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## REVIEW

# Image reconstruction

**Michel Defrise<sup>1</sup> and Grant T Gullberg<sup>2</sup>**<sup>1</sup> Department of Nuclear Medicine, Vrije Universiteit Brussel, AZ-VUB, B-1090 Brussels, Belgium<sup>2</sup> E. O. Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA

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Online at [stacks.iop.org/PMB/51/R139](http://stacks.iop.org/PMB/51/R139)**Abstract**

We give an overview of the role of *Physics in Medicine and Biology* in the development of tomographic reconstruction algorithms. We focus on imaging modalities involving ionizing radiation, CT, PET and SPECT, and cover a wide spectrum of reconstruction problems, starting with classical 2D tomography in the 1970s up to 4D and 5D problems involving dynamic imaging of moving organs.

**1. Introduction**

This text offers a short celebration, for its 50th anniversary, of some great papers published in a great journal. The story will be far from exhaustive: since its creation, 548 articles in *Physics in Medicine and Biology* have had the word ‘reconstruction’ in the title or abstract, and the selection below is strongly biased by our own interest and vision. In particular, we will focus on the imaging modalities with ionizing radiation: CT, PET and SPECT. We apologize in advance for omitting many important contributions either by ignorance or because of lack of space, and we refer the reader to more systematic and comprehensive reviews of image reconstruction (Natterer and Wubbeling 2001, Lewitt and Matej 2003).

**2. A slow but brilliant start**

The story of image reconstruction in *Physics in Medicine and Biology* begins shortly after the introduction of the EMI scanner in 1972. Prior to this date only a few papers in the journal reflected, from some distance, the rising intellectual activity occurring between the end of the second world war and 1972 that produced the basic algorithms for two-dimensional (2D) tomography: the direct Fourier reconstruction, the convolution-backprojection method, the algebraic reconstruction techniques, etc. As is nicely described by Steve Webb in his book ‘From the Watching of the Shadows’ (Webb 1990), to which we refer for a complete story, these developments have been the result of several largely independent research streams in the 1960s and 1970s: in radio-astronomy (R N Bracewell and A C Riddle), in electron microscopy (R A Crowther, D J De Rosier and A Klug) and of course in the emerging radiological

applications of tomography, both with radioisotopes (D E Kuhl, G Muehllehner, G L Brownell, M E Phelps and E J Hoffman, J W Keyes, R J Jaszczak, and many others) (Kuhl *et al* 1965, Muehllehner 1971, Brownell *et al* 1972, 1973, Phelps *et al* 1975, Keyes *et al* 1977, Jaszczak *et al* 1977) and with x-ray transmission tomography that culminated in the 1979 Nobel prize awarded to Cormack (1973) and Hounsfield (1973).

Prior to 1972, Physics in Medicine and Biology also featured only a few papers on the new detector technologies that were going to enable transaxial tomography. Several contributions on the sodium iodide gamma camera appeared however, most notably a review ‘Clinical applications of a gamma camera’ by Mallard and Myers (1963) and a paper by Kuhl (1965) on a converging collimator. The pinhole collimator<sup>3</sup> has been around since the early years of nuclear medicine (Copeland and Benjamin 1949, Mortimer *et al* 1954, Anger 1958) and on this subject also we find papers that still make excellent reading today, amid blooming activity on microSPECT with pinhole collimators (see the review by Meikle *et al* (2005)). The work by D Paix (1967) (‘Pinhole imaging of gamma rays’), which investigated the effective area of a pinhole and its sensitivity map, has often been repeated but much less frequently cited. There are other examples of such concepts and ideas that appear, fade away and reappear decades later in new technological clothes. Imaging of positron emitting radioisotopes appeared in ‘The Localization of positron sources by coincidence counting’ by Doust and Simons (1961), but the first device with limited-angle tomographic capability described in Physics in Medicine and Biology appeared in ‘A hybrid positron scanner’ by Burnham *et al* (1970), initiating a long series of papers describing PET scanners, often with titles as ‘Performance evaluation of the ... PET tomograph’. In 1971, the same year he published ‘Section imaging by computer calculation’ with R A Wetzel (in the *Journal of Nuclear Medicine*), Muehllehner (1971) described ‘A tomographic scintillation camera’ based on a rotating slant hole collimator.

Most of these early works dealt with longitudinal tomography. This technique, which can be defined as limited-angle 3D tomography, would soon be superseded by transaxial tomography, and later by fully 3D tomography. However, as recently reviewed by Dobbins and Godfrey (2003) there is still considerable interest in longitudinal tomography.

During the 1970s the number of papers on transaxial tomography in *Physics in Medicine and Biology* grew, and the journal attracted contributions from some of the major authors in the field, many from North America and many of whom are still active in the field. In a remarkable paper, ‘Reconstruction of densities from their projections, with applications in radiological physics’, Cormack (1973) compared different approaches to transaxial section reconstruction and related how ‘it has recently come to the author’s attention that the problem of determining a function in a plane from its line integrals was first solved by J Radon in 1917.’ Cormack also discussed the specificities of the application to transmission tomography (both with x-rays and charged particles) and emission tomography. Concerning the latter, he was fairly pessimistic: ‘using single gamma-ray scanning, practical difficulties make almost useless the mathematical methods to be described below.’ One possible solution was to apply an iterative reconstruction algorithm, based in those years on least-square estimation, as in the paper by Budinger and Gullberg (1974) that already incorporated attenuation correction: in their example, ‘the data are digitized in  $64 \times 64$  frames, and profiles from 36 frames corresponding to a transverse section 1.5 cm thick are manipulated by the Hewlett-Packard 2100A small computer system (HP-5407). Computation time is 25 min for 18 views using the iterative least squares technique, and 1 min using a filtered back-projection technique. The resolution of the reconstruction is such that 1.2 cm holes are easily detected.’ Also among these early works were ‘Quantification of the depth effect of tomographic and section imaging

<sup>3</sup> ‘collimateur sténopé’ in French.

devices' by Muehllehner and Hashmi (1972), and 'Three-dimensional radionuclide imaging' by Powell and Monahan (1972). Brookes and Di Chiro (1976) published a review article in *Physics in Medicine and Biology*, 'Principles of computer assisted tomography (CAT) in radiographic and radioisotopic imaging' that presented a fairly complete account of the state of the art for analytical and iterative reconstruction techniques.

This section on the early days concludes nicely with the introduction of the term 'sinogram' by Edholm (1977), and later in *Physics in Medicine and Biology* by Edholm *et al* (1978) in 'Transverse tomography with incoherent optical reconstruction.' The word was promised a brilliant fate: as of January 2006 a search engine finds close to 40 000 references to 'sinogram'! This word later inspired the similar naming of other sampling schemes in tomography such as linograms, planograms and timograms.

### 3. Why an image?

Very early it became obvious that image reconstruction was more complex than the mere problem of analytically inverting the Radon transform, and then discretizing the resulting inversion formula. By the 1970s papers discussed the influence of sampling, resolution and noise. A classic and much cited reference came from the Lawrence Berkeley National Laboratory with the lengthy but well to the point title 'The effects of a finite number of projection angles and finite lateral sampling of projections on the propagation of statistical errors in transverse section reconstruction' by Huesman (1977), which gave the fundamental relation

$$\frac{\sigma_\rho}{\langle \rho \rangle} \simeq \left( \frac{D^3}{nd^3} \right)^{1/2} \frac{\sigma_I}{\langle I \rangle}, \quad (1)$$

where  $\sigma_\rho/\langle \rho \rangle$  is the relative RMS error in the reconstructed value of a resolution element (say, a pixel) of diameter  $d$  located at the centre of a uniform disc of diameter  $D$ . The disc is reconstructed from  $n$  line integrals measured with a relative RMS error  $\sigma_I/\langle I \rangle$ . The key point is the noise dependence on  $(D/d)^{3/2}$  rather than on  $(D/d)$  as would be expected by simply counting the number of photons detected per resolution element. Note that the dependence on  $(D/d)^{3/2}$  as described in equation (1) holds for linear algorithms such as the filtered-backprojection method. Another set of papers in *Physics in Medicine and Biology* would later present a similar analysis of the noise propagation by the maximum-likelihood expectation-maximization algorithm (Barrett *et al* 1994, Wilson *et al* 1994). This analysis was itself extended to Bayesian reconstruction by Wang and Gindi (1997).

Results in these papers and others, such as 'The noise power spectrum in computed x-ray tomography' by Riederer *et al* (1978), slowly popularized the significance of the ill-posedness of tomographic reconstruction. The concepts of 'ill-posedness' and 'regularization' are familiar to any PhD student today, but were mysterious to most in the 1970s. Some time would be needed to clarify to the medical imaging community the link between the mathematical works on regularization—notably by the Russian school of A Tikhonov—and the empirical observation that the signal-to-noise ratio in the reconstructed image can be much worse than in the measured data. For some time one would still find proposals such as the idea of improving SPECT imaging by combining, on a two-head scanner, a high resolution collimator (to get good spatial resolution) with a low resolution collimator (to get good counting efficiency). An efficient way to explain the limitations of this type of approach is to qualitatively translate equation (1) by 'the information content of a detected photon is roughly inversely proportional to the number of image pixels from which that photon could have been emitted.' This is not a theorem of course; it is deceptively difficult to reliably

estimate (let alone optimize) the balance between resolution and noise, the balance between relaxing collimation to improve counting efficiency and strengthening collimation to improve resolution. Other examples of this dilemma include the Compton camera (see e.g. Zhang *et al* (2004)), the multi-pinhole collimators for micro-SPECT (Meikle *et al* 2005), the rotating slit collimator (e.g. Lodge *et al* (1995)) or the Fresnel zone plate camera (Dance *et al* 1975).

