PROPOSED PROTOCOL FOR INTERNAL DOSIMETRY USING PATIENT-SPECIFIC ATTENUATION-CORRECTED SPECT SCANS

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The Medical Internal Radiation Dose (MIRD) protocol has provided a solid foundation over the years for calculating the internal absorbed dose but as for providing an assessment that is specific to the individual patient's organ/tumor anatomy, it falls short. Various methods have been proposed to overcome the shortcomings of the MIRD protocol, but each has its own limitations.

Quantitative SPECT proves to be the most desirable option for determining dose estimates, yet the prolonged scan times prevent SPECT from becoming a clinical protocol in dosimetry. Given the time constraints of clinical SPECT, planar quantitative imaging has proved a popular choice for dosimetry studies, but the resulting dose overestimates may prevent maximum therapy from being achieved.

Proposed here is a protocol that contends to be clinically feasible, patient-specific, and promising in its results. This protocol combines the benefits of both quantitative planar and SPECT imaging. By maintaining the majority of scans as planar yet incorporating the benefits of attenuation corrected SPECT scans, a more accurate, yet attainable clinical protocol can be achieved. The 2 or more SPECT scans suggested make use of a Gadolinium-153 transmission source so that a simultaneous emission/transmission scan provide a patient-specific, attenuation corrected SPECT image. The SPECT data is then used to constrain the planar data, resulting in a more accurate dose estimate than would arise from planar alone. Phantom experiments demonstrate that the errors in absorbed dose estimates have improved from an average of 159% for planar methods alone to 14% by the addition of a SPECT constraint.
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For my brother Mitch.
Unlike external radiation sources, such as X-ray tubes and isotope units, Nuclear Medicine utilizes radiation from within the body to perform its diagnostic and therapeutic applications. This internal radiation originates from a radiopharmaceutical that has either been injected, ingested, or inhaled by the patient. The radiopharmaceutical is a pharmaceutical agent with a radionuclide (or radioactive nuclide) bound to it. The unstable atom(s) in the radionuclide can result in the emission of alpha particles, beta particles, gamma rays, Auger electrons, and/or low energy x-rays. All of these types of radiation are capable of giving rise to ionization when they are absorbed in matter. Absorption of energy from ionizing radiation may cause damage to living tissue and it is therefore of interest in Internal Dosimetry to quantify the radiation deposited in tissues and organs.

Since Nuclear Medicine is primarily focused on diagnostic imaging, internal dosimetry has been implemented as a means to calculate internally absorbed doses to assess the potential risks to the patient. For therapeutic applications, ionizing radiation can be viewed as beneficial when considering damage to unwanted (ie. malignant) tissue, however, it is necessary to quantitatively assess dose distributions to ensure satisfactory therapy while minimizing dose to critical organs. Radionuclide therapy involves the use
of larger amounts of radioactivity than in diagnostic studies, thus greater care must be used when assessing absorbed dose distributions in the body.

The Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine has established a formalism to provide a general framework for the dosimetry of administered pharmaceuticals. This framework, which employs the use of planar imaging techniques, was initially established to aid in the determination of absorbed dose from diagnostic radiopharmaceuticals. Although this method provides a consistent but simplified approach, the estimates are generally conservative – and in the case of radiotherapy, applicability of the method tends to be quite limited [1].

1.1 Aim of This Work

A major obstacle in attaining accurate quantitation in dosimetry is the attenuation of photons in the patient. The availability of Single Photon Emission Computed Tomography (SPECT), together with transmission scanning, allows a more accurate means of determining dose distributions in the body as compared to planar imaging techniques. The use of a transmission source in SPECT makes possible the construction of an attenuation map of the patient and, thus, patient-specific correction for the attenuation of photons passing through the patient – allowing for a more accurate estimation of the activity in the body. Transmission sources can be used in both SPECT and planar studies but the fact that SPECT provides a 3-dimensional way of accounting for activity arising from regions surrounding the source regions of interest, makes it superior to quantitative planar imaging. Quantitative SPECT provides the volumetric information needed for dosimetry whereas the planar scans cannot.

Unfortunately this is where the obstacle of practicality comes in. Regardless of the
Chapter 1. Introduction

Improvement quantitative SPECT can provide, it is just not practical in internal dosimetry to do SPECT full body scans every time that a scan is required. This is precisely why quantitative planar methods are still used, even in the presence of quantitative SPECT. Presently, even a single full body SPECT acquisition is very time consuming for regular clinical use, let alone implementing multiple full body SPECT scans as a protocol in internal dosimetry (as multiple scans are required to calculate the internal radiation dose).

This work involves an investigation into utilizing the benefits of regional quantitative SPECT scans in internal dosimetry while still allowing the majority of scans to be planar. The hope is that the incorporation of attenuation-corrected SPECT scan(s) into the common planar protocol will provide a useful improvement to internal dose estimates while staying within the limits of clinical practicality.

1.2 Structure of This Thesis

This introductory chapter builds the necessary foundation for an understanding of radiation relevant to Nