

# Medical Image Processing in Nuclear Medicine

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## Aims and Objectives

The aim of this module is to provide an understanding of the special nature of medical image processing in the area of nuclear medicine applications. Firstly, the acquisition of data and their pre-processing to correct for sources of error will be described. Secondly, the particular nature of tomographic reconstruction in Single Photon Emission Computerised Tomography (SPECT) and Positron Emission Tomography (PET) will be presented. Thirdly, different types of processing algorithms for handling dynamic sequences of images as are normally handled in nuclear medicine will be discussed with particular reference to the extraction of physiological data, normally after fitting a model. Lastly the needs of interconnecting a nuclear medicine image network to other systems will be indicated with specific reference to multi-modality image handling and image registration and fusion.

## 1. Acquiring data

The signal used in nuclear medicine is basically that of emitted ionising radiation from internal sources of radioactively labelled material. In general these will be gamma rays of energies from 30KeV up to 500KeV where the radioactive material has been administered by injection or orally. The original classical example was the oral absorption of I131 which then goes to the thyroid, decays to produce 364KeV gammas, which are then detected to form an image of the thyroid. The most commonly used radioisotope is that of Tc-99m, which is used to label a wide variety of substances, and which decays to produce a 140KeV gamma. Other interesting isotopes are the positron emitters C-11, N-13 O-15, F-18, all of which generate coincident pairs of 511KeV gammas and are used for PET.

The most common device used for imaging in nuclear medicine is the gamma camera. Here, a collimator being a sheet of lead with holes, is used to select photons arriving from a particular (set of) directions, and then the gamma events are detected from a scintillation occurring most commonly in a sheet of a material such as NaI(Tl) producing light which is then converted to electrical signals by an array of photomultipliers.

Data are acquired on an event by event basis. The position (and energy) of each individual detected gamma event is recorded or used to create images. Thus two basic detection modes are used, frame mode and list mode. Additional information such as from the ECG may be employed as in so called gated studies to create time-lapse averaged images. Quite significant pre-processing is included as part of the acquisition system to correct for errors notably in energy, uniformity and of spatial distortion.

Frame mode acquisition is the most commonly used. The form of the data coming from the detector is as a sequence of x,y coordinates. At some point we must form images. If we form images directly as part of the acquisition, this is called frame mode, whereas if we store the list of x,y coordinates, this is called list mode. In frame mode, a buffer exists, which could be a slab of memory in the acquisition interface, or could be part of the computer memory, which has been allocated to an image (a frame). As each event arrives, after being digitized and corrected, the x,y coordinate is used to form an address, and the corresponding location in the frame incremented by one. The frame therefore acts as a counter, and (provided that it was initialised to zero) after some interval of time, corresponds to the (digital) image.

The parameters of the frame size which can vary are the frame size, and the bit depth. Frames are usually in powers of two for nuclear medicine applications, going from as little as 32x32 up to 512x512. Sampling theory states that we should sample at twice the frequency of the maximum frequency in the signal, depending on depth etc, almost certainly not less than 6mm. Thus we should sample at 3mm intervals, that is, for a 40cm field of view, the matrix size should be about 133x133. Thus 128x128 is a reasonable matrix size, and there is little point in theory to going to finer matrices than this. The only justification might be for display or for correction of errors such as spatial distortion.

The frame time is the length of time for which data is collected. The maximum count which might occur at a pixel is dependent on the total number of counts collected (which depends on count rate and frame time), and the activity distribution. If the activity is distributed over a small area, the maximum count rate will be much higher for example as might occur with a point source. The number of bits available should be enough to accommodate the maximum number of counts. The normal choices are between byte mode where 8 bits per pixel are allowed, word mode where typically 16 bits per pixel are allowed, and certain system which use intermediate values such as 12 bits per pixel. The data is normally considered as being an unsigned integer and thus the maximum number of counts in a byte mode acquisition is 256, and 65536 for a word mode acquisition. Action must be taken on overflow, that is when the maximum value is exceeded. One possibility is to start a new frame, but that would make the frame timing irregular. The interframe time is the time gap between two frames, and is normally very short, when double buffering is used.

The term Gated study is used to indicate a study where a set of images are acquired for a whole range of time delays, for example, throughout the cardiac cycle. Gating is equivalent to time lapse averaging that is, data is averaged together for some time delay after some signal. The signal used here, in cardiac studies, is the R wave of the ECG. Thus essentially, a gated image is formed by acquiring data in frame mode, but only accepting events which occurred during some time interval after the R wave of each cardiac cycle.. Thus we could gate an image coincident with the R wave to give an image of the heart at end-diastole, or use an appropriate delay to obtain an image at end-systole. There are many details of importance, primarily resulting from the fact that the cardiac rhythm is unlikely to be completely regular. The first choice for a Gated acquisition is to acquire a set of frames at fixed time intervals after the R wave, for example every 10 milliseconds. When this is chosen, when a shorted beat occurs, fewer counts will be added into the last frames, and the count density of these frame will be less. When a time activity curve is drawn, it will tend to droop at the end. An alternative

is phase gating where the cardiac cycle is divided into a fixed number of frames, for example 32, and the time per frame is chosen from the R-R interval of the current beat. However, the R-R interval cannot be known in advance, and this implies either buffering the data on input, and storing at least one beat's worth of information, or using list mode. In addition, the components of the cardiac cycle, for example time between e-d and e-s may not change proportionally to the change in R-R interval. If the data is buffered, it is also possible to perform backwards gating, that is forming images with respect to fixed time intervals before the next R wave. Indeed it is possible to perform hybrid gating, forward gating the start of the cardiac cycle, and backwards gating the end (and hoping it matches in the middle). Bad beat exclusion also needs to be performed, that is, rejecting data coming from an R-R interval which is either too long or too short, or following a bad beat, when the heart may not have filled adequately. There is some clinical disagreement on what is the best technique to use.

List mode acquisition is a very important extra to have in addition to frame mode. The data is directly stored to disk and then replayed to create images and enables 'impossible' acquisitions to be created by choosing frame times after the acquisition. Although frame mode data collection is used for the bulk of acquisitions in nuclear medicine, there are occasions when list mode is essential. List mode acquisition is that mode where the individual x and y coordinates of each pulse recorded is sent directly to some backing store (such as a hard disk) without being turned into image frames. It therefore can occupy quite a lot of space on disk, approximately 2 bytes per event recorded. Usually the acquisition system is double buffered. Having stored the data, one usually wants at some time, to do something with it. This involves replay of the data, that is, recalling it so as to be able to form image frames. The way in which image frames are formed is just like the way in which they were created in frame mode acquisition, except that the source of the data is the backing store, rather than the camera. The reason for doing this is that the parameters of the image frames created can then be selected AFTER the acquisition. Thus we do not need to choose in advance the frame times, this could be chosen a posteriori, when we know what frame times are appropriate. However, in order to be able to reframe at all, we must store timing information with the raw data. This is usually performed by inserting codes into the list mode data, for example time ticks and physiological markers when appropriate. There are several other reasons why list mode data could be useful. It is possible using list mode to create image frames which could not have been created directly. For example, given the available amount of memory available for acquisition, there is a maximum number of frames that could be created for a gated study. Using list mode data, and replaying the data, possibly several times, this limit can be exceeded. Similarly, backwards gating, that is forming images at fixed time with respect to some event in the future, can be easily handled by list mode acquisition. Handling bad beat rejection can be much more sophisticated in list mode. The drawbacks of list mode acquisition is that the maximum count rate that can be handled is low, limited by the speed of writing onto disk, the space required is usually rather large, typically several megabytes, and finally the replay process is time consuming. List mode data seems to be of particular interest in PET imaging.

Data acquired by a gamma camera often appear to be non-uniform. Corrections are required for this, primarily energy correction and spatial distortion correction. When an event is detected at a position  $x,y$  it is observed to have an energy  $z$ . Two maps are normally created, the exact form of which can vary. The first map contains for example correction terms in  $z$ ,  $dz$  for all values of  $x,y$ . The second contains correction terms in  $x$