Using the word ‘optimize’ leads to another challenge of tomography: how should one compare the ‘performance’<sup>4</sup> of different imaging systems or reconstruction algorithms? Already with other types of image data (in radar detection for instance) scientists have recognized the often poor correlation between standard mathematical measures of image quality (such as the RMS error) and the practical usefulness of the image to fulfil a specific task such as lesion detection. This problem is particularly dramatic in medical imaging because a radiologist extracts a large amount of information from an image, using a mental process that cannot easily be modelled in a way that is both accurate and mathematically tractable. Even the problem of modelling the mental process involved in searching a signal of unknown location turns out to be a formidable challenge. For addressing this question too, *Physics in Medicine and Biology* has played an important role. C E Metz of the University of Chicago was one of the main investigators, his first contribution in this journal being ‘Evaluation of receiver operating characteristic curves in terms of information theory’ with Goodenough (Metz and Goodenough 1972), which described a task specific approach for evaluating the performance of the combination imaging system-human observer. The work of H H Barrett at the University of Arizona also played an important role in introducing these concepts to the community. A good example is the paper in which Rolland *et al* (1991) investigate ‘whether the ideal observer is a good predictor of human performance for systems described by long-tailed point spread functions and whether deconvolution is helpful in such cases.’ Recent developments and a good bibliography can be found in ‘Fast LROC analysis of Bayesian reconstructed emission tomographic images using model observers’ by Khurd and Gindi (2005). See also the related chapter in the book by Barrett and Myers (2004).

We finish this section with an anecdote. In 1983, attending his first conference on medical imaging<sup>5</sup>, one of us (MD) was giving a talk based in part on ‘Methods for evaluation of diagnostic imaging instrumentation’ by Shosa and Kaufman (1981). After that talk, H H Barrett stressed how inappropriate the RMS was as an error measure. This remark opened new horizons to a recent renegade from theoretical physics; medical imaging was much more difficult than expected, and hence considerably more interesting.

Since images are so reluctant to undergo analysis, one could legitimately ask: do we need images at all? To quote Jaffe’s provocative statement (Jaffe 1982), ‘By grossly oversimplifying, one could argue that any diagnostic procedure relying on an image for presentation to the human cognitive system is an admission of failure. [...] It is a testimony to our gross lack of information that requires us to synthesize an image as the signal output of our system.’ However, in the present state of artificial intelligence and pattern recognition science, there is only a small number of image interpretation tasks for which the computer is superior to the radiologist. An interesting perspective is the automatic, or at least computer-aided, detection of micro-calcification in digital mammograms (with several papers in the last ten volumes of *Physics in Medicine and Biology*). To date, the Intelligent Eye nicely praised in the book of Gregory (1970) remains an essential component of the imaging chain.

<sup>4</sup> 5569 papers in *Physics in Medicine and Biology* have the word ‘performance’ in the title or abstract, which is a nice record for such an ill-defined word! The score is 4131 for ‘optimum’, ‘optimization’ or ‘optimal’.

<sup>5</sup> The 8th biennial Conference on Information Processing in Medical Imaging organized by F Deconinck in Brussels.

#### 4. Beyond the voxel?

The representation of an image as a linear combination of voxel basis functions is omnipresent in iterative reconstruction algorithms, and is usually taken for granted. Yet this representation is not necessarily the best: first, the voxel basis does not even approximately diagonalize the matrix that models the imaging system; second the discontinuous voxel contains high frequency components that are spurious since they cannot be recovered due to the finite spatial resolution of the detectors. These observations provided motivation for the study of alternative image representations. Ideally a family of basis functions should, at the same time, diagonalize the system matrix, allow a natural expression of the (implicit or explicit) prior knowledge needed to regularize the reconstruction and of course also allow an efficient numerical implementation.

The singular value (SVD) basis satisfies by definition the first goal, but is in general ill-adapted in expressing local smoothness constraints. Additionally the SVD is difficult to calculate. In ‘Cone-beam tomography with discrete data sets’ Barrett and Gifford (1994) modelled the imaging system as a continuous to discrete mapping, and represented the image using truncated Fourier basis functions. These functions achieve a rough diagonalization of the system (recall the central section theorem!) and are better suited than singular (SVD) functions or natural pixels to represent smoothness constraints. The *wavelet-vaguelette decomposition* introduced by Donoho (1995) is another possible tool for solving this problem but so far has been the object of relatively little attention in the reconstruction community.

The finite-element basis allows fitting of the image sampling to the object being reconstructed, and may therefore provide an economic, adaptative representation. Well suited to the solution of partial differential equations, finite elements are applied for example in elastography (e.g., Doyley *et al* (2000)) and in magnetic resonance electrical impedance tomography (e.g., Lee *et al* (2003)). Finite elements have also been applied (Brankov *et al* 2004) to the maximum-likelihood or Bayesian reconstruction from 2D gated cardiac SPECT data, using an adaptative nonuniform mesh in which samples are placed most densely in areas that contain significant detail.

To our knowledge, the only alternative basis that is applied for clinical emission or transmission tomography is the ‘blob’ basis. ‘Blob’ is the nickname for a radially symmetric Kaiser–Bessel window function introduced in tomography by R M Lewitt, first in the *Journal of the Optical Society of America*, then in *Physics in Medicine and Biology* (‘Alternatives to voxels for image representation in iterative reconstruction algorithms’ (Lewitt 1992)). The blob has a limited support in image space and is essentially band-limited. The latter property allows us to achieve an aliasing-free representation of the images with a number of blob coefficients that is smaller than the number of coefficients needed when using voxels. This advantage is partially offset by an increased computational complexity, and aliasing artefacts may also be suppressed by using voxels with a finer grid (Zbijewski and Beekman 2004). The benefits of using blobs are illustrated in Matej *et al* (1994) and Yendiki and Fessler (2004).

The representation of the image as a linear combination of a discrete set of basis functions amounts to restricting the class of admissible solutions to the problem of tomographic reconstruction. The choice of the basis functions is therefore closely linked with regularization. An alternative approach to regularization is based on the variational methods, which define the desired solution as one that minimizes a cost function. The cost function is the sum of two terms. The first term is related to the data likelihood (e.g. a least-square functional in the case of a Gaussian noise model) and its definition is straightforward. The second term, which aims at penalizing images that are deemed *a priori* unlikely, should describe our prior knowledge on the solution and is often defined in a Bayesian framework. In *Physics in Medicine and Biology*,

the Bayesian concept was described and applied to a deconvolution problem as early as 1979 (Kennett and Prestwich 1979). Application to PET has been proposed by Mumcuoglu *et al* (1996) and in many other papers since. One major issue here is the choice from a menagerie of possible penalty functionals (quadratic, total variation, median root prior, etc). This choice is (or should be) done as a function of the task for which the image is reconstructed.

## 5. 3D tomography

Since about 1980, *Physics in Medicine and Biology* has played a prominent role in the development of fully 3D tomography. ‘Fully 3D’ refers to scanning geometries where the 3D volume cannot be separated into independent transaxial sections, each of which is reconstructed from a separate set of projection data. This is in contrast with ‘standard’ 2D tomography with systems such as a single-row CT scanner, a SPECT scanner operated with a parallel-hole collimator and a circular acquisition or a multi-ring PET scanner with annular collimators (septa). All these systems separate the 3D image into independent sections by collimating the radiation into transaxial planes. Especially in SPECT and PET, this collimation results in an extremely poor (possibly unethical!) utilization of the radiation dose to the patient. By relaxing collimation (or removing it altogether in PET), a ‘fully 3D’ acquisition significantly improves dose utilization. Similarly, in CT, collimating the x-rays in a cone-beam rather than a fan-beam leads to a more efficient utilization of the power of the x-ray source and thereby to potentially faster imaging.

The ‘3D’ logo is trendy but the idea that tomography should be fully 3D is quite old: one of the first tentative designs for a PET scanner was an arrangement of 32 NaI scintillators built in 1960 at the Brookhaven National Laboratory. The nickname of this scanner, the ‘hair-drier’, was suggestive of its ‘fully’ 3D geometry, which could not however be exploited in those early days, both because of insufficient sampling and of the then lacunar understanding of image reconstruction. Later G Muehllehner, following pioneering works by H Anger, designed the first 3D PET scanner based on a pair of gamma cameras operated without any collimators (Muehllehner *et al* 1976). This, and geometrically similar designs with multi-wire proportional chambers at CERN, at the Lawrence Berkeley Laboratory and at Rutherford Appleton Laboratory, led to a new challenge: the reconstruction of a function  $f(x, y, z)$  from the measurement of a limited family of line integrals, i.e., the problem of inverting the 3D x-ray transform with incomplete data. These data may be described as a set of 2D parallel projections along a family of orientations  $\vec{n} \in \Omega$  defined by some subset  $\Omega \subset S^2$  of the unit sphere  $S^2$ . This subset  $\Omega$  is determined by the geometry of the scanner<sup>6</sup>.

Only for the case of a scanner covering the full  $4\pi$  solid angle ( $\Omega = S^2$ ) was the generalization from 2D tomography to 3D tomography straightforward. Many of the major breakthroughs in this field were published in *Physics in Medicine and Biology*, notably ‘Three-dimensional imaging in the positron camera using Fourier techniques’ by Chu and Tam (1977), the generalization of the ramp filter by Colsher (1980), alternative filters for the handling of truncated projections with a spherical positron emission tomograph (Ra *et al* 1982) and a fully general method for three-dimensional filter computation by Schorr and Townsend (1983). The journal also published an overview of these results by Defrise *et al* (1989). Even though these algorithms were developed for scanners based on large planar detectors, the main application after 1989 would be commercial multi-ring scanners operated without any collimator (‘septa’) in the field-of-view.

<sup>6</sup> The case of 2D tomography corresponds to  $\Omega$  being just one equatorial circle on the sphere.



In SPECT too, ‘fully 3D’ tomography became a popular topic in *Physics in Medicine and Biology*, using either converging cone-beam collimators or pinhole collimators, both of which provide divergent beam projections of the 3D tracer distribution. Again, the purpose is to increase the sensitivity for a fixed resolution, but in SPECT the price to pay is a reduced field-of-view. Jaszczak *et al* (1988) performed the first cone beam SPECT on the brain and Gullberg *et al* (1991a, 1991b) performed the first cone beam SPECT on the heart. The first pinhole SPECT imaging was reported by Palmer and Wollmer (1990) in *Physics in Medicine and Biology*. A review was published by Gullberg *et al* (1992).

Geometrically, a scintigraphic image acquired with a diverging (cone-beam or pinhole) collimator is similar to a radiograph acquired with a cone-beam x-ray system. Therefore, the cone-beam filtered-backprojection algorithm developed by Feldkamp, Davis and Kress for industrial non-destructive CT was applied with success to the reconstruction of SPECT data acquired with diverging collimators. Such an analytic algorithm is not optimal however. Since the early 1980s, it was clear that better image quality could be obtained using iterative algorithms that model the Poisson statistics of the data and the various physical effects that make the 3D x-ray transform a very rough approximation. As we have already seen with Cormack’s pessimistic remark in section 2, it is in retrospect remarkable that clinically exploitable SPECT images could be recovered at all using algorithms based on a line integral model that so drastically idealizes reality. After 1990, an increasing fraction of the papers dealing with image reconstruction in SPECT has been based on iterative algorithms, and the transition would essentially be completed after the introduction of the ordered subset expectation maximization algorithm (Hudson and Larkin 1994). Henceforth most efforts in SPECT have been aimed at a better modelling of the physics of data acquisition during iterative reconstruction, with many papers demonstrating the benefits for quantitative imaging of modelling the collimator response function, the photon attenuation and the scatter in patient tissues. Many of these works are at least partially based on Monte Carlo simulation, and in the future SPECT will likely rely on a full Monte Carlo based reconstruction. This idea was proposed by Floyd *et al* (1986) for 2D problems. Later, key contributions by the group of F Beekman in Utrecht (Beekman *et al* 1999, de Jong and Beekman 2001) showed how to accelerate Monte Carlo simulations using variance reduction techniques. These works and the recent paper ‘Fully 3D Monte Carlo reconstruction in SPECT: a feasibility study’ by Lazaro *et al* (2005) show that a fully 3D Monte Carlo reconstruction from SPECT data can be achieved within 15–60 min. Incidentally, it is interesting to note that accurate system modelling in SPECT is one of the issues in which the gap between proven technical feasibility and clinical routine is the widest; in many nuclear medicine departments, routine clinical scans are still processed without any of these corrections.

A similar story holds true for 3D PET, which underwent the same progressive transition to iterative reconstruction, though at a slower pace because the larger and ever increasing data size results in more severe computational requirements than in SPECT. This computational constraint has motivated the development of hybrid reconstruction algorithms for 3D PET (Kinahan *et al* 1997) that combine an analytical *rebinning* algorithm with a 2D ‘slice-by-slice’ iterative reconstruction. This hybrid method is faster than a fully 3D iterative reconstruction, and yet is sufficiently accurate for many types of clinical PET studies. A rebinning algorithm can be seen as a data compression method in that it maps the large 3D data set onto a smaller data set comprising one ordinary 2D sinogram for each transaxial slice of the image. Several approximate or exact rebinning algorithms have been proposed (Daube-Witherspoon and Muehllehner 1987, Lewitt *et al* 1994), the most popular one being the Fourier rebinning algorithm (Defrise *et al* 1997) based on the frequency-distance relation of Edholm *et al* (1986).



Until 1990, medical applications of cone-beam CT were limited, in contrast to the applications for industrial non-destructive testing. One can mention the ‘Dynamic Spatial Reconstructor’ of the Mayo Clinic or the ‘Morphometer’ built at the LETI laboratory of the French Commissariat à l’Energie Atomique (both in the 1980s). The latter development led P Grangeat to propose in his PhD thesis in 1987 a key relation between divergent projections and the 3D Radon transform. The introduction of helical scanning with a single row detector revolutionized radiology after 1990 but did not really modify the nature of the data, which remain 2D and are reconstructed, provided some axial interpolation, as a stack of independent transaxial sections. Only with the introduction of multi-row scanners featuring a steadily increasing axial field-of-view would fully 3D reconstruction in CT become a popular field of research. Since about 1995, the journal has hosted many papers on analytic reconstruction from truncated cone-beam projections, with helical CT as the major application (Kudo *et al* 1998). Among these the remarkable results of A Katsevich on exact reconstruction from helical cone-beam CT data have stamped a major step forward and have triggered renewed interest for 3D and also 2D (see section 8) reconstruction. In *Physics in Medicine and Biology*, these results were first published in ‘Analysis of an exact inversion algorithm for spiral cone-beam CT’ (Katsevich 2002) where the reference to his seminal 2002 paper (in *SIAM Journal of Applied Mathematics*) can be found.

In x-ray CT the line integral model is a much better approximation than in PET and SPECT, and the analytic algorithms remain at the forefront, if only because the large amount of data in cone-beam CT still precludes routine utilization of iterative techniques such as the algebraic reconstruction technique (ART). This is ironic, recalling that the EMI scanner in 1972 was using an iterative algorithm. Nevertheless iterative algorithms for cone-beam CT are likely to play an increasing role in the future. The maximum-likelihood algorithm proposed by Lange and Carson (1984) for transmission tomography has first been applied to 3D problems with modest sampling, such as the reconstruction of transmission maps for cone-beam SPECT pioneered by Manglos (1992). Faster algorithms for transmission CT later introduced by Erdogan and Fessler (1999) and by Beekman and Kamphuis (2001) might open the way to improved cone-beam x-ray CT, especially for low-dose imaging where modelling the Poisson statistics of the data is important.

We have only superficially sketched the recent history of 3D image reconstruction. This story is well illustrated in *Physics in Medicine and Biology* by the proceedings of some of the biennial International Conferences on Fully Three-Dimensional Image Reconstruction in Radiology and Nuclear Medicine (the 1991, 1993, 1997, 2001 and 2003 proceedings are in the journal). The first meeting organized in 1991 in Belgium was almost exclusively devoted to nuclear medicine (PET and SPECT), even though the theory in some of the papers was independent of the imaging modality (e.g. Yan and Leahy (1992)). Over the years the fraction of papers on CT increased dramatically, and it exceeds 50% in the proceedings of the 2003 Conference (vol 49, no 11).

## 6. 4D and 5D tomography

*Physics in Medicine and Biology* has also played an important role in the growth of 4D and 5D tomography. With the significant interest for time-dependent problems there has also arisen some confusion about the terminology. In some cases, the term 4D tomography refers to the reconstruction of motion fields from projection data acquired while the organ of interest is deforming or moving. For example in CT, SPECT and PET several applications involve cardiac and lung motion, which are often registered by means of some external ‘tracking’ signal. In other cases the term 4D tomography refers to the estimation of tracer kinetic parameters from

projection data acquired while the concentration of the tracer or contrast agent in an organ is changing as a function of time. With 5D tomography there can be very little confusion since 5D refers to both the organ motion and the non-stationary bio-distribution of the tracer.

The 4D tomography of motion fields has found importance in the area of CT imaging of lung, heart and other organs as well as radiotherapy of organs affected by respiratory and cardiac motion. With the increase in the development of hybrid technologies such as PET-CT and SPECT-CT there is a significant interest in 4D tomography of organ motion in order to match the inconsistent timing resolution between the modalities. Probably the most significant problem is that of respiratory motion. This affects both cardiac imaging and diagnosis of lung tumours, especially tumours at the edge of the lung. Respiratory motion also affects therapy planning for organs such as lung and liver. For PET-CT it is important to develop a method for 4D respiration-correlated acquisition from both CT and PET scans in order to fuse images from these modalities. An external tracking signal of the patient's breathing can be obtained by using either a thermometer in the breathing airflow of the patient (Wolthaus *et al* 2005), a spirometer, a laser positioning system, a load sensor or a position-monitoring system using two infrared reflective markers (Keall *et al* 2004, Vedam *et al* 2003). These devices have been used with both diagnostic hybrid PET-CT scanners and hybrid radiotherapy-CT machines to retrospectively sort the data according to the respiratory gating signal. There has also been an effort to develop deformable registration between modalities since organs typically deform in a non-rigid way (Li *et al* 2006), see also the review 'Medical image registration' by Hill *et al* (2001)). With the development of multislice CT scanners there is growing interest in developing cardiac CT with the hope of eventually being able to image coronary arteries with the quality of coronary angiography. Significant work is being put forward to use cardiac gating to reduce the motion of coronary arteries. For example, scanner rotation speeds chosen as a function of heart rate have been shown to reduce motion artefacts (Kachelriess *et al* 2000). Another example is the introduction of heart rate adaptive cardiac CT reconstruction algorithms that retrospectively sort gated cardiac CT imaging data (Manzke *et al* 2005). Still another interesting approach is to pre-compute a model of the 4D coronary artery motion field from *a priori* information (Blondel *et al* 2004). For some time there has also been interest in improving gated cardiac SPECT imaging (Lalush and Tsui 1998). It is expected that in the future both respiratory and cardiac gating will be important for obtaining optimum cardiac CT images and for merging mutual information between dual modalities.

The 4D tomography of tracer kinetics on the other hand has had significant impact on PET and SPECT. There are two approaches to the tomography of tracer kinetics. The first approach involves producing a dynamic sequence of three-dimensional reconstructions from which time-activity curves are extracted and, if needed, further processed to estimate kinetic parameters (Lawson 1999). The second, 'fully 4D', approach involves estimating the time-activity curves or kinetic parameters directly from the projection data.

Publications related to tomographic estimation of time-activity curves directly from projections first presented methods in which only the region-of-interest time-activity curves were reconstructed without reconstructing the entire sequence of 3D volumes. In PET this is fairly easy to do because the stationary ring detectors acquire a complete set of consistent data for each sampled time interval. This approach was proposed for the filtered-backprojection algorithm by Huesman (1984) in 'A new fast algorithm for the evaluation of regions-of-interest and statistical uncertainty in computed tomography'. To compensate for physical factors such as attenuation and detector resolution, iterative algorithms that maximize a likelihood function have to be used. Carson (1986) presented a method for estimating uniform activities in a set of regions-of-interest assuming a Poisson distribution; Formiconi (1993) did the same assuming a Gaussian distribution. A group at USC (Nichols *et al* 2002) later presented a method for

estimating time-activity curves for regions-of-interest with cubic spline basis functions from a consistent set of dynamic PET tomographic data.

For SPECT, the estimation of time-activity curves directly from projections is more difficult because the tracer concentration distribution changes during the rotation of the detectors (Links *et al* 1991). Original work to solve this problem was presented in *Physics in Medicine and Biology* by Celler *et al* (2000). They presented a method called dSPECT that reconstructs the dynamic data from a rotating gamma camera by constraining the kinetics to either monotonically increase or decrease. Other work related to the handling of inconsistent data in dynamic cardiac SPECT estimates time-activity curves as linear combinations of cubic splines, derived directly from projection data (Reutter *et al* 2002). No constraints were placed on the dynamics of the curves but a model of the projected region-of-interest was required.

Another approach to ‘fully 4D’ tomography aims at directly estimating the parameters of the kinetic model from projection measurements. The goal in this active area of research is to produce estimators with the lowest possible bias and variance from either consistent PET or inconsistent SPECT data. It is assumed that the regions-of-interest are specified and that the relation between the parameters of the compartment model and the dynamically acquired projections can be expressed in a chi-square formulation (Huesman *et al* 1998). Originally at the University of Michigan, Chiao *et al* (1994a, 1994b) estimated region-of-interest kinetic parameters for a one-compartment model and estimated boundary parameters for the regions from simulated transaxial PET measurements. They showed that biases of estimates are reduced by including region-of-interest specification inaccuracy. Huesman *et al* (1998) used hard boundary constraints and demonstrated bias improvement by estimating kinetic parameters for a one-compartment cardiac perfusion model directly from cone-beam SPECT projections. Kadmas and Gullberg (2001) formulated the problem as a Bayesian reconstruction for which both the time-activity curves and compartment model parameters were estimated using the prior constraint that the time-activity curves fit a one-compartment model.

A more general parameterization of the kinetics, independent of any particular compartment model, is the tomographic estimation of characteristic curves. The spectral-based approach builds on the early work of Cunningham and Jones (1993), who suggested replacing the nonlinear problem of estimating the kinetic parameters of a model with the linear problem of estimating the coefficients of a predefined spectrum of exponentially decaying factors. Efforts were also made to calculate these coefficients directly from projections. This has been done for two (Hebber 1997, Limber *et al* 1995) and for several spectral terms (Matthews *et al* 1997). In the former case, the fit of the parameters of a single exponential decay were used to model fatty acid metabolism in the heart directly from simulated projections from a rotating detector SPECT system. Variations of this work involve research into using factor analysis of dynamic structures (FADS) to estimate characteristic time-activity curves that have some physiological relevance (Sitek *et al* 2001).

Work in 5D tomography of motion fields that estimates both the motion and the changing concentration of the tracer with time continues to push image reconstruction to new frontiers. The group at the University of Massachusetts has extended the dSPECT method to obtain dynamic reconstructions of the time variation of  $^{99m}\text{Tc}$ -teboroxime in the heart from gated cardiac SPECT data (Farncombe *et al* 2003). A group at MIT (Shi and Karl 2004) has taken a different approach; they estimate the variation in the tracer concentration using level sets to delineate boundaries of moving organs like the heart while including the variation in the tracer concentration. 5D tomography faces the challenges of modelling both rigid body and non-rigid body deformation simultaneously, combined with the modelling of a time varying tracer concentration from tomographic projections. In the future this will have important

applications in diagnostic medicine and in radiotherapy. *Physics in Medicine and Biology* is an ideal forum for the dissemination of these works.

## 7. Links with other imaging modalities

This review focuses on the mainstream tomographic techniques that use ionizing radiations: CT, PET and SPECT. An attractive feature of *Physics in Medicine and Biology* is that it covers a wide spectrum of imaging techniques, and thereby allows a cross-fertilization between research projects over different image reconstruction problems. A few examples are presented here.

