect worse as the LOR moves from the center of sight because there are more possible LOR at angles of 90° and is therefore seen as a distortion of the crystal size that increases the radial position as the annihilation events increase.

When an electron and a positron collide, it may retain some residual time; therefore, to save time, the two photons cannot move in directions exactly opposite, i.e., less than 180° between them, resulting in the effect of non-collinearity.
The positron range is a statistical measure of the distance traveled from the positron which separates the atom till the annihilation and differs from isotope to isotope; the smaller is this range, the smaller the degradation caused in the image.

The resolution of the system is the combination of all these effects. Equation (3) allows calculating the resolution of the system. Note that the DOI effect is included as a modification of the detector element size and therefore the resolution of the detector \( R_{\text{detector}} \). All effects of the components depend on the radial distance from the center of the scanner and thus the resolution changes with the radial position.

\[
R_{\text{sistema}} = \left( R_{\text{detector}}^2 + R_{\text{non-collinearity}}^2 + R_{\text{gamma}}^2 \right)^{\frac{1}{2}}
\]  

(3)

3.2.8. PET Multimodalities

The great disadvantage of functional PET imaging is the fact that it has relatively low resolution, leading to a lack of anatomical information and then the anatomical location of some lesions are often limited. For this reason, multimodalities have been developed.

PET/CT multimodality, shown in Fig. 13 and Fig. 14, is a reality, as it brings together the anatomical accuracy of CT with metabolic PET (Cohade, Osman, Marshall, & Wahl, 2003). However, this involves several problems because the PET acquisition is often deformed days after a CT scan, causing repositioning may not be as accurate and lead to displacement of internal organs, and that during CT, patients must hold arms over the head, hold breath to reduce the effects of attenuation and beam hardening, but due to the time of performance of PET, it is not feasible (Namdar et al., 2005). All these factors can result in major changes to body profiles and in body position of the organs, causing the fusion of these modalities very difficult, even with alignment programs and innovative models for 3D elastic images transformations of the thorax.

To solve these problems, CT and PET studies are acquired sequentially during the same scan, ensuring the same profile of the bed, not repositioning, and in very short time.
interval between two acquisitions, as well as the attenuation correction of PET emissive images, consisting of a first segmentation of CT images to separate soft tissue from bones, followed by the application of different scale factors for energy equivalent to 511keV (Tarantola et al., 2003).

![Fig. 13. (a) Scanner PET / CT schematic. (b) Individual and simultaneous PET and CT scan images. (From Wacholtz, E. H.)](image)

These systems are commercially available by the trademarks CTI, Siemens, GE, and Phillips. However, the high price can be reduced since it is possible to avoid data acquisition duplication and image reconstruction functions, as well as a more integrated design (Townsend, 2003).

![Fig. 14. 18F-FDG image of a patient with colorectal cancer: CT image (left), fused PET/CT (middle) and PET image (right) (From Pimlott & Sutherland, 2011).](image)

The modalities integration of PET and MRI (magnetic resonance imaging) is also being heavily used as a new integrated approach to functional and morphological imaging. As CT, MRI provides high resolution anatomical information, allowing a wide variety of tissue contrast, diffusion imaging, spectroscopy and functional magnetic resonance. Unlike CT, which presents a limited soft tissue contrast and high dose radiation, the combination of
PET/MRI does not require ionizing radiation and has an excellent soft tissue contrast with flexible scan protocols. Thus, both the acquisition of various functional parameters and high anatomical resolution create enormous potential and offer new opportunities to study pathological and biochemical processes in vivo, which with the separate technologies is not a possible examination.

The integration of MRI and PET is a challenge, since PET devices are composed of PTM, which are extremely sensitive to magnetic fields. As a solution, it is possible to use optical fibers to conduct the flickering light out of sight or MRI view field, which ensures the reduction of interference from magnetic fields, radio frequency and gradient (Pichler, Judenhofer, & Wehrl, 2008).

The attenuation correction can be applied to different methodologies (Hofmann et al., 2009), using methods based on the combination of local pattern recognition and atlas alignment (Hofmann et al., 2008).

3.2.9. Clinical Applications

Currently, clinical applications of positron emission tomography are recommended in various specialties, as it allows the analysis of whole body and multi-organ, with emphasis on oncology, cardiology and neurophysiology.

