# CHAPTER 17

# QUANTITATIVE NUCLEAR MEDICINE

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Planar imaging is still used in clinical practice although tomographic imaging (single photon emission computed tomography (SPECT) and positron emission tomography (PET)) is becoming more established. In this chapter, quantitative methods for both imaging techniques are presented. Planar imaging is limited to single photon. For both SPECT and PET, the focus is on the quantitative methods that can be applied to reconstructed images.

## 17.1. PLANAR WHOLE BODY BIODISTRIBUTION MEASUREMENTS

Planar whole body imaging is almost always carried out by translating the patient and bed in the z direction between opposed heads of a dual head standard scintillation camera, typically in the anterior and posterior positions. The resulting images are 2-D projections of the 3-D object being studied. The attenuation of photons varies with the distance and the material the photons have to travel through the object before reaching the detector. One approach to compensate for attenuation in planar imaging is to perform conjugate counting with the geometric mean, which consists of acquiring data from opposite views and combining them into a single dataset. Figure 17.1 shows an imaging object with uniform attenuation viewed by two gamma detectors placed in opposite directions. A point source in the object has attenuation depth $d_1$ and $d_2$ to detectors 1 and 2, respectively. The projected counts $P_1$ and $P_2$ measured on detectors 1 and 2, respectively, are:

$$P_1 = I_0 \exp(-\mu d_1), \quad P_2 = I_0 \exp(-\mu d_2) \tag{17.1}$$

where

$I_0$ is the 'unattenuated' number of counts that would be detected (in the absence of attenuation);

and $\mu$ is the attenuation coefficient in the object.

These two conjugate views are combined using the geometric mean $P_G$ defined as:

$$P_G = \sqrt{P_1 P_2} = I_0 \exp(-\mu D/2) \tag{17.2}$$

where $D$ is the total thickness and $D = d_1 + d_2$.

The geometric mean depends on the total thickness, but not on the source depths. This result is exact only for a point source. Corrections can be made for extended sources [17.1]. The geometric mean using conjugate views is a popular quantification method for planar imaging. The arithmetic mean (average of opposite views) has also been proposed previously, but yields inferior results to the geometric mean approach described here.

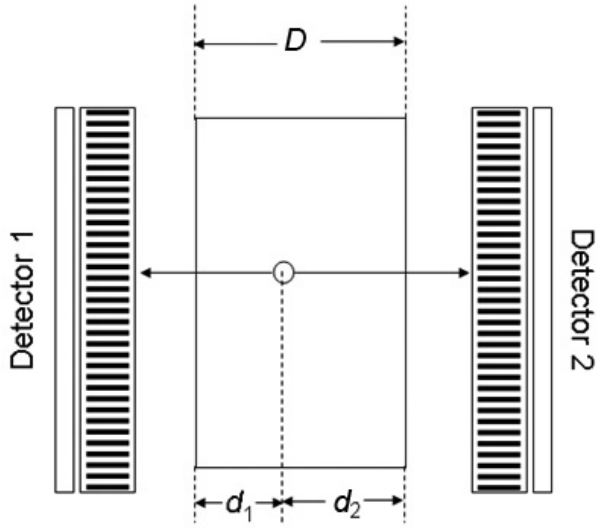


*FIG. 17.1. Illustration of conjugate viewing with the geometric mean for attenuation compensation.*

## 17.2. QUANTITATION IN EMISSION TOMOGRAPHY

### 17.2.1. Region of interest

Quantitative measurement of tracer uptake often requires the definition of a region of interest (ROI), where the tracer uptake is to be quantified. A reliable

although time consuming way to define an ROI is to draw the boundary of the volume of interest on every slice containing the organ or tumour of interest. It is difficult and time consuming to manually draw the boundary of an ROI because the activity profile at the edge of the area of interest is not abrupt, but changes slowly, and, therefore, deciding on a threshold to determine such a boundary is not always straightforward. The manually drawn ROIs are, therefore, generally not reproducible. Alternative semi-automatic and automatic methods use edge detection techniques, which include count threshold, isocountours, maximum slope or maximum count gradient, to improve reproducibility. Finally, another approach that has been successfully used to determine organs or volumes with a specific time–activity behaviour in a dynamic acquisition is factor analysis of dynamic sequences [17.2, 17.3].

### 17.2.2. Use of standard

When performing quantification from projections in the clinic, it can be helpful to image a standard activity (known measured activity) along with the patient (i.e. in the same projection). The standard (usually a small flask of the radiotracer) provides a conversion between radioactivity concentration (MBq/mL) and counts in the projections. It should be noted that the use of standards does not guarantee accurate absolute quantification because the standard activity is not affected by scatter, attenuation and partial volume effects in the same way as the activity distribution in the patient.