Though *Physics in Medicine and Biology* has not been a mainstream journal for MRI, this field is well represented. Image reconstruction in MRI is closely related to standard ‘tomography’ in the case of projection reconstruction. Two early papers on reconstruction from plane integrals by Lai and Lauterbur (1981), and by Taylor *et al* (1981) discuss zeugmatography, proposed as a potential method ‘to improve the performance considerably, and to obtain practical NMR zeugmatographic images of the human body with three-dimensional resolution better than the slice thickness usually used in x-ray CT scanning.’ Projection imaging in MRI is still considered for some applications because of a good robustness to motion artefacts. It might also be relevant for diffusion tensor imaging.

Proton transmission tomography was discussed in Cormack’s 1973 paper, as we saw, and also in his paper ‘Quantitative proton tomography: preliminary experiment’ with Koehler (1976). Experimental results are presented by Hanson *et al* (1982). This is a problem of reconstructing from weighted line integrals, related to the generalized Radon transform (another example is the attenuated Radon transform in SPECT). Proton tomography is relevant for treatment planning with proton therapy. A different method for using protons for 3D reconstruction is to use nuclear scattering, as proposed at CERN by Saudinos *et al* (1975).

Leaving the problems where the data are a good approximation of integrals of the quantity of interest along straight lines, we find thermoacoustic tomography and its associated reconstruction problem, which were recently investigated by Patch (2004). This relatively well-conditioned inverse problem can be modelled as that of recovering a 3D image from its integrals over a family of spheres.

As the dimension of the region of space probed by each data sample increases, the ill-conditioning of the associated inverse problem increases in general as well. This is the case with various reconstruction problems in biomedical optics (see the special issue edited by Wang *et al* (2004)), impedance tomography and magnetoencephalography, which are all well represented in the journal. These problems are best described by partial differential equations, and the reconstruction is generally based on finite element or boundary element solvers for the direct problem (which is far from trivial, in contrast to the case of the Radon transform). Incorporation of prior knowledge on the solution is absolutely crucial with these methods.

## 8. Conclusion: the story is not finished

Twenty years ago, Natterer (1986) published ‘The Mathematics of Computerized Tomography’. This book could be seen as marking the end of the exploration of 2D tomographic reconstruction with analytic methods, after two extraordinarily productive decades (or much more if we start with J Radon). Indeed, Natterer’s book gave a fairly exhaustive account: inversion algorithms with full or limited data, sampling and stability theorems, consistency conditions and already some results on 3D reconstruction. The

dominant feeling then was that that chapter was as good as closed, and that the major avenues of exploration would in the future be in investigating iterative reconstruction with statistical algorithms, 3D reconstruction and of course the persistent problem of system modelling. After all, the inversion of the 2D Radon transform is supposed to be a simple problem.

If there is one lesson science teaches us, it is that things rarely go as expected. Since 2000, new results have significantly modified our understanding of limited data 2D reconstruction: exact and stable analytical reconstruction of regions-of-interest has been demonstrated from new classes of limited data sets that were previously assumed to be intractable. Once more, *Physics in Medicine and Biology* is present with among others 'A two-step Hilbert transform method for 2D image reconstruction' by Noo *et al* (2004), and 'Exact image reconstruction on PI-lines from minimum data in helical cone-beam CT' by Zou and Pan (2004). An interesting point is that these works rely on previous results by Hamaker *et al* (1980) and by Gelfand and Graev (1991), the significance of which had been overlooked, probably because these results were published in mathematical journals. This example illustrates the importance and the difficulty of efficient communication between mathematics, physics and engineering.

Concluding with this description of the renewed interest for an old topic, analytic 2D reconstruction, this text hopefully has provided the reader with a very lacunar, but enthusiastic, view of a fascinating research field that spans from 2D to 5D problems.

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## Biography



**M Defrise** received his PhD degree in theoretical physics from the University of Brussels in 1981, and was a visiting professor in the Department of Radiology of the University of Geneva in 1992–1993. He is currently research professor in the Department of Nuclear Medicine at the VUB University Hospital in Brussels. He has participated actively in the advancement of 3D PET methodology. His current research interests include 3D image reconstruction in nuclear medicine (PET and SPECT) and in CT.



**Grant Gullberg** received his PhD in biophysics from the University of California, Berkeley (1979). His research interests involve the study of inverse problems with application to medicine and biology that involve the use of positron and single photon emission computed tomography, magnetic resonance imaging and magnetocardiography. He has worked in both industry and academia. During the 1970s he worked as a staff scientist at the Lawrence Berkeley National Laboratory. He then worked in the Applied Science Lab of the General Electric Company for 5 years before taking a position at the University of Utah where he was Professor of Radiology and Director of the Medical Imaging Research Laboratory for 17 years. In 2002 he returned to the Lawrence Berkeley National Laboratory as a Senior Staff Scientist. His current research focuses on improving the imaging of cardiac function using finite element mechanical computer models, animal models and human studies to develop better methods to image heart failure.