Perspectives in Quantitative Brain Positron Emission Tomography Imaging

a report by
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Positron emission tomography (PET) provides qualitative as well as quantitative information about the volume distribution of biologically significant radiotracers after inhalation, ingestion or injection into the human body. Unlike X-ray computed tomography (CT) or magnetic resonance imaging (MRI), which look at anatomy or body morphology, PET studies metabolic activity and tissue function. Sensitivity ranges from the detection of millimolar concentrations in functional MRI to picomolar concentrations in PET, which gives a 10^9 difference. With respect to specificity, the range is from detecting tissue density and water content to a clearly identified molecule labelled with a radioactive form of one of its natural constitutive elements.

The information provided by functional imaging can be exploited in one of two ways in a clinical and research environment: pure qualitative interpretation for diagnostic purposes or quantitative analysis of images to extract useful parameters. Within the context of this article, the aim of quantification is to provide a reliable and reproducible numerical measure of brain function in different areas. Nevertheless, in order to evolve to quantitative analysis of PET images, it is necessary to take into account several physical degrading aspects. The algorithm used for image reconstruction of the raw data sets is based on a mathematical model of the acquisition process. Due to the complexity of that process (attenuation, scatter, partial volume effect and patient motion, etc.), many approximations are introduced. The resulting deviations between the acquisition process and the mathematical model cause artefacts in the reconstructed images.

In an attempt to obtain quantitative measurements in PET, significant efforts need to be made to ensure that data contains an optimal amount of fully correct information. Therefore, the accuracy of the mathematical model needs to be improved, and the effects not taken into account during reconstruction of the data need to be corrected. The following sections explore some applications of quantitative brain PET and discuss the current limitations as well as methods and instruments developed to improve the capabilities of quantitative brain PET imaging.

Quantification of the Regional Distribution of the Brain Perfusion

For many years, interest in the regional distribution of brain perfusion has increased significantly, primarily because many neurological disorders are associated with a decrease of regional cerebral blood flow (rCBF). Once injected, the radiotracer flows through the right heart chamber, the lung and the left heart chamber. Afterwards, in the aorta, the blood flow splits into the brain circulation and the systemic circulation. Only the fraction of activity given by the ratio of cerebral blood flow on cardiac output reaches the brain.

The amount of radioactivity retained in the brain depends on the extraction and retention fraction of the brain. To quantify the retention fraction in the brain, arterial and venous blood samples are needed. Since this approach remains difficult and time-consuming in daily practice, a technique that avoids blood samples is mandatory for clinical applications. Generally, for practical reasons, it is also considered that the retention fraction is constant over the brain and that the PET image mainly represents a distribution of blood flow.

Besides arterial sampling methods, compartmental models have been developed, such as the absolute quantification method. This technique uses the brain input and aortic arch curves to calculate a brain perfusion index, which is correlated to blood flow. These non-invasive rCBF measurements are applicable without any blood sampling and may be quite useful, especially in cases where an overall change in blood flow can be expected (i.e. carotid obstruction). Since quantification remains difficult in routine practice, most physicians evaluate the distribution of blood flow in the brain by visual interpretation. In order to be more sensitive and to reduce the variation coefficient by referring to a stable region, many semi-quantitative methods have been described over the past years. Operator-defined or automatic left-to-right ratios have been used. In addition, in an attempt to delineate the anatomical structures more precisely, PET images have been matched to CT or MR images.

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Furthermore, the volume of the defect has been calculated by comparison with the controlateral healthy structures. This method, first used by J M Mountz, consists of drawing regions of interest (ROIs) over the lesion on all slices involved. Afterwards, these ROIs are mirrored to the controlateral homologous region. The total functional volume loss, expressed as an imaginary volume of zero perfusion, can then be calculated. This technique takes into account the pixel volumes, number of slices and the activity difference at each slice between the normal and the defect hemisphere. Another absolute quantification method has been developed by A Dobbeleir and R Dierckx. This approach does not quantify blood flow, but quantifies exactly what is seen in the images: the regional brain uptake of a known tracer, which is the product of blood flow and retention of the brain. This allows intra or interindividual comparison between different studies.

germanate (BGO) crystals, the use of layered crystals and other schemes for depth of interaction (DOI) determination (for dedicated systems).