### 17.2.3. Partial volume effect and the recovery coefficient

Ideally, the activity intensity within a region in a reconstructed image should be proportional to the actual activity level in the region if scatter, attenuation, randoms (PET only) and dead time corrections are properly applied, and if it is assumed that there is very little noise. However, the partial volume effect (PVE) significantly affects the quantification based on the size of the object of interest. The PVE includes two different phenomena. One is the image blurring effect caused by the finite spatial resolution. The blurring results in spillover between regions. The image of a hot region, such as a tumour, appears larger and dimmer. This limited resolution effect is theoretically described by a convolution operation. The other PVE phenomenon is the so-called tissue fraction effect caused by the fact that the boundaries of certain voxels do not match the underlying activity distribution. The net PVE effect is the reduced contrast between the object and the surrounding areas, as well as the reduced absolute uptake in a hot region. For tumour imaging, the PVE can affect both the tumour apparent uptake and tumour apparent size.

The PVE is dependent on the size and shape of the region, the activity distribution in the surrounding background, image spatial resolution, pixel size and how uptake value is measured. The PVE correction is complicated by the fact that not only activity from inside the region spills out but also activity from outside the region spills in. As these two activity dependent flows are not usually balanced, it is difficult to predict the overall PVE effect.

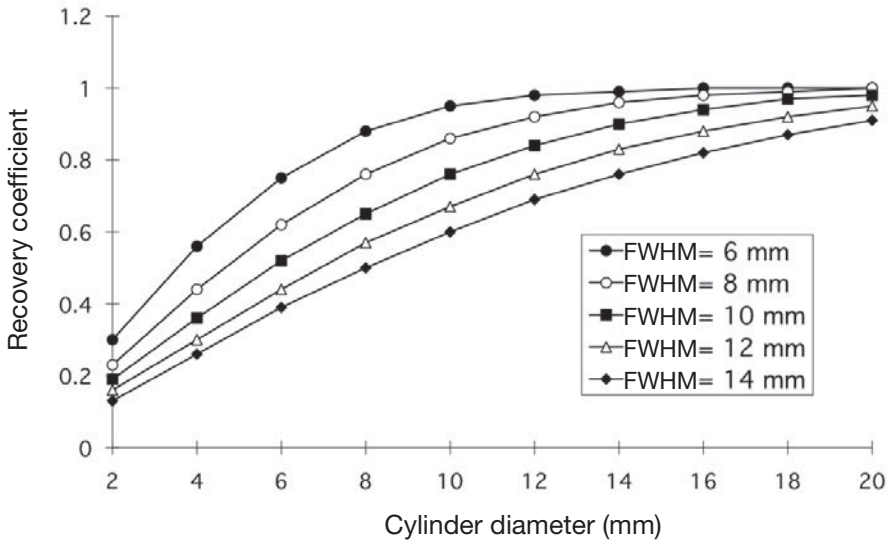


*FIG. 17.2. Recovery coefficient versus cylinder diameter for different full widths at half maximum (FWHM) when imaging a cylinder filled with radioactivity in a 'cold' background.*

The ratio of the apparent concentration to true concentration is called the recovery coefficient (RC). If the spatial resolution of the system can be characterized at the location where the object of interest is (this is usually the case in both SPECT and PET as the dependence of spatial resolution on location is known), and if the size and shape of a region are known (i.e. from a different modality such as computed tomography or magnetic resonance imaging), the RC can be pre-calculated and then applied to the measured concentration value in the region. Figure 17.2 illustrates RC versus cylinder size for different SPECT or PET spatial resolutions in the case of a cylindrical region which contains a uniform level of radioactivity, surrounded by a 'cold' (i.e. has no radiotracer uptake) background. An RC close to one is obtained when the size of the object is more than twice the full width at half maximum. As the RC depends on the activity concentration in the region and in the surrounding background, the RC will be different if the surrounding background is also 'hot' (i.e. has radiotracer

uptake). The RC correction method is a very simple method commonly used for PVE correction in nuclear medicine [17.4]. However, the RC method can only be used to correct the spillover between two structures. Geometric transfer matrix is an approach that can account for the spillover among any number of structures [17.5]. Deconvolution is another approach to perform PVE correction without any assumption regarding tumour size, shape, homogeneity or background activity. These three correction methods are used to correct the uptake value in a region. It is also possible to model PVE in image reconstruction to obtain PVE corrected images.