and  $y$ ,  $dx$  and  $dy$  for all observed values of  $x$  and  $y$ . The sequence of operations (in pseudo-C) is as follows

```
z+= dz
x+= dx
y+= dy
if z between zlower and zupper then IMAGE[x][y]++.
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Some details need to be taken care of such as rounding and variations in energy resolution.

A second correction often applied just after acquisition is matrix multiplication uniformity correction. Let  $CORR[i][j]$  be the  $1/\text{probability}$  of expecting a count at  $i,j$  for a uniform source. The matrix multiplication correction is just

$$IMAGE[i][j] = IMAGE[i][j] * CORR[i][j] \text{ for all } i,j.$$

The presence of scatter degrades resolution and reduces quantitative accuracy. Various methods exist for correcting scatter which can be classified as dual window, multi-window, and spatial varying object dependent methods. Because of the finite energy resolution of detectors in nuclear medicine, it is inevitable that scattered events are detected as well as 'good' (unscattered) events. The result of including scattered events is to degrade the spatial resolution of the image. The point spread function (PSF) will be degraded in two ways. The central portion will be broader, meaning that the intrinsic resolution of the system will be poorer, and there will be long tails present, which will generally increase the background level, and reduce quantitative accuracy. The scatter fraction (the ratio of scattered to unscattered events) in many images is of the order of at least 30%. However, scattered events do contain some useful information, an image of scattered events will look like (be correlated with) the true activity distribution, an effect which is very dependent on energy. The angle of scatter for Compton scattered events, is a function of energy, as determined by the Klein Nishina formula. The use of this energy dependent angular information has also been the basis of Compton cameras.

Thus a number of different techniques exist for scatter correction, or the reduction of the harmful effects caused by the contamination of the observed image by scattered events. (Note that there is a significant difference between removing scatter, and eliminating its harmful effects.). The simplest of these is the dual window scatter correction often called the Jaszczak method. Here an image is acquired for a lower energy window, and a constant fraction of it subtracted from the higher (photopeak) window. The use of the asymmetric high energy window is also aimed at removing most scattered events by excluding them from the energy window. An even simpler technique called the Axelsson method estimates the scatter contribution by assuming an exponential tail to the central part of the PSF and then subtracting this from the photopeak image. More sophisticated techniques have been developed using the energy information itself to assist in the scatter correction. These methods could be called multiple energy methods, or wide energy window methods, where events are collected over many energies, and recombined using some rule to improve image quality. A number of patient dependent methods have been proposed, for example using factor and principal component analysis. Another very powerful method of scatter correction is to fit the energy

spectrum at every point (or over a region) within the image, and from this fit to estimate the scatter fraction, and to correct for scatter, based on this spatially varying estimate, everywhere within the image. Scatter correction in SPECT presents additional problems, in particular, related to quantitation. However the planar images may first be scatter corrected and then reconstructed, provided that the SPECT uniformity is adequate.

The gamma camera and the computer system are (or should be) tightly coupled. An important part of the acquisition is to ensure good image quality for example by performing uniformity correction. The corrections for energy uniformity and spatial distortion are performed in the gamma camera head, but all correction maps are stored and maintained in the computer system. All the acquisition programs therefore are designed to know about the gamma camera, and to be able to control its functioning, for example by taking care of the energy window under computer control. Likewise the gamma camera is capable of passing information back to the computer system, for example to indicate what collimator is being used. Since a great deal of information is therefore required to specify any acquisition, all acquisitions are performed under the control of an acquisition protocol, which is general specifies all these parameters, obliging the user to define only those essential for a specific study.

Features of special interest indicated in this section are:

- the ability to acquire data very fast, needed for first pass studies
- gated acquisition for cardiac studies
- the ability to acquire and reprocess data in list mode
- the ability to handle whole body scans
- techniques for Compton Scatter correction

## 2. Tomographic reconstruction

Tomography or ECT is the ability to image and reconstruct slices representing slices through the activity distribution within a patient. A gamma camera is normally used to acquire such data by rotating about a patient, either continuously, or at a set of predefined angular positions (step and shoot). As for planar imaging, data can be acquired in many different ways, for different matrix sizes, gated with respect to the cardiac cycle, correcting for Compton scatter, for circular or elliptical orbits. Even more than for planar imaging, quality assurance procedures are essential in order to ensure good image quality (for example to measure the position of the axis of rotation). Tomography is a chain of operations: we need to first acquire, then normalize, then reconstruct (having chosen the right filter) then attenuation correct, and then display, after perhaps having chosen to reorientate the slices. This section describes some of the functions provided by the system, all linking together, to ensure high quality clinically useful tomographic images.

As for planar imaging, the gamma-camera and computer system should tightly coupled, and all the acquisition functions need to be able to pass lots of information backwards and forwards to the gamma camera. Thus they (too) function under control of acquisition protocols to facilitate this operation for the user. Tomographic reconstruction is a complex operation and is very sensitive to errors. Thus the tomographic reconstruction programs all link together, and great care has been taken

with respect to interpolation, to the design of the filters, within all the components to ensure that image quality is maintained, and that the data is as quantitatively accurate as is possible.

The basic principle of a SPECT system depending on the rotating camera concept is that a series of planar images are collected while the camera is rotated through either  $180^\circ$  or  $360^\circ$  around the patient. These planar images are called projection images and are used to create transaxial slice images by some method of tomographic reconstruction such as filtered back-projection of the data into the transaxial plane. Each row of pixels across the projection image gives a projection line, in fact a profile of counts for a common Y value in that image. The counts in these projection lines may be back-projected at the appropriate angle across the transaxial plane, which would result in a first order approximation of the data that gave rise to the set of projection images. A projection ray is a line perpendicular to a projection, going through the volume which is being examined or reconstructed such that the sum of data along the ray (or weighted sum) is equal to the value of that point on the projection from which the ray was cast. A projection line is the set of values along one line, at some given angle, the value at each point corresponding to the sum of values along the projection ray cast from that point. A projection image is a 2 dimensional projection (for example a function of x and y) , at some given angle, comprising a set of parallel projection lines. A sinogram is an image formed from a set of projection lines, for some fixed offset (for example a constant distance along the axis of rotation) for angles around the object to be reconstructed. In order to improve this image formed by back-projection alone it is necessary to apply a filter in addition to back-projection. When applied to the projection line in the spatial domain, this filter has a central maximum with negative side lobes. This corresponds to a ramp filter in the frequency domain. Given perfect (noise-free) data with an infinite number of projection images this ramp filter would give perfect reconstruction in the tomographic slice. Unfortunately, the number of projection images that can be collected is limited and the data are far from perfect, being limited by Poisson statistics. As a result of this it is usually necessary to apply a windowing function to the filter used to modify the back-projection when using real data. The reconstructed image must also be corrected for other effects such as attenuation and scatter. If this is not performed, as a result of attenuation, the data in the centre of an object will appear to have been recorded with a decreased sensitivity with respect to the periphery. In addition the data will not be quantitatively accurate. The common reconstruction process of filtered back-projection can and is increasingly being replaced by iterative procedures which are described later. The original data are stored as a series of projection images and, depending upon the operator's commands, can be reconstructed to give one or a number of transaxial slices after appropriate filtering. and processing. Once the transaxial slices have been created it is possible to use the same data to create sagittal, coronal or oblique slices through the object, essentially by reordering the data. Fan beam reconstruction and Cone beam reconstruction are the modified reconstruction procedures employed when a converging collimator is used instead of a parallel hole collimator, that is data are acquired in fans or cones rather than have parallel projection rays..

In filtered backprojection reconstruction, the basic filter which must be used is a ramp. However to reduce the noise, this filter is usually used in combination with a window

function or low pass filter. There is an enormous choice of filters which have been suggested. Some typical filters are:

The Shepp and Logan window

$$w(f) = \text{sinc}(f/2f_m)$$

where  $\text{sinc}(x) = \sin(\pi x) / (\pi x)$

The modified Shepp Logan window:

$$w'(f) = w(f) \cdot (0.4 -$$

The Hann window:

$$w(f) = 0.5 + 0.5 \cos(\pi f/f_m) \text{ for } f < f_m$$

$$= 0 \text{ for } f > f_m$$

The Hamming window:

$$w(f) = 0.54 + 0.46 \cos(\pi f/f_m) \text{ for } f < f_m$$

$$= 0 \text{ for } f > f_m$$

The Butterworth window:

$$w(f) = (1 / (1 + f/f_m)^{2n})^{0.5}$$

where n is an arbitrary constant

The Parzen window:

$$w(f) = 1 - 6(f/f_m)^2 \cdot (1 - f/f_m) \text{ if } f < f_m/2$$

$$= 2(1 - f/f_m)^3 \text{ if } f_m/2 < f < f_m$$

$$= 0 \text{ if } f > f_m$$

All these filters are used in combination with the ramp and act as smoothing filters. There are two parameters which may be selected, the cut-off frequency  $f_m$ , and the fall off rate. The lower the cut-off frequency the smoother the resulting image. The sharper the fall-off rate, the more ringing may be perceptible in the image. The choice of the best filter is largely made on empirical grounds, that is, how many counts were in the images, how were they distributed, and how smooth a resulting images does one want.

However, many other reconstruction methods, in particular iterative methods such as ART, Maximum Entropy, Ordered Set Entropy Maximisation etc, may be employed. The interested reader is recommended to consult the literature for further information. The use of more complex iterative reconstruction techniques will considerably influence the signal to noise ratio found in the final images, and may also slightly affect the resolution and contrast of objects detected. They may have a considerable influence on the uniformity of reconstruction of a uniform object in particular with respect to the attenuation correction.

Data are normally acquired by acquiring an image for a fixed time at a specific angle and then rotating the detector to a new angular position. However for gated SPECT, it is required to acquire a sequence of images as in a planar gated images averaged over several heart beats. Variations in beat length and the limited time available at each angular position entail various somewhat ad hoc corrections to be applied to ensure reasonably uniform gated images.

Attenuation correction is that part of the reconstruction process whereby those counts (events) assumed lost due to attenuation within the object are restored. This correction may be performed prior to, during, or after the main reconstruction operation, and usually requires a knowledge of the distribution of attenuating tissue, for example, of the outside surface of the patient (the body contour), and not just of the distribution of the radioactivity within the body. Depending on the system, various methods have been employed for determining the body contour of the patient; by using external markers; performing a transmission study; or by using an additional lower energy acquisition window to detect scattered events. A transmission study can also determine the attenuation coefficient of different tissues within the body and an attenuation correction taking these differences into account can then be performed.

The partial volume effect is the loss of signal (normally observed as a loss of contrast) that occurs when an object to be detected or measured does not fully occupy the slice that is being reconstructed. This should be distinguished from the point spread function (PSF) effect which also results in a loss of signal for objects which are small or comparable in size to the resolution of the system. The effect of this is important in that the apparent contrast of small objects is reduced as if their activity concentration (or the difference in activity concentration with respect to the surrounding area) is reduced. This effect will depend not only on the size of the object but also to some extent on its shape.

Features of special interest indicated in this section are:

- the ability to acquire over different angular extents, in particular, to facilitate cardiac tomography
- gated tomographic acquisition for cardiac ECT
- the use of a wide variety of filters which can be optimised for different types of tomographic studies
- techniques for Tomographic Attenuation correction
- the ability to correct for patient motion
- a series of clinical tools, to choose oblique slice, and to generate bull-eye displays for Thallium ECT studies
- 3-D displays of tomographic images.

### **3. Processing and the Extraction of Physiological Data**

Having acquired the data, we want to be able to enhance the images, and, if possible, quantitate the results. A very large collection of functions are provided for image (or frame) processing, all of which link together to permit powerful clinical protocols to be defined. Some of these are quite simple, such as those provided to contrast enhancement, or to change the matrix size. Some of them are a bit more complex, such as median filtering to remove noise and similar procedures generally known as image processing methods, while some of the methods for generating functional image can be very complex. Functional images are images where, instead of showing the activity distribution, we try to indicate some physiological function, such as lung washout, cardiac regional ejection fraction, renal clearance etc.

A basic tool in image processing is the filter.. A second basic tools is the ability to perform arithmetic with images, that is, to multiple divide, add or subtract a constant to every pixel in an image, or to perform the same operations between two frames. Using these basic building blocks, quite complex operations can be performed. Some special utilities, for example performing a Fourier transform on every pixel as a function of time can help, especially for the analysis of cyclic (gated) data such as in cardiac studies. In general functional images are created by fitting various mathematical functions as a function of time to every pixel in a dynamic series. The ability to link together such building blocks by using a 'macro' language is the key to being able to provide powerful clinical protocols.

It is very hard to determine the overall image quality of an imaging procedure. However, one parameter which strongly influences image quality is the signal to noise ratio. Noise in conventional planar imaging is supposed to be Poisson distributed. For Poisson noise, the variance (S.D. squared) of an estimate is equal to the mean value. Thus if an image contains N photons which have been detected at some position, then the S.D. of the number of photons which could have been detected is equal to  $\sqrt{N}$ . Note this is NOT true for SPECT. Thus a crude estimate of the signal to noise ratio in nuclear medicine is  $\sqrt{N}$ , since the signal can be supposed to be equal to N and the noise as  $\sqrt{N}$ . However, in general, what we are interested in doing is detecting objects, such as small lesions. We then become interested in contrast. Although there are several definitions of contrast, the most commonly used is

$$\text{abs} [ (\text{max} - \text{min}) / (\text{max} + \text{min}) ]$$

where max and min are pixel value within and outside some object to be detected. Contrast is affected by the size of the lesion, the resolution of the system, and by the uptake ratio of a tracer. Contrast to noise ratio is essentially the contrast in a lesion, such as just defined, divided by the noise (here expressed in terms of the coefficient of variation that is the S.D. divided by the mean. This is often expressed a a percentage. Thus we might observe that a lesion had a contrast of 50%, but that the coefficient of variation over the background was 5%. Thus the contrast to noise ratio would be 10, that is the signal observed is 10 times the variation (S.D.) which could be expected from the noise. These definitions are critically dependent on the details of how they are measured. Another helpful concept is that of the minimal detectable contrast, that is, what is the smallest contrast for a lesion of a given size was can be perceived. The minimal detectable contrast will depend on lesion size, the imaging system, but not on the uptake ratio. From a knowledge of the uptake ratio, we can then estimate what is the smallest lesion that could then be detected. Quantitation is rather different. We are particularly interested in accuracy that is how close to the true answer out estimates lie, and precision how close together the estimates were (how reproducible they were, but not how close to the true answer they lay). We may also be interested in absolute accuracy and relative accuracy that is how accurate our estimates of the differences (ratio) of different regions within an image were.

Quantitation is one of the keys to nuclear medicine. The starting point is to be able to defined a region of interest (ROI) and to assess the number of events detected within that ROI. A flexible set of functions is required to be able to generate ROIs in many different ways, of fixed size and shape, of completely flexible shape, and to be able to

manipulate and edit these, for able to create pairs of mirror image ROIs. Having created an ROI, we may want to create time activity curves (TACs) or to perform some other kind of image processing. Cardiac analysis in particular requires some special functions, to detect the edges of the ventricles, to estimate the ejection fraction, and then for using in assessing cardiac wall motion. Thallium quantitation usually requires the determination of circumferential profiles, which are then compared for different studies, often with respect to a normal data base. The functions described here are some of the tools available in creating such clinical protocols.

Using a mouse or other graphics device, the user can create various types of region of interest (ROI) on a display, and then manipulate them as desired. Information about the ROI can be transmitted between different functions for example, in cardiac analysis, a function is provided to detect the position of the centre of the left ventricle LV, which is then passed to the function to create a region of interest about the LV which is then passed to a function which performs the edge detection of the LV within this region of interest.

While a gamma-camera computer system creates images initially, when quantitative data are to be generated and analyzed, this usually means working with curves, in particular time activity curves generated from regions of interest. We need the following tools: methods to generate curves easily from the raw data, methods to display, manipulate and intercompare curves, the ability to perform various types of arithmetic with a curve, or with several curves, and the ability to fit many different mathematical functions to observed curves. An example of this last type of operation is that of fitting a gamma function to observed blood flow curves, when looking for shunts. In addition rather more specialized operation such as that of deconvolution are required for certain types of clinical functions. A collection of some of the functions available in the tool kit for curve processing is presented in this section.

An example of such a dynamic sequence is a renogram. Here a labeled molecule is injected into a patient which is removed by the kidneys. Typically, images (for example 64x64) are acquired for example every second, for about a minute, immediately after the injection. This shows blood flowing to the kidney in the so called first pass. Images (128x128) are then acquired every 10-20 seconds for up to 20mins, showing radioactivity in the kidney at first increasing as the isotope is removed from blood and concentrates in the kidney, and is then excreted from the kidney and reappears in the bladder. There are similar processes for other organs for example liver, lungs, brain etc. The analysis of the data normally involves the creation of a time activity curve. Firstly we create one or several regions of interest, then we sum all the pixel values, for a given image at a given time, within those regions of interest, finally we create curves with the x axis being time, and the y axis being the sum of the pixel values for each of the regions of interest. We may also require to convert the curves into density e.g summed values within the ROI divided by the area of the ROI, and rate, i.e. values divided by the corresponding length of sampling interval for the frame being used, that is divide by the length of time for the frame. Note that the sampling interval, and the size of frame may change several time over the complete length of the study.

Time activity curves are then used to derive different parameters, depending on the study, for example time to peak, maximum rate of rise, maximum rate of fall, integral etc. Alternatively we may fit other functions, for example exponentials, look at rates of increase or decrease, or gamma functions, looking at the passage of a tracer. In the kidney case we may also perform deconvolution. If the kidney may be represented by a function  $h(t)$  and the input of radioactivity in the blood is known and has a function  $i(t)$  and the summed radioactivity in the kidney is also known and has a function  $o(t)$  it is possible to write an convolution equation of the form

$$o(t) = i(t) * h(t)$$

We may then solve for  $h(t)$  which is unknown by many methods, for example by using the Fourier transform. If  $O(u)$  is the FT of  $o(t)$  as usual then

$$O(u) = I(u) \cdot H(u)$$

and therefore  $H(u) = O(u) / I(u)$ . This is called deconvolution. In order to avoid dividing by zero, the operation must be windowed (a smoothing filter used). Several other algorithms are available.