The development of multimodality imaging systems is an emerging research field. In particular, phoswich detectors are receiving considerable attention for the design of dual-modality scanners (PET/single photon emission computed tomography (SPECT)). This may be implemented with solid-state photodiode read-outs, which also allow electronically collimated coincidence counting.

Different designs of combined PET/CT tomographs were developed for diagnostic purposes in clinical oncology and are now available commercially. One of the major advantages is that PET data is aligned intrinsically to anatomical information from the X-ray CT without the use of external markers or

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### High-resolution PET Instrumentation Dedicated to Brain Research

An important consequence of the cost and performance-conscious environments of healthcare today is the constant pressure to minimise the cost of PET tomographs by reducing the geometry from a full ring to a dual-headed device, while, at the same time, there is also pressure to provide the most accurate diagnostic answers through the highest performance possible. The dilemma is that both approaches can lower the cost of healthcare. Continuous efforts to integrate recent research findings for the design of both geometries of PET scanners have become the goal of both the academic community and nuclear medicine industry. Wire chambers of various kinds are also still being developed for PET applications.

As PET has become of more interest for clinical practice, several different design trends seem to have developed. Systems are being designed for 'low cost' clinical applications, very high-resolution research applications and just about everywhere in between. New technologies that are emerging include the use of new scintillating materials as detectors, including new cerium (Ce)-doped, fast and high effective-Z crystals like gadolinium silicate (GSO:Ce), lutetium oxyorthosilicate (LSO:Ce) and Ce-doped ortho-aluminate crystals like yttrium orthoaluminate perovskite (YAP):Ce and lutetium orthoaluminate perovskite (LuAP):Ce, as alternatives to bismuth

internal landmarks. Quantification is also improved by using the low-noise CT transmission information during the correction of the PET data for self-attenuation and for contamination from scattered photons. The University of California at Los Angeles (UCLA) PET Group has developed a prototype PET detector that is compatible with a clinical MRI system to provide simultaneous PET and MRI. A second prototype has been developed in collaboration with King's College London and was used for animal studies at different magnetic field strengths. Thus, there are many different design paths being pursued and it will be interesting to see what technologies become the most popular in the future.

To improve the capability for investigating the living human brain using PET with regard to blood flow, metabolism and receptor characteristics for small structures such as cortical sublayers and nuclei, the spatial resolution has to be improved relative to what is available today. A spatial resolution of 2mm or less in all three dimensions over the entire field of view (FOV) and a record of the DOI information may be necessary to reach these research goals. In order to meet this goal, new next-generation high-resolution, three-dimensional (3-D)-only brain PET tomographs have been designed or are under development by different groups. The high-resolution research tomograph (HRRT) is the first LSO PET with full DOI capability over an extended

Figure 1: Image-degrading Effects Illustrated Using Monte Carlo Simulated Projections of the Digitised 3-D Hoffman Brain Phantom
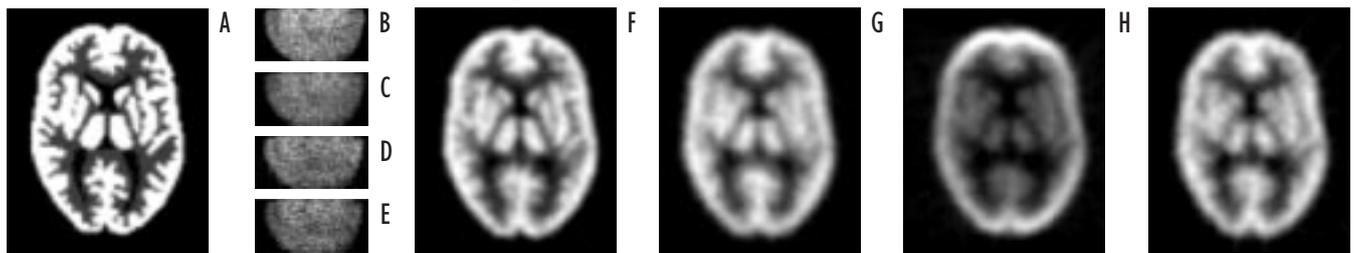
A: Transaxial slice of the digital 3-D Hoffman brain phantom, B–E: Monte Carlo simulation of the 3-D Hoffman brain phantom in different imaging situations showing 2-D projections and F–I: their filtered backprojection reconstructions (F–I). In cases B and F, a 2-D projection and reconstructed image neglects attenuation, scatter and detector blurring. In C and G, effects of detector blurring are included while, in D and H, effects of detector blurring, attenuation and scatter are included in the simulation and no corrections performed on the simulated data sets. Finally, in E and I, effects of detector blurring, attenuation and scatter are included and appropriate corrections for attenuation and scatter applied.

