New Frontiers in Quantitative Molecular Imaging using PET

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Abstract— **Nuclear medicine has a long tradition of incorporating quantitative analysis in its diagnostic and therapeutic procedures. Many of the clinical and research applications of molecular imaging rely on a solid quantitative foundation, which is highly dependent on the performance characteristics of nuclear medicine instrumentation and the accuracy of image correction and reconstruction algorithms. This paper reflects the tremendous increase in interest in standalone (PET) and dual-modality (PET/CT and PET/MR) molecular imaging as both clinical and research imaging modalities in the past decade. New algorithmic developments of image correction and reconstruction techniques are aiming at attaining better image quality and achieving more accurate and automated quantification of physiological parameters of interest in clinical and research settings. Impact of physical degrading factors including attenuation of photons and contribution from photons scattered in the patient and partial volume effect on diagnostic quality and quantitative accuracy of PET data will be discussed. The fundamental concepts of quantitative image analysis techniques as they are applied in diagnostic and therapeutic nuclear medicine using dedicated PET instrumentation and dual-modality imaging devices will be explored. Potential future applications of quantitative molecular imaging are also addressed especially its use prior to therapy for dose distribution modelling and patient-specific 3D dosimetry in treatment planning towards the concept of image-guided radiation therapy.**

Keywords— **PET, Molecular Imaging, Quantification, Modeling, Image Reconstruction.**

I. Introduction

Molecular imaging using positron emission tomography (PET) has evolved into an academic field and is progressively gaining importance in the clinical arena. Significant progress has been made in the design of high-resolution three-dimensional (3-D) PET units dedicated to brain research and the development of accurate quantitative imaging protocols incorporating accurate image correction techniques and sophisticated reconstruction algorithms. However, emerging clinical and research applications of molecular brain imaging promise even greater levels of accuracy and precision and therefore impose more constraints with respect to the quantitative capability of PET. Although the use of nuclear imaging for diagnosis and therapy has origins dating back almost to the inception of nuclear medicine following the pioneering work of Dr G. de Hevesy, quantitative imaging has only recently emerged as a promising approach for diagnosis and therapy of many diseases. Over this time, its use has evolved from a tool available to only a few expert physicists and research biomedical scientists to one that may be integrated in commercial software that is now potentially available for routine use. This evolution has been driven by four fundamental and critical developments [1]:

1. The ever-increasing sophistication of nuclear imaging instrumentation and associated hardware developments for image correction (e.g. transmission scanning for accurate attenuation correction);
2. The rapid evolution and widespread clinical acceptance of PET and dual-modality imaging as effective diagnostic tools, requiring improved and accurate quantitative analysis;
3. The availability of open source libraries for simulation, image registration, reconstruction, processing and objective assessment of image quality methodologies; which spurred the development of more complex and ambitious computational tools (e.g. anatomically-guided reconstruction and partial volume correction);
4. The near exponential increase in preclinical research studies using small-animal imaging devices; an area in which quantification is always essential.

It is worth emphasizing that quantification has been traditionally performed in the case of PET, which started mainly as a research tool where there was greater emphasis on accurate quantitative measurements, and more recently has been applied for SPECT. There are many historical and methodological reasons for that, which are addressed in this volume. Different strategies for image reconstruction and accurate attenuation, scatter and partial volume effect corrections have been proposed so far with various degrees of success [1].

Fig. 1 visualizes image quality degradation by comparing an ideal ^{18}F-FDG PET study of the Hoffman 3-D brain phantom without any physical or instrumentation-based limitation and a realistic brain PET study obtained by Monte Carlo simulations including all degradation effects. The differences in image quality between both images mainly consist of degraded spatial resolution and contrast

resolution, due to limited system resolution, contribution from scattered events, and the limitations of the reconstruction algorithm. The difference is striking and show how complicated it will be to properly obtain a correct activity quantification from PET imaging.

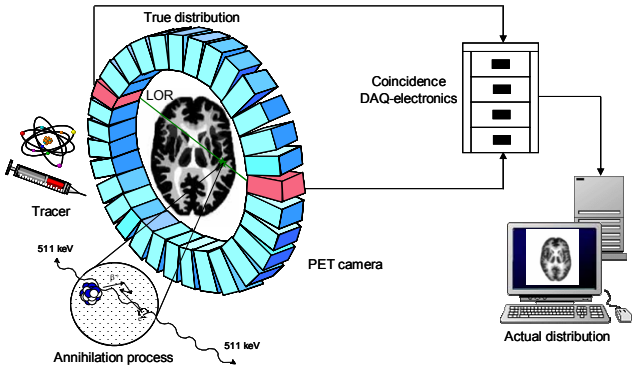

Fig. 1. Principle of PET data acquisition showing expected differences in terms of image quality and quantitative accuracy between the true activity distribution (left) and actual activity distribution (right) for the Hoffman 3-D brain phantom. The differences are mainly due to intrinsic limitations of the PET scanner and inherent imperfections of image correction and reconstruction techniques.

The number of scientific contributions related to this subject has been increasing steadily, which spurred the writing of this invited contribution as a snapshot of the dynamically changing field of quantitative 3D PET imaging. This paper presents the physical and methodological basis of quantitative image analysis and summarizes state of the art developments in algorithms aiming at accurate quantification of PET data. Future prospects and suggestions for future research will also be given.

II. Scatter compensation strategies

In the earliest literature on scatter correction, the main import of scatter was considered to be a loss of contrast in the image. In the simplest of descriptions, this means that a true zero in a reconstructed image occurs as a positive value. This effect was demonstrated by imaging nonradioactive spheres in a radioactivity surround. The corruption was frequently described as a pedestal upon which the true image sat. It was soon after realized that for quantitative imaging, Compton scatter causes a more complicated distortion in at least parts of the image. So, to the extent that clinicians want an accurate quantitative image, including the best contrast possible, scatter is always a problem. The extent to which it can be shown to have a disabling effect upon the goal for which the image is to be employed is a much more difficult matter to discuss and to document.

Despite the importance of scatter for quantitative imaging, scatter correction strategies in PET have only been briefly discussed in the literature [2] with the exception of extensive reviews provided in book chapters (e.g. [2]). Over the last two decades, many methods have been developed for the purpose of reducing the resultant degradation of image contrast and loss of quantitative accuracy in PET due to scattered events. The main difference among the correction methods is the way in which the scatter component in the selected energy window is estimated. The most reliable method to determine the actual amount of scatter in the image is accurate modelling of the scatter process to resolve the observed energy spectrum into its unscattered and scattered components.

A number of scatter-correction algorithms for PET have been proposed in the literature. They fall into four broad categories:

- Multiple-energy-window (spectral-analytic) approaches;
- Convolution/deconvolution-based approaches;
- Approaches based on direct estimation of scatter distribution;
- Statistical reconstruction-based scatter compensation approaches.

Different versions of the above methods have been successfully implemented for 3D PET and are discussed in [3]. There is little in the literature reporting systematic studies on the clinical impact of different scatter correction techniques versus no correction in 3D PET. It is well known that subtraction-based scatter correction increases statistical noise. However, in general scatter correction improves the contrast compared to the case where no correction is applied. In particular, the low-count regions and structures are better recovered after scatter compensation.

It can be argued that there is consensus within the nuclear medicine community with respect to the potential usefulness and necessity of scatter correction for either qualitative interpretation of patient images or extraction of clinically-useful quantitative parameters. The main application which is still the subject of debate is ^{15}O-[H_2O] brain activation studies characterised by low-count imaging protocols where scatter subtraction might jeopardize the power of statistical analysis significance. In these cases, PET studies focus on identification of functional differences between subjects scanned under different conditions. Whether the scatter component can be considered as constant between the two conditions for inter-subject comparisons still needs to be demonstrated. This constancy is required to confirm the hypothesis that the outcome of statistical analysis (reflecting subtle changes in distribution of radiotracer) does not change greatly with and without scatter compensation.

It is gratifying to see the progress that scatter correction has made in the last twenty years, from very crude energy-based approaches, through analytic and Monte Carlo modelling, and more recently iterative reconstruction-based scatter correction approaches. Recent developments have been enormous, especially improved accuracy, precision, and computational speed, in conjunction with decreased calibration data. The necessity for scatter correction is well understood in research environments. Moreover, scatter correction in now carried out in some clinical settings, even in institutions without extensive physics and computing support. Implementation of validated techniques in commercial software packages would be useful to further attract the interest of the clinical community. This greater interest would in turn lead to increased refinement of scatter correction techniques. It is expected that with the availability of greater computing power in the near future, more complex and ambitious computer-intensive scatter modelling and correction algorithms will increasingly become clinically feasible [3].

III. Attenuation correction strategies

The accuracy achieved by attenuation correction procedures depends mainly on the rigour followed to derive patient-specific attenuation map. Two broad classes have emerged: (i) calculated (transmissionless) methods, which are based on an assumed anatomical model representing the shape and spatial distribution of attenuation coefficients in the head and (ii) measured (transmission-based) methods, which in general rely on supplementary acquisition of a transmission scan. These techniques vary in complexity, accuracy, and computation time required [5].

The fundamental equation that links the imaged object $f(x,y)$ and corresponding attenuation map $\mu(x,y)$ to its measured projections $p(s,\phi)$ is called the attenuated Radon transform and is given in the case of PET by:

$$p(s,\phi) = \int_{L(s,\phi)} f(x,y)\, dr \times \exp\left[- \int_{L(s,\phi)} \mu(x,y)\, dl \right] dr \qquad (1)$$

where $L(s, \phi)$ is as defined in Equation (1) above and ϕ is the angle between the rotating detector plane and the stationary reconstruction plane.

The ideal solution would have been to use an exact solution for the inverse problem to solve the Radon transform and reconstruct the spatial distribution of the tracer $f(x,y)$. However, owing to the complexity of the equation in the case of nonuniform attenuation, an exact solution is not possible in general. The seminal contribution by Novikov [4] who recently gave an explicit inversion formula for the attenuated Radon transform for a particular important family of weights was a major breakthrough in the field. Moreover, Novikov's formula was proven for a somewhat larger class of weight functions using a completely different and more straightforward method. In spite of recent progress, various approximate methods have been proposed and are still used to solve the problem of reconstructing an object from its measured projections.

Several methods have been devised to achieve accurate quantitative analysis of PET studies. Significant attention has been devoted to optimizing computational performance and to balancing conflicting requirements. Both approximate methods suitable for clinical routine applications and more complicated approaches for research applications where there is greater emphasis on accurate quantitative measurements have also been addressed [5].

Because attenuation correction in PET is relatively straightforward and its accuracy being limited only by the noise (statistics) present in the acquired transmission scans, only two techniques have materialized and both require the computation of the attenuation correction factors (ACFs) through forward projection of the attenuation map at appropriate angles. To reduce processing time and data storage requirements for 3-D PET data collection mode, it is often convenient to work with pre-corrected data. This is the basis of the first approach where data correction is carried out in projection space through multiplication of the ACFs by the measured emission data by using the following expression:

$$p_{AC}(s,\phi) = ACF \times p(s,\phi) = \int_{L(s,\phi)} f(x,y)\, dr \qquad (2)$$

The attenuation corrected projections $p_{AC}(s,\phi)$ are then used to reconstruct the images using either analytic or iterative reconstruction techniques. An attractive option is to produce a smaller sinogram by pre-correcting the data and applying Fourier rebinning (FORE). However, the data are no longer Poisson distributed. It has been shown that OS-EM yields suboptimal images from such data. Alternatively, when an iterative algorithm (e.g. OS-EM) is used, the ACFs can be used to provide proper statistical weighting to the data as is done in attenuation-weighted OS-EM (AW-OSEM). This latter technique has better noise properties and is now part of commercial software used routinely used in many clinical PET facilities.

IV. Partial volume effect correction strategies

The limited spatial resolution of PET causes an object to appear enlarged if its true size is less than 2-3 times the

system resolution. While the total reconstructed counts within the object are conserved, the count density is decreased from the true value because the data are "smeared" over a larger area. This characteristic is known as the partial volume effect [1].

Attempts to compensate for partial volume effects date back to the time where they were first pointed out as a serious limitation in quantitative analysis. Although the partial volume phenomenon was first addressed in the context of "hot" objects in a "cold" background, emphasizing on the apparent loss of radioactivity due to the small object size with respect to the spatial resolution of the system, it became obvious that it was necessary not only to account for activity "spilling-out" of the "hot" region, but that "spill-in" from the surrounding usually "warm" area should also be accounted for in the regional measurements. Several authors attempted some sort of partial volume correction (PVC) by applying the recovery coefficients formulation.

PVC remains a priority for accurate image quantitation. The ability to compensate for partial volume effects usually requires to: (i) characterize the PSF of the imaging system, (ii) characterize the tissue components that participate in the uptake and metabolism of the tracer, and (iii) characterize the resolution effects in terms of correction factors or maps. Some correction methods require only the original emission data. These include methods making all the necessary corrections for physical effects at the projection level. There has also been a great deal of search for image processing tools that would restore, or at least visually enhance, the noisy images obtained in emission tomography. Those can be regrouped into the general class of filters used during image reconstruction (low-pass filtering), and those used post-reconstruction for the purpose of restoration filtering.

Another approach that does not require additional data is based on the computation of correction factors during mathematical modelling of kinetic data, such as regional cerebral blood flow (CBF) measurement with PET, both in the heart and brain. A distinct class of correction methods requires the definition of the various objects being imaged in addition to the characterization of the scanner's point-spread function (*PSF*). These include anatomy-based post-reconstruction correction methods that make use of concomitant high-resolution structural information from MR imaging or CT. These currently constitute the most popular methods and are finding their way to the clinic. Finally, empirical methods based on the derivation of correction factors from experiments with physical test objects remain an active way of characterizing partial volume effects.

Those methods proved to be sufficiently accurate to be applied in a growing number of research studies, if one considers that the number of publications related to the effect of the application of PVC algorithms to research data has grown significantly in the past few years. PVC is now a powerful and reliable tool that should become systematically used in research or clinical studies involving the use of emission tomography. It is expected that improvement in all aspects of the prerequisite for accurate partial volume correction are still required, especially for what concerns the quality of anatomo-functional mapping needed for accurate quantitation of cell-specific function and metabolism.

V. Conclusions

In many situations, absolute quantification is desirable to obtain a truthful representation of the biological process or metabolic function being imaged. In quantitative metabolic imaging studies, there is always a tension between the desire for more data (e.g. MRI, CT, blood samples, … etc), which ultimately improves the understanding of the process being studied and the accuracy of the reported results, vs. logistic considerations, including cost, time, imaging unit throughput and patients or healthy volunteers' comfort. One must consider what is logistically possible for the staff in a busy clinical nuclear medicine facility and what is tolerable by the patients and/or subjects. Likewise, accurate quantification requires extensive technical and organizational efforts that may be unaffordable for a small clinical department with limited scientific support. In the clinical setting, it has become standard practice to use simplified imaging protocols compared to the often complex methods developed for research using emission tomography.

The development of newer, faster and more robust algorithms remains an open research field which requires further research and development efforts. In summary, quantitative analysis of nuclear medicine images is an area of considerable research interest and many research groups are very active in this field, leading the nuclear medicine community to forecast a promising progress during the next few years.

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