Curves are an important type of data within the nuclear medicine system, and information is attached about how they were generated, which is important from the point of view of quantitation. Arithmetic can be performed on curves, for example adding, subtracting, multiplying, dividing curves and constants, or pairs of curves, all of which can be linked using the 'macro' language to provide the tools for more complex clinical protocols. Various methods for smoothing curves are provided, or perhaps better, a wide range of utilities for fitting many different types of mathematical function must be provided.

An example of this is Cardiac Fourier analysis. The sequence of values in time for a gated study at each spatial position can be considered as a set of time curves. Each of these could be Fourier transformed to extract frequency components and phase values. Since only lower frequencies are of interest, a simpler technique is to compute two values at each positions  $i,j$

$$\begin{aligned} A[i][j] &= \text{SUM of } C[i][j][t].\text{Cos}(\omega.t) \\ B[i][j] &= \text{SUM of } C[i][j][t].\text{Sin}(\omega.t) \\ \text{AMP}[i][j] &= \text{SQRT}( A[i][j]^2 + B[i][j]^2 ) \\ \text{PHASE}[i][j] &= \text{Arctan}( B[i][j] / A[i][j] ) \end{aligned}$$

Where  $C[i][j][t]$  is the original sequence of images in time and  $\omega$  is a suitable constant. AMP and PHASE are the resulting so called Amplitude and Phase images. A more complex variant on this is the use factor analysis to generate the basis functions from the data (minimizing variance) with an oblique rotation (summation of different factors based on a positivity constraint).

Many other functional images exist, based on the fitting of exponential functions to the time curves at each position, time to peak, fitting special functions such as the Gamma function for modelling blood flow and looking at phenomenae such as shunt, or the use of compartmental models. Here, for each time curve, a model is fitted and the functional images are maps of the coefficients of the model. It is common to mask such images to exclude regions where the functional values are incorrect, or by

excluding regions where the signal to noise ratio does not permit such calculations or by the use of other a priori information. It may also be more efficient to perform such computations over small regions rather than pixel by pixel. The extension to 4d data, 3d+ time is essentially trivial.

Segmentation is also very important, and in many respect does not differ enormously from that of other types of images. A particular feature of nuclear medicine images is that they are very noisy and do not have sharp edges. This is for example true of cardiac images where the wall thickness is comparable to the resolution of the imaging system. However several classical algorithms have been developed. One important aim has been to outline the left ventricle LV, and then to assess the activity in that region of interest (ROI) in order to determine cardiac function, for example ejection fraction EF. If counts at the time of maximum expansion, end-diastole (ED) are called  $C_{ED}$  and counts at minimum expansion end-systole are called  $C_{ES}$  then ejection fraction is defined as

$$EF = (C_{ED} - C_{ES}) / C_{ED}$$

normally expressed as a percentage. This is incorrect since background needs to be taken into account. Thus if the estimate of background is obtained, for example at BOTH ES and ED then these background corrections have to be applied e.g.

$$C'_{ED} = C_{ED} - C_{BGD}$$

At ED where the primed value replaced the unprimed value in the above equation. Now background is difficult to define, and is usually done by assuming a background region about the LV, and shown below. The LV ROI may be defined manually, or automatically.

It has been found that a good automatic method for determining the LV ROI is as follows. Firstly, transform the system into polar coordinates, that is in practice, make profiles through the LV at various angles and place each profile in a matrix, row by row. Now apply 1-D filters (e.g. [-1,1]) to the polar matrix. A single 1-D filter will determine the gradient, and 2 1-D filters are the same as a Laplacian [-1,2,-1]. Looking for peaks in the Laplacian is the same as looking for points of inflection and seem to be good for estimating (the outside edge) in the cardiac image. So for each line (row) in the polar map we can determine a peak. Now we need to connect the peaks on each line together to make a ROI. The best method is (yet again) to minimise some function.

Let total cost be defined as

$$COST = a \cdot \text{SIGMA } L(i,i+1) + b \cdot \text{SIGMA } V(i,j)$$

where  $L(i,i+1)$  is the length of the line segment and  $V(i,j)$  is the value of the point on the (Laplacian) image. Let  $a$  be negative and  $b$  be positive. COST will be minimized by finding the shortest line which connects the highest values, allowing the line to be adjusted at points on each horizontal line. The resulting set of values  $(i,j)$  when turned back into  $x,y$  coordinates defines the ROI. The algorithm is called a minimum cost

contour. Other similar algorithms exist such as snakes or deformable contours. Again for gated SPECT the algorithms needs to be extended into 3D.

Similar requirements exist for comparing images at different times, for example cardiac images at stress and rest. One conventional technique in 3d is to measure the myocardial wall thickness for each slice through a 3d cardiac image at a number of angles for example 32. This is effectively a low resolution polar transform for cardiac images aligned along the long axis of the heart. This is then remapped into a so-called bulls-eye map. Here radial distance indicates slice position (distance from the apex of the heart). Angle in the slice is mapped onto angle in the bull-eye map. The value placed at the point is dependent on myocardial wall thickness in the corresponding slice at the corresponding angle. Wall thickness may be estimated from the pixel/voxel values observed (assuming wall thickness is equivalent to isotope uptake), or by estimating the distance corresponding to the thickness of the wall, or by some hybrid measure. In 2D, such a method would generate so-called circumferential profiles as often used with planar cardiac analysis.