In oncology, the application to perform this additional diagnostic system has grown significantly since PET can be a more accurate technique for diagnosis, with fewer surgical procedures, development stage and treatment decisions as well as the respective evaluation, reducing the cost of unnecessary treatments (Strauss & Conti, 1991). Cancer is a systemic pathology, whose result ends with the appearance of metastasis. The completion of the medical PET examination, most of the times PET / CT (Kluetz et al., 2000; Beyer, Townsend & Blodgett, 2002; Been et al., 2004, Fox et al., 2005; Gerasimou et al. 2006) permits the detection of tumors at an early stage, since it is capable of detecting and analyzing the development state of cancer (Lodge et al. 2000; Beyer et al. 2000), using FDG as a marker of metabolic processes in all organs (Conti et al. 1996; Fletcher, et al. 2,008; Varagnolo et al. 2000; Macfarlane et al. 1995; Nestle, Kremp, & Grosu, 2006) and subsequently a proper choice to carry out the treatment and evaluating the therapeutic response (Ambrosini et al., 2012). The lung cancer (Greco & Rosenzweig et al., 2007), head and neck (Lindholm et al. 1993; McGuirt et al. 1998) and detection of melanoma and lymphomas (Schröder, Larson & Yeung, 2004) are examples of PET case studies.

In cardiology, PET allows the assessment of myocardial viability in coronary patients, allowing a more accurate selection of patients for revascularization procedures, avoiding the need for angiograms, angioplasties and bypasses (Schwaiger & Hicks, 1991; Namdar et al. 2005). Several studies have been developed (Jaffer, Libby & Weissleder, 2007), particularly in the study of chronic ischemia (Kühl et al., 2003, Haas et al. 1997), perfusion (Schwitter et al. 2001; Maes et al., 1994, Ross, 1991, Wu et al. 2,007; Bonow, 1991; Wagner et al., 2003), atherosclerosis rate (Sanz & Fayad, 2008; Rudd, 2002), angiography (Di Carli et al., 2007), microcirculation (Kaufmann et al. 2000), post-transplantation (Bengel et al. 1999), cholesterol (Gould et al. 1,994), coronary flow (De Bruyne et al. 1994; Kuhle et al. 1992), sarcoidosis (Okumura et al. 1989), coronary nervous system evaluation (Goldstein et al. 1990; Schwaiger, et al. 1990; Araujo et al. 1991), as well as the movement of stem
cells that influence heart diseases (Frangioni & Hajjar, 2004). However, there is still a majority consensus among physicians regarding the role of PET in cardiology (Hesse & Lindhardt et al., 2008).

As regards the neurological and psychiatric disorders, PET has the ability to reveal no detectable lesions in anatomical examination, providing information on the physiological and biochemical properties and subsequent determination of the functional integrity of the regions adjacent to brain damage (Jueptner et al. 1995; Theodore et al. 1986; Tai, & Piccini, 2004). The pre-surgical evaluation of partial epilepsy, guided biopsy in brain tumors, evaluation of primary brain tumors, dementia diagnosis and selection of stroke patients for surgical treatment are the main applications, allowing the study of Parkinson’s disease (Rosenberg & Neil et al. 1989; Whone et al. 2003; Doder et al. 2003; Khan et al. 2002), Alzheimer (Rowe et al. 2,008; Edison et al. 2,007; Mega et al. 1997; Dubois et al. 2,007; Herholz et al. 2002; Villemagne et al. 2,013; Samson, 2013; Buckner et al. 2005; Kadir et al. May 2011), amyloid disease (Okello et al. 2,009), dystonia (Kumar et al. 1999), cognitive impairment (Kemppainen et al. 2,007; Mosconi et al. 2004; Belin et al. 1996; De Leon et al. 2001; Jagust et al. 2,007), epilepsy (Gaillard et al. 1995; Muzik et al., 2000, Juhasz et al., 2001, Juhasz et al. 2000; Toczek et al. 2003) and movement disorders (Ruottilen et al. 2000; Turjanski, Lees & Brooks, 1999; Cappa et al. 1997; Brooks et al. 1992; Chugani et al. 2004).
3.3. Single Photon Emission Computed Tomography