### 17.2.4. Quantitative assessment

Reconstructed images can be assessed qualitatively and quantitatively. Qualitative interpretation is based on visualization that identifies regions with abnormal patterns of uptake of the injected radiopharmaceutical as compared to the known variants of radiotracer distribution. Quantitative assessment can be either relative or absolute:

— Target to background contrast: The target to background contrast is the ratio between the concentration within the target region and the concentration within the surrounding background. Therefore, contrast is considered a relative quantification metric.
— Radiotracer concentration: The radiotracer concentration (Bq/mL) is the amount of radioactivity per unit volume within a defined ROI. Sometimes, radiotracer concentration is converted into a different metric. For example, the standardized uptake value (SUV) is the radiotracer concentration normalized by injected dose and patient weight, and is mainly used to assess tumour glucose utilization for fluorodeoxyglucose (FDG) PET. Therefore, SUV is a semi-quantitative metric.
— Kinetic parameters: A time sequence of PET measurements, i.e. dynamic quantitative PET, makes it possible to measure tracer kinetics that describe the interaction between the tracer and physiological processes. For example, a water based tracer can be used to measure blood flow; a glucose based tracer, such as FDG, can be used to measure metabolic rate. This is the most accurate and absolute quantification metric that can be derived from PET measurements. Usually, absolute quantification is best achieved with PET because all projections are acquired simultaneously and, therefore, dynamic imaging can be more easily performed than with rotating SPECT cameras.

Clinical studies are generally analysed using qualitative and semi-quantitative (e.g. contrast, SUV) information. This is also the case for clinical trials and drug development.

*17.2.4.1. Relative quantification using contrast ratio*

Image contrast is the ratio of the signal level of a target relative to the signal level in the surrounding background. The contrast ratio (CR) is defined as:

$$\mathrm{CR} = \frac{C_\mathrm{T} - C_\mathrm{B}}{C_\mathrm{B}} \tag{17.3}$$

where $C_\mathrm{T}$ and $C_\mathrm{B}$ are the mean concentration within the defined target and background region, respectively.

*17.2.4.2. Relative quantification using the standardized uptake value*

The SUV [17.6] is a widely used semi-quantitative metric to measure tumour glucose utilization in, mostly, PET imaging. SUV (g/mL) is defined as:

$$\mathrm{SUV} = \frac{C_\mathrm{i}(\mathrm{kBq/mL})}{\mathcal{A}(\mathrm{kBq})/W(\mathrm{g})} \tag{17.4}$$

where

$C_\mathrm{i}$ is either the mean (for $\mathrm{SUV}_{\mathrm{mean}}$) or maximum (for $\mathrm{SUV}_{\mathrm{max}}$) decay-corrected activity concentration (kBq/mL) within the defined region in the image (or tissue);

$\mathcal{A}$ is the injected activity (kBq);

and $W$ is the patient weight (g).

It is normally assumed that the density of tissue is equivalent to 1.0 g/mL, such that the units effectively cancel and the SUV becomes a dimensionless measure. The primary use of the SUV is to quantify activity in an ROI independent of administered activity and patient weight. It has been shown that the SUV may correlate with the metabolic rate of FDG in different tumour types, especially when normalized for plasma glucose levels [17.7]. $\mathrm{SUV}_{\mathrm{max}}$ instead of $\mathrm{SUV}_{\mathrm{mean}}$ is often used because it is less sensitive to PVEs and it avoids including necrotic or other non-tumour elements. However, $\mathrm{SUV}_{\mathrm{max}}$ has lower reproducibility and a larger bias than $\mathrm{SUV}_{\mathrm{mean}}$ as it is computed over a smaller number of voxels [17.8].

To address this issue, a further term has been introduced, '$SUV_{peak}$', which is defined as the mean SUV value in a group of voxels surrounding the voxel with the highest activity concentration in the tissue. The SUVs will be affected by the level of image noise, which is affected by the reconstructed activity concentration, the parameters chosen in the reconstruction algorithm and a myriad of other factors. $SUV_{peak}$ is intended to be a more robust measure than $SUV_{max}$.

The primary drawback with the SUV is that it is affected by many sources of variability [17.9]. In addition to mathematical factors (e.g. ROI, noise and PVE) that can alter the accuracy of the SUV, there are a number of biological factors that can variably and unpredictably impact the SUV. Firstly, the SUV calculation is based on the total administered dose. If a portion of the radiotracer becomes interstitially infiltrated during intravenous injection, it is not routine practice to correct for the activity that is trapped at the injection site and, therefore, failing to circulate through the body. As a result, the calculated SUV can be artificially low, because the total administered dose used in calculating the SUV is greater than the actual dose reaching its intended intravascular target. Secondly, the glucose avidity of tissues in the body is dependent on numerous factors such as the presence of diabetes, insulin level and glucose level (the latter two fluctuate widely depending on the patient's most recent meal). If a patient is diabetic, glucose is metabolized poorly by normal tissues, therefore leaving more glucose available in the bloodstream to be metabolized by abnormally glycolytic tissues such as tumour and infection, theoretically resulting in an artificially elevated SUV. Conversely, if a diabetic patient has just received a dose of insulin, the opposite effect may occur, lowering the SUV. In non-diabetic patients, a patient who has recently eaten will have high glucose and insulin levels, with a similar effect of lowering the SUV. Thirdly, FDG is cleared from the body through urinary excretion. Patients with impaired renal function will extract FDG more slowly from the bloodstream, leaving more FDG available for metabolism by both normal and hypermetabolic tissues. Finally, body mass is also a parameter used in calculating the SUV. In patients with a large number of ascites, or other significant '3rd-spacing' processes, the body mass of the patient will be elevated by the presence of fluid that is neither intravascular nor capable of uptake of radiotracer. Therefore, the denominator used in calculating the SUV will be artificially large due to overestimation of the size of the patient, theoretically causing an artificially low SUV to be calculated. Another factor that plays a key role in standardization of tumour uptake is the reproducibility of the measurement, and it has been previously shown that the correlation between uptake measurements made in an identical manner at different clinical sites was relatively low and significantly different to the standard reference measurement. It is not uncommon that the SUV can vary 50% because of one or more such effects. Therefore, the SUV should be properly corrected for all of these effects.

Another useful metric to assess tumour response to therapy is total lesion glycolysis (TLG) defined as:

$$\mathrm{TLG} = \mathrm{SUV}_{\mathrm{mean}} \times V \tag{17.5}$$

where $V$ is the tumour volume (mL) that can be obtained using 3-D contour software.

TLG provides a measurement of the total FDG uptake in the tumour region, which reflects total rather than average tumour metabolism.

*17.2.4.3. Absolute quantification using kinetic modelling*

Dynamic imaging consists of acquiring data as a series of time frames that capture the time–activity curve in each voxel over time, making it possible to quantify tracer kinetics in vivo. Using a given radiotracer, the interaction of the radiotracer with the body's physiological, biochemical or pharmocokinetic processes can be monitored. For example, glucose metabolism can be assessed by FDG, a glucose analogue radiotracer. With an understanding of the underlying physiological factors that control the tissue radioactivity levels, mathematical models, known as kinetic models, can be constructed with one or more parameters that describe the distribution of radiotracers as a function of time in the body and fit the time–activity curves in each voxel in the organ of interest. Kinetic models used in nuclear medicine are based on compartments within a volume or space within which the radiotracer becomes uniformly distributed almost instantly, i.e. contains no significant concentration gradients. In other words, compartmental modelling describes systems that vary in time but not in space. More complicated kinetic models that include spatial gradients are generally not applicable to nuclear medicine because of limited spatial resolution.

For a single-tissue compartmental model illustrated in Fig. 17.3, the rate of change in tracer concentration in a tissue is:

$$\frac{\mathrm{d}C_{\mathrm{t}}(t)}{\mathrm{d}t} = K_1 C_{\mathrm{a}}(t) - k_2 C_{\mathrm{t}} \tag{17.6}$$

where

$C_{\mathrm{t}}(t)$ is the tracer concentration in the tissue;
$C_{\mathrm{a}}(t)$ is the tracer concentration in the blood;

and $K_1$ and $k_2$ are the first order rate constants for the flux into the tissue and out of the tissue, respectively.

The solution for the above equation is:

$$C_t(t) = K_1 C_a(t) \times \exp(-k_2 t) \tag{17.7}$$

As the blood is the tracer delivery compartment, $C_a(t)$ is also known as the input function. The input function is directly measured from blood samples or images of the blood, typically using the left ventricular blood pool. The tracer concentration in the tissue $C_t(t)$ is usually obtained from ROI analysis of a dynamic series of images. Knowing both $C_a(t)$ and $C_t(t)$, regression analysis can be applied to solve both $K_1$ and $k_2$. These kinetic parameters can be used to interpret the underlying physiology. $K_1$ is closely related to blood flow when the extraction fraction is large, but is more related to permeability when the extraction fraction is small. The ratio $K_1/k_2$ is the equilibrium volume of distribution that is defined as $C_t/C_a$ when the net tracer flux between compartments is zero after sufficient time. By plotting the kinetic parameters as a function of the spatial coordinates, parametric images of the radiotracer can be constructed.