FOV for human studies. The GSO-based prototype has some interesting design features and constitutes a good starting point for future and innovative designs.

Steps Towards PET Image Quantification

PET offers the possibility of quantitative measurements of tracer concentration *in vivo*. However, there are several issues that must be considered in order to realise this potential fully. In practice, the measured line integrals must be corrected for a number of background and physical effects. These include dead-time correction, detector normalisation, subtraction of random coincidences, resolution recovery and attenuation and scatter corrections. Whilst the low sensitivity of PET systems remains a limitation of practical quantitative PET, the three most significant effects are the limited spatial resolution, the photon attenuation in the object and the contribution in the images of events arising from photons scattered in the object and the gantry.

Image-degrading effects are illustrated using Monte Carlo simulated projections of the digitised 3-D Hoffman brain phantom. A slice of this phantom is shown in *Figure 1A*. The ratio between the activity in white, grey matter and ventricles has been chosen as 1:4:0, respectively. The projections of this phantom at different levels of fidelity are generated. The strengths of the image-degrading factors are characteristic of an [18F]fludeoxyglucose (FDG) brain study. *Figures 1F–I* show the effects of different aspects of image degradation on filtered backprojection (FBP) reconstructions. The loss of resolution caused by detector blurring (full width at half maximum (FWHM) = 4mm) on projection data and FBP reconstructions is shown in *Figures 1C* and *1G*, respectively. In *Figures 1D* and *1H*, effects of detector blurring, attenuation and scatter are included in the simulation and no corrections performed on the simulated data sets. Finally, in *Figures 1E* and *1I*, effects of detector blurring, attenuation and scatter are included again and appropriate corrections for attenuation and scatter applied.

The non-homogeneous distribution of attenuation coefficients due to presence of air cavities and sinuses in the brain complicates the interpretation of these images and precludes the application of simple methods of scatter and attenuation correction developed for homogeneous media. The problem of scatter correction is more complicated to solve and becomes of paramount importance in high-resolution PET imaging in which the scatter degradation features become more complex. Different models for attenuation and scatter corrections have been investigated during the last few years. However, many research and development efforts focused on correction schemes for resolution recovery and attenuation and scatter applied either before or integrated in the reconstruction process.

The development of fully 3-D reconstruction algorithms has been necessary in order to take advantage of the acquisition of PET data without septa. Reconstruction methods are being improved continuously and scanner manufacturers are optimising the performance of dedicated software by integrating latest algorithmic developments. It has been shown that maximum *a posteriori* (MAP) reconstructions using a Bayesian model in combination with a Poisson likelihood function and a Gibbs prior on the image allow the obtainment of images with FWHM resolutions of approximately 1.2mm at the centre of the FOV, compared with approximately 2mm when using an analytic 3-D reconstruction algorithm. Summarising, improvement of PET quantification is an area of considerable research interest and an important number of researchers are working on the subject. The development of more sophisticated techniques for quantification of PET images is still required. ■

Additional Information

The complete version of this article, including references, can be found in the Reference Section on the CD-ROM accompanying this business briefing.