Analysis of brain images requires detection of regions of high or low uptake (in 3D) and then assessing their significance, often by comparison to an atlas. The atlas corresponds to a set of normal data giving expected values and corresponding variance. The unknown image needs to be registered to the atlas.

Features of special interest indicated in this section are:

- Cardiac analysis using Fourier methods
- many different types of functional images, in particular the use of Factor analysis
- advanced methods for removing noise from functional images
- automatic region of interest analysis for gated cardiac studies
- circumferential profiles for Thallium studies
- Gamma function fitting for shunt evaluation
- deconvolution for kidneys studies and correction of bolus injections.
- mathematical functions such as curve power spectrum, Chebychev smoothing etc

#### 4. Multi-modalities and Image Networks

Computing in nuclear medicine is often no longer about a single computer being connected to single camera, but in many cases, about managing a network, where there any several computer, several gamma cameras, and many users. The systems need to be linked together so that data can be transferred easily from system to system, and robust methods of backing up data and archiving studies must be provided. In this section, some of the utilities provided for system managements, handling the archive and in particular networking are described. Making the collection of system work together well on a network is one of the most important methods of improving productivity and efficiency.

The use of a large archive, for example on optical disks must provided as a more efficient way to handle such patient data. Networking can be provided by linking all the systems together on Ethernet/ FDDI etc. This also provides the ability for the system to connect with other (parts of) the network such as the HIS/RIS in particular the patient record. Remote access can be provided to provide tele-medicine facilities such as remote diagnosis or tele-consultation. The ability of the system to share files and have access to data throughout the network is central to the way in which the system functions.

Registration is important both within nuclear medicine image processing and for handling image from different modalities. It means the ability to superimpose data from different sources, that is computing the transformation which will map a pixel from one source into a pixel from the other.

This is normally a transform of type

$$\mathbf{X} = \mathbf{T} \mathbf{Y}$$

where  $X$  is the coordinate position in one image data set,  $Y$  in the other and  $T$  is an appropriate transform (rotations, scale changes, translations etc. There are a number of methods which have been employed.

Point based methods include the use of:

External markers-

Internal reference points-

find a distance measure for example sum for all point I of  $x_i - x_i'$  squared and then minimize this with respect to the transform (find the transform which gives the smallest value) Here this can be done by matrix solution in particular SVD..

Edge based methods include:

Principal axes-

compute the centre of gravity and the principal axes and superimpose them (not good with defects).

Cap-hat-

find edges/surfaces, estimate distance function for example by polar ray casting from the centre of gravity of each image dataset, and using an L2 distance measure from matching rays.

Chamfer filtering

Grey scale based methods include:

Stochastic sign change-

maximize the number of crossings that is one image data set has values greater than the other followed by the next position where this is reversed. This is particularly useful in nuclear medicine images where the data are noisy, and where extent of the images may be dissimilar. The technique only matches similar regions. It is thus very helpful for oncological studies where images at different times are compared, where the uptake of a label tends to concentrate in a tumour.

Co-occurrence map method-

Plot co-occurrence map of pixels from the two images, compute some distance function such as variance, mutual information etc, and minimize the transform with respect to this measure.

Image fusion is the display of two different images together - for example by use of checkerboard pattern of grey scale and colour for each image data set respectively.

Multi-modality image fusion is probably the future in nuclear medicine image processing and registering in particular MR data and nuclear medicine SPECT and PET data has given good clinical results. This requires that file formats being exchangeable and the use of DICOM has facilitated this.

Thus a nuclear medicine network can become part of a Picture Archiving and Communication System (PACS) network. However, there are some notable differences between a typical nuclear medicine workstation and a PACS workstation. Unlike most radiology applications where the most common operation to perform on an image is to change the window levels, nuclear medicine image processing involves much handling of dynamic sequences of data and performing various algorithms to extract dynamic information such as rate constants etc. The requirement to define regions of interest either manually or automatically is essential. Thus will the original nuclear medicine images may be perceived as being very low resolution and low quality, the clinical information that can be extracted indirectly can be very important. Thus the time spent in the analysis of nuclear medicine image data including PET can be very considerable and may amount to hours of processing per patient study.

Special features provided by the system include

- handling of large archives on optical disks
- the patient database
- standardised networking between all acquisition and image processing workstations
- remote access to other networks
- multi-modality image registration and fusion
- special need of nuclear medicine image processing workstations.