After the Anger camera, with the capability of enhance the gamma ray detection efficiency, the longitudinal emission tomography, i.e., focal-plane tomography, that could not provide an artifact-free image, the transaxial section tomography with a discrete detector approaches, using a translate-rotate motion of the detectors, or using multiple Anger scintillation camera or even using stationary detector configuration had been important contributions to the development of the single photon emission computed tomography that has increased in the 60’s, such as PET. However, it just became truly popular when the rotating gamma cameras for SPECT were widely explored. Then, the multinational medical imaging companies started to took up the technology in a big way. The use of HMPAO as a radioactive drug with tomography to image blood flow in the brain had shown the potential of this technology to clinical applications such as Alzheimer’s dementia, movement disorders, ischemic heart disease, stroke, epilepsy and brain tumors.

Also 3-D algorithms’ development were fundamental to the evolution of SPECT till nowadays, that had been tried before the digital era, using a radioisotope distribution and consequent subtraction of count from over- and underlying structures, which has proven impractical by the use of a computer to calculate de 3D images. Without improvements of the Anger camera with a rotating collimator attachment, giving tomographic images and processed with analogue electronics and record on Polaroid film to show four longitudinal slices simultaneously, it was not possible to improve the low contrast characteristic of the blurred SPECT images. So, the use of FBP is often applied.

The high-speed digital computer system for the acquisition and display of dynamic processes in the body such as the development of high-speed dynamic radionuclide, dual- and triple-camera contributed to a final result of deep research of four decades in the multiple areas of knowledge implied that is a molecular image that “uses time as an additional coordinates, by collecting different information as a function of time and translating this into special information” (Muehllehner G, 2006), making it a valuable diagnostic imaging modality (Jaszczak, 2006).

3.3.1. Radiotracers

In single photon emitting radiopharmaceuticals, it must consider its cost and the wide availability of the radioligands as a relative ease of labeling consisting of the consumption of oxygen, causing in SPECT the ability to detect and monitoring biological and pathophysiological processes, using radiolabeled peptides and drugs (Pimlott & Sutherland, 2011).

The radiotracers used can be classified as:

- Radiolabeled molecular imaging probes (RMIPs), including endogenous molecules and exogenous probes, that are highly specific radiolabeled that allow the visualization, characterization and measurement of biological processes in living systems, that must be design and chosen depending on the organ of study; this way, they are classified based on their utility and nature of application, what result in radiolabeled drug substance, radioligands (Meyer & Ichise, 2001), pathway marker and biomarkers.
- Peptides and proteins are also radiotracers; within this group we can find radiolabeled monoclonal antibodies (MAbs) which are immunoglobulins produced in vivo in response to the administration of an antigen and its specifically binding forms an antigen-antibody complex, $^{99m}$Tc-labeled monoclonal antibodies, sulesomab, annexin V and radiolabeled peptides.
- RMIPs for metabolism that allow achieving metabolic imaging using natural or exogenous radiolabeled substrates as glucose metabolism, amino acid metabolism and nucleosides metabolism.
- Hypoxia imaging and cell labeling are also used radiotracers, but in a less number of applications.

Table 5. Commonly used single photon emitting radionuclides (Adapted from Khalil et al., 2011).

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Energy</th>
<th>Mode of decay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc-99m</td>
<td>6.92h</td>
<td>142keV</td>
<td>Isometric Transition (100%)</td>
</tr>
<tr>
<td>I-131</td>
<td>8.03 days</td>
<td>364keV</td>
<td>Beta-minus (100%)</td>
</tr>
<tr>
<td>I-123</td>
<td>13.22h</td>
<td>159keV</td>
<td>Electron Capture (100%)</td>
</tr>
<tr>
<td>In-111</td>
<td>2.80days</td>
<td>171,245keV</td>
<td>Electron Capture (100%)</td>
</tr>
</tbody>
</table>

The radiopharmaceuticals used in this molecular imaging contain long-lived radioisotopes emitting gamma rays, such as $^{99m}$Tc, as the Table 5 shows, that decays through an isometric transition, i.e. a nuclear deexcitation resulting in the emission of a gamma ray or an electron by the process of internal conversion. So, the contrary of PET occurs and the radioisotopes are metastable characterized by long lifetimes making them appropriate for in vivo imaging.

### 3.3.2. Detectors

Such as PET, a biomarker, highly specific with sensitive characteristics to properly study the molecular or cellular phenomenon, and an imaging device, consisting in a radiation detector with specific performance to localize the activity distribution within the human body as the Anger gamma camera which is a gamma ray position sensitive detector with crystal scintillators having position circuitry and energy determination, are the key element in SPECT since it is a radionuclide imaging technology (Jaszczak & Coleman, 1985; Rahmim & Zaidi, 2008).

The detection principle of gamma radiation is the same as PET, but the collimation principle is different (Rahmim, 2006), i.e. SPECT collimators are a mechanical structure made of high-Z material, which enhances the absorption of the oblique gamma rays, allowing the passage of radiation through the collimator openings, and its geometries varies in parallel hole, pinhole, converging and diverging with various hole geometries. So, it allows estimating the trajectories of the detected gamma rays that have been subjected to Compton scattering inside the patient's body. It is reduced and limits the background in the reconstructed image, through the setting of a lower limit to the achieved spatial resolution and sensitivity.

As said above, pinhole collimators of very small aperture size are used in a gamma camera, the main detector module of SPECT imaging device, providing a large field of view, or a
pixilated detectors with intrinsic properties or semiconductor detector. The bigger is a field of view, the most improvement of magnification the gamma camera does, through providing large projection area onto the detector surface, but when pixilated detectors with intrinsic resolution are equivalent to the segmentation size, it is necessary to use detector width of size equivalent to the standard clinical gamma camera.

The design of those detectors include rotating gamma camera, stationary detector and interchangeable multi-hole collimators, which have a cylindrical shape with large number of pinholes, but rotating collimators or completely stationary camera, but it depends on the camera trademarks specifications, such as Siemens, Gamma-Medica and Bioscan. Fig. 15 presents different configurations of detector in gamma cameras.

Summarizing, a gamma camera has as key elements a collimator, a scintillation crystal, usually a continuous NaI(Tl), a light guide to collect efficiently the scintillation of light and distribute it among a number of PTMs, close-packed positioned, through its sum of signals acquires the energy information and a centroid algorithm determines the position of interaction of the gamma ray within the crystal.

![Fig. 15. Different configuration of detectors in gamma camera: single head (a), two orthogonal heads (b), two opposed heads (c), three heads (d), four heads (e) and multiple small-FOV scintillation detectors (From Spanoudaki & Ziegler, 2008).](image)

Dedicated sodium iodide detector cardiac, dedicated upright and semi-reclining cardiac, cardiocentric, cardio-focused collimation, art detector geometry with rotating slit-hole collimation, multiple scanning parallel-hole collimators, multi-pinhole collimation such as solid-state detectors, indirect and direct solid-state detectors are some of the innovations in gamma cameras lately (DePuey, 2012; Peterson & Furenlid, 2011).

### 3.3.3. Deterioration factors and corrections

Attenuation, scatter and resolution effects, such as motion artifacts are degradation factors of SPECT imaging, which can be improved with the use of multimodality systems as SPECT/CT.

As PET degradation factors, the attenuation in SPECT modality is the most important factor of influence in spatial resolution, so the attenuation coefficients within the patient
must be known, whose map is incorporated into an iterative algorithm such as OSEM, also used in PET. Besides the application of attenuation correction algorithms, the use of a CT scanner able the image noise at the attenuation map become lower, due to the less noise of CT image, faster acquisition, higher flux and are not influenced by cross-talk from the SPECT radionuclide. However, its higher resolution implies fewer accuracy of the attenuation compensation. It can be done converting CT images in attenuation coefficients through segmentation, scaling or hybrid techniques (O’Connor & Kemp, 2006).

The precision and noise in the attenuation correction also depends on the emission and transmission statistics, since that noise in the transmission emission and attenuation coefficients propagate into the images and the attenuation coefficients derived from the transmission image increase bias and noise as source decays, requiring that sources transmissions must be replaced frequently to maintain properly the transmission statistics. This way, it allows having noise propagation at minimum values and ensure that the emission contamination do not overwhelm the transmission counts (Rosenthal et al., 1995).

Another way to apply attenuation correction is the use of algorithms capable of remove the cross-contamination between the emission and transmission photons, whose simultaneous acquisition of emission and transmission data eliminate the misregistration between SPECT data and attenuation maps. The distance-dependent attenuation can also be eliminated through the acquisition of the projection scans for a complete rotation of the detector head, combining the measurement of opposing projections.

The Compton and Rayleigh (coherent) scattering is also a common problem and depends on the energy of the emitted photons, making the photon to be deflected from its initial trajectory but still being detected from another detector or even never detected, and on the composition of the material through which the photons are travelling. The compensation can be made without correction through minimizing the amount of scatter, modified attenuation correction, filtering, or based on measurements, as dual and triple energy window corrections, spectral models, or even based on modeling the scatter distribution, using analytical models based on Klein-Nishina scatter equations, transmission-dependent convolution subtraction, object shape or slab-derived scatter estimation and reconstruction-based scatter correction including incorporation of fast Monte Carlo scatter estimation. Incorporating multiple energy windows using multi-radionuclide SPECT and multi-energy radionuclides are other valuable scatter corrections (Hutton, Buvat & Beekman, 2011).

The sensitivity, already talked about previously, is dependent on the material used and the thickness of the crystal, such as the geometry and material of mechanical collimation, which means that a scintillator stopping will be increased with the use of long crystals and then the number of detected events.

The dead-time losses and pile-up effects, dependent on processing electronics and systems’ detectors, cause underestimation of counts and can be compensated through mathematical models based on a count rate measure covering the anticipated activity levels.
Note that a routine quality control of SPECT instrumentation is fundamental to detect changes in performance from a baseline condition, including a comprehensive suite of individual measurements to ensure adequate sensitivity to detect detrimental changes. So it should not be burdensome, reflect the clinical use of the system, emphasize measures about the system stability and reflect the system state adequacy to the clinical use (Hines, et al., 1999; Hines et al., 2000; Zanzonico, 2008).

### 3.3.4. Image reconstruction algorithms

Image reconstruction in tomographic radionuclide-based systems is based on measured estimation of the integral of radiotracer distribution and the algorithms used are the same of PET, to produce a volume representation of the radiotracer distribution inside the patient’s body.

The acquired data is organized as number of counts along each LOR, that is the radial extension of the collimator hole across the FOV in SPECT systems, for each projection, into a 2D matrix that contains the number of count of every LOR at each angular view, the sinogram, that are then used as reconstruction algorithms input in order to generate the final image.

Such as in PET, FBP has been used as an analytical reconstruction algorithm, that model the measurement of radiotracer distribution calculated analytically, backprojecting and filtering homogenously each LOR, but statistical iterative techniques that solve many problems of diagnostic quality and quantitative accuracy that, with analytic approaches, would not be possible, compensating the inaccuracies introduced to the image. Iterative methods start with an estimate of the tracer distribution and compute the forward-projection, comparing calculated and measured projections; then, the image is updated according to the differences found. Some examples already referred in this monograph are MLEM and OSEM, the most widely used iterative algorithms.

The WBR is a noise compensation technique that suppresses noise and enhances the signal-to-noise ratio through modeling the statistical characteristics of the emission process and of detected data, counting for the Poisson distribution, what able this algorithm to regularize the likelihood objective function adding a Gaussian component, being an iterative and automatic algorithm (DePuey, 2012). While the application of Gaussian components results in suppressed high-frequency components presented in the projections, the Poisson component results in the recovery of high-frequency signal; then, the balance between them is adaptively and automatically determined according to the data analysis and desired smoothness.

Other methods as Maximum A Posteriori (MAP) suppresses the impact of noise, using a modified one step late (OSL) algorithm with a Green prior optimized for each clinical protocol and for gated and attenuation corrected image and a Median root prior as last iteration (DePuey, 2012). More iterative algorithms commonly used are algebraic reconstruction techniques (ART), multiplicative ART (MART) and weighted least-squares conjugate gradient (WLS-CG) (Erwin, W., Online).

An adequate filter such as the cut-off frequency is fundamental to obtain the optimal resolution and noise level in reconstructed images. The blurring effect can also be reduced
with modeled edge penetration (Bouchara & Ramdani, 2007) and parallax errors in the reconstruction scheme (Khalil et al., 2011).

3.3.5. Spatial Resolution

The spatial resolution of this type of cameras can achieve a sub-millimeter range, being even possible sub-half millimeters when it is used a specialized dedicated multi-pinhole geometry, a function of the object distance from the aperture and its distance from the detector surface, by minimizing the aperture size and specialized collimator geometry. However, it causes a reduction of detection efficiency, partially tackled by increasing the number of holes, and of the image field of view, such as insufficient data acquisition.

The better SPECT resolution when compared to PET is due to the fact that SPECT systems are not affected by physical and fundamental limits as PET is, but a new design of semiconductor system can provide a better spatial resolution.

Besides that, how SPECT collimation is geometrical, spatial resolution depends on the distance between the source and the detector head, leading to distortions in the image if the process of reconstruction is not taken into account, a problem that can be minimize with the use of reconstruction algorithms as descriptions of the resolution degradation based on measurements.

Consequently to a limited spatial resolution, a partial volume effect appears that corresponds to the bias introduced on the estimation of the radiotracer concentration and depends on the size and shape of the object, such as the relative radiotracer concentration with respect to the surroundings. It can be minimized with a large object's size and its compensation is needed when the acquisition of quantitative information about the radiotracer distribution is wanted.

Respiratory, cardiac and patient motion can be compensate with a number of gated acquisitions realized for every breathing or cardiac cycle to produce a reconstructed image correspondent to a specific time frame.

3.3.6. SPECT Multimodalities

Molecular SPECT imaging provides functional images with high spatial resolution but anatomical correlation using structural imaging modalities is needed, as in PET modality. To solve this problem, SPECT/MRI, SPECT-optical devices and SPECT/CT are used to extract more biological information with the same spatial and temporal framework, such as higher anatomical image resolution that generates a subject-specific attenuation map to correct photon attenuation and a better soft tissue contrast. This way, image fusion from different modalities images can aid in the decision making process, once it enables a better localization and definition of organs and lesions such as improves the precision of surgical biopsies, as exemplified in Fig. 16.

Respecting the software approach to image fusion, a considerable work has been done on the development of algorithms for the co-registration of anatomical and functional images, making them more robust and accurate, providing accurate registration, using feature-based or volume-based. Those algorithms are fundamental to avoid misregistration due
to patient motion and breathing artifacts, such as the fact that the acquisition of SPECT and CT or MRI data must be sequential.

In SPECT/CT multimodality, there are scattering problems, truncation and beam hardening artifacts, besides misregistration between the emission and transmission in data, resulting on incorrect matching of the attenuation map to the emission data and due to sagging of the emission table, respiratory and cardiac and patient motion. To minimize the effect of table sagging, the SPECT/CT systems employ a dual-table configuration whose patient pallet is a low attenuation carbon fiber tabletop, sited on top of a second lower table, more rigid. Respiratory and cardiac motions are more complicated to solve, such as in the PET/CT imaging, once that CT is affected by these motions. So, it is fundamental SPECT/CT systems use a co-registration program to ensure correct alignment, associated with a quality control (QC) program to allow the re-alignment of different modalities images in manual or semiautomatic mode. Quantifying coronary artery calcium, evaluating the patency of vascular and coronary arteries and assessing myocardial perfusion such as viability in one clinical setting are some of the multiple applications where SPECT/CT has been applied, but it is necessary it becomes more available in the market what requires lower costs.

Fig. 16. Detection of liver abnormalities using CT (on the left), SPECT (on the middle) and fused SPECT/CT (on the right) (From Jacene, Goetze, Patel, Wahl, & Ziessman, 2008).

In the last few years, integrated SPECT/CT systems have been widely used but MRI presents specific advantages compared with CT such as lack of ionizing radiation, high soft-tissue contrast and sensitivity to tissue alterations evidenced by specific imaging sequences. However, using SPECT followed by MRI in clinical applications is a complicated task (Chen, C. L., Wang, Y., Lee, J. J., & Tsui, B. M., 2009), once it requires the transfer to another system table and inherently separate dual-modality scans, followed by image fusion, are also potential sources of misalignment due to uncontrolled movements and displacements of tissues and organs as said about integrated PET systems. Multiple anesthesia sessions are needed when SPECT and MRI devices are located in separate places, what involves a greater risk to the patient due to different biologic responses to anesthesia. Attempting to compensate these problems, there are studies using SPECT followed by low spatial resolution MRI and also SPECT/MRI performed at very high magnetic fields to achieve high anatomic resolution benefiting from a higher signal-to-noise ratio but leading to field susceptibility artifacts and preventing closer proximity of SPECT scanner (Goetz, Breton, Choquet, Israel-Jost, & Constantinesco, 2008; Weber, D. A., & Ivanovic, M. (1999). Hence, it is needed to minimize technical limitations of SPECT/MRI dual imaging, such as enhance registration methods (Pfluger et al., 2000). Prototypes are being constucted to allow the minimization of all these problems to apply dual modalities in clinical application, besides the many applications in pre-clinical applications (Stokking,
Zuiderveld, Hulshoff Pol, van Rijk, & Viergever, 1997; Azman et al., 2007; Booij et al., 2003; Breton et al., 2007).

This way, integrated SPECT systems "enables a direct correlation of anatomic information and functional information resulting in better localization and definition of scintigraphic findings" (Bhargava, P., 2011).

3.3.7. Pre- and Clinical Applications


The preclinical application in SPECT leads to consequent applications in clinical cases, usually the same areas as PET and the state-of-art of all the cases study is enormous (Bailey & Willowson, 2013; Bhargava, He, Samarghandi, & Delpassand, 2012; Erwin, W., Online; Mariani et al., 2010). In oncology, it permits the detection of tumors at an early stage, since it is capable of detecting and analyzing the development state of cancer (Even-Sapir, E., et al., 2006; Schirrmeister, H., et al., 2001; Römer, W., et al., 2006; Lerman, H., et al., 2006; Yamamoto, Y., et al., 1998; van der Ploeg, I. Met al., 2007; Sodee, D. B., et al., 1998; Bockisch, A., et al., 2009). In cardiology, it allows the assessment of myocardial viability in coronary patients, allowing a more accurate selection of patients for revascularization procedures (Rispler, S., et al., 2013; Botvinick, E. et al., 2013), through the evaluation of myocardial perfusion (Gewabsource, Online; Nichols, K., et al., 2001; Sandler, M. P., et al., 1998; Jaarsma, C., et al., 2013; Ben-Haim, S., et al., 2010; Cuocolo, A., et al., 2010). In neurological and psychiatric disorders, SPECT has an important role in the study of Parkinson's disease (Catafau & Tolosa, 2004; Nocker, M., et al., 2012; Hattori, N., et al., 2013; Rossi, C., et al., 2010; Scherfler, C., & Poewe, W., 2011), Alzheimer(Fung & Stoeckel, 2006; Chen, Y. J., et al., 2012; Habert, M. O., et al., 2011) epilepsy (La Fougère, Rominger, Förster, Geisler, & Bartenstein, 2009), brain dementia (Ryding, 1996) and movement disorders (Kägi, G, et al., 2009; Kägi, G, Bhatia, K. P., & Tolosa, E., 2010; Di Giuda, D., et al., 2012).
3.3.4. Conclusions

Despite the satisfactory resolution and quality of images, research is ongoing to develop improved instrumentation and new software for improved performance, to reduce cost and make the system more user-friendly. The high price of the technology and the technical and operational complexity serves as a barrier to expand the access to specialists and patients. Thus, despite the immense potential of this technology, these disadvantages require a clear definition of their usefulness in all fields of medicine.

In the last two decades, the greatest changes have been improved spatial resolution by decreasing the crystal size and there was also a significant progress in image quality by combining 3D reconstruction algorithms and attenuation correction, to enhance temporal resolution capabilities and get a maximum artifact-free imaging modalities, such as from dual-tracers imaging and the use of specialized collimators in the case of SPECT. Co-registration with images from complementary modalities has been employed in nuclear medicine acting as an adjunct to interpret functional nuclear medicine images, as well as offering the ability to overcome some intrinsic limitations.

We are currently witnessing an increasing convergence in the combination of structural and functional data, most notably in the development of dual modality imaging devices. Even with single modality devices, further developments of algorithms and software to enhance the information provided in combination with other complementary data must be close. The applications and use of image registration in nuclear medicine at the near future will include correlative image interpretation, attenuation correction, scatter correction, correction for limited resolution, improvement of reconstruction accuracy in emission tomography, co-registration of serial functional studies, transformation to standard space for comparison with normal studies, transformation to standard space for comparison with data from other modalities, conformal radiotherapy treatment planning and functionally guided biopsy.

Respecting to multimodalities, PET/CT has been widely clinical used and already had a valuable outcome on clinical oncology practice and cancer treatment and SPECT/CT systems use is increasing slower due to its high cost and taking into account the low fraction of clinical indications, since nuclear medicine can only benefit from such evolving integration, in which image registration plays a central role.

Due to the functional diagnosis that molecular imaging provides, SPECT and PET will maintain its applications in clinical diagnosis, assessment of response to treatment and delivery of targeted therapies, being fundamental to decrease its costs, becoming more accessible.
4. FINAL CONCLUSIONS AND FUTURE PERSPECTIVES
4.1. Final Considerations

Most current algorithms for medical image registration use rigid body transformations or affine transformations, but they are restricted to parts of the body where tissue deformation is small compared with the desired registration accuracy, what makes them appropriate to images of the head once mass deformation is constrained by the skull.

To inter-modality registration, the most accurate algorithms are based on optimizing a voxel similarity measure and information theory based. These algorithms can be applied automatically to a variety of modality combinations for inter- and intra-modality registration, without the need of pre-segmentation the images and can be extended to non-affine transformations.

Inter-modality registration is still unusual in the clinical setting but image registration is being widely used in medical research, especially in neuroscience where it is used in functional studies, in cohort studies and to quantify changes in structure during development and ageing. However, its routine clinical use maybe the logistical difficulties due to the need of acquire and register a lot of images in the same computer in a few interval of time, what requires a more integrated infrastructures.

Those problems are being minimized with the integration of patient text-based and image information to produce multimedia electronic records, accommodating an easier and efficient image registration process. Another reason for the lack of clinical use of image registration might be that traditional radiological practice can provide all the necessary information for patient management, and registration is unnecessary. However, the increasing data generated by successive generations of scanners will steadily increase the need for registration to assist the radiologist.

The increasing use of dynamic acquisitions will necessitate the use of registration algorithms to correct patient motion and, consequently, non-affine registration methods must be developed to enhance the monitoring of changes due to disease progression and response to treatments.

This way, image registration has a potential to aid in diagnosis, surgery and therapy. Some examples are the combination of functional and high resolution anatomical information as an aid to diagnosis with better localization and determination of extent of abnormalities, planning treatment and surgeries, once it provides a more specific irrelevant information as multimodalities as PET/CT, PET/MRI or SPECT/CT and SPECT/MRI. Besides that, differences can be more directly quantified, providing more objective evidence of effects of intervention or response to therapy in serial studies.

4.2. Futures Perspectives

The present document has the goal of contextualize the dissertation project being a state-of-art of medical image registration, nuclear imaging modalities and their interaction. As future perspective, it is intended to implement registration methods previously described applied to molecular medical images, as an aid to diagnosis, monitoring of disease development such as planning of treatments or surgeries, become it easier, more efficient
and effective, through the development, test, use, comparison and validation of the developed algorithms using real data sets of patients with a neurological disease.
5. REFERENCES


Cuoco, A., Petretta, M., Acampa, W., & De Falco, T. (2010). Gated SPECT myocardial perfusion imaging: the further improvements of an excellent tool. The quarterly journal of nuclear medicine and molecular imaging; official publication of the Italian Association of Nuclear Medicine (AIMN)[and] the International Association of Radiopharmacology (IAR)[and] Section of the Society of Radiopharmaceutical Chemistry and Biology, 54(2), 129.


63


IMAGE REGISTRATION USING COMPUTER TECHNIQUES: APPLICATIONS ON NUCLEAR MEDICINE IMAGING


IMAGE REGISTRATION USING COMPUTER TECHNIQUES: APPLICATIONS ON NUCLEAR MEDICINE IMAGING