Other applications of kinetic modelling in PET imaging include measurement of glucose metabolic rate [17.10], and measurements of receptors and neurotransmitters [17.11], etc.

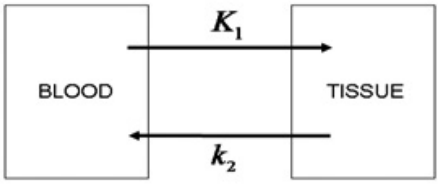


*FIG. 17.3. Single-tissue compartmental model that describes the tracer exchange between blood and tissue.*

### 17.2.5. Estimation of activity

Bias, precision and accuracy are three important statistical concepts for quantitative nuclear medicine. Bias is the difference between a population mean of the measurements or test results and an accepted reference or true value.

The bias is mainly due to faulty measuring devices or procedures. One common bias measure is defined as:

$$\text{BIAS} = \frac{1}{N}\sum_{i=1}^{N}(x_i - t) \tag{17.8}$$

where

$N$ is the total number of measurements;
$x_i$ is the measured value for the $i$th measurement;

and $t$ is the true value.

Random error is a variable deviation and arises from the fluctuations in experimental conditions, such as Poisson noise. Random error is also called variance, but it is also often defined as the inverse, namely precision, referring to the absence of random error. Precision can be quantified by the variance defined as:

$$\sigma^2 = \frac{1}{N}\sum_{i=1}^{N}(x_i - \bar{x})^2 \tag{17.9}$$

where

$$\bar{x} = \frac{1}{N}\sum_{i=1}^{N}x_i \tag{17.10}$$

It is important to note that the calculation of precision does not require knowledge of the true value. Therefore, precision alone cannot be used to evaluate the performance of a measurement.

Bias and precision can be combined to assess the performance of a measurement. Less biased and more precise measurements yield more accurate estimations. Accuracy is, thus, defined as the overall difference between the measured value and the true value. Accuracy can be quantified by the mean square error (MSE) [17.12] defined as:

$$\text{MSE} = \frac{1}{N}\sum_{i=1}^{N}(x_i - t)^2 \tag{17.11}$$

It can be shown that [17.13]:

$$\mathrm{MSE} = \sigma^2 + \mathrm{BIAS}^2 \tag{17.12}$$

To have the same scale as the mean value, precision is also quantified by standard deviation, defined as the square root of variance. Similarly, accuracy is also quantified as root MSE defined as the square root of MSE.

### 17.2.6. Evaluation of image quality

Image quality is a concept that has received a lot of attention recently in an effort to better define what image quality is. A good surrogate for image quality is image utility, i.e. the usefulness of an image for a particular detection or quantification task, rather than measures of image properties, such as resolution, contrast or stationarity of the point spread function, or of image fidelity, such as normalized MSE. Measures of quantitative accuracy, precision and root MSE are, of course, very useful when first assessing a new system or a quantification method; however, for more rigorous evaluation or for definitive optimization of data acquisition strategies, reconstruction techniques or image processing procedures, it is recommended to carry out an objective assessment of image quality based on detection or quantification tasks. Performance metrics for task based estimation or detection tasks can be viewed as measures of image utility which are the most clinically relevant bases on which to evaluate or optimize imaging systems.

The most conclusive assessment of image quality is based on human-observer studies. However, such studies are not routinely performed clinically because they are time and resource consuming. Instead, a numerical (or mathematical) observer is often used. It is beyond the scope of this chapter to detail the different numerical observers used in SPECT and PET (for a review, see Refs [17.13, 17.14]).

One of the simplest numerical observer methods is the non-prewhitening matched technique, which is the optimal observer when images have uncorrelated noise. Assuming $N$ noise realizations of target-present image $\boldsymbol{S}$ and $N$ noise realizations of target-absent image $\boldsymbol{B}$, the non-prewhitening signal to noise ratio ($\mathrm{SNR}_{\mathrm{NPW}}$) can be calculated as:

$$\mathrm{SNR}_{\mathrm{NPW}} = \frac{\left|\langle \boldsymbol{S}\cdot\boldsymbol{T}\rangle - \langle \boldsymbol{B}\cdot\boldsymbol{T}\rangle\right|}{\sqrt{1/2[\sigma^2(\boldsymbol{S}\cdot\boldsymbol{T}) + \sigma^2(\boldsymbol{B}\cdot\boldsymbol{T})]}} \tag{17.13}$$

where $\boldsymbol{T}$ is the target matched filter.

More sophisticated numerical observers include the channelized Hotelling observer that is a better surrogate for a human-observer under less ideal situations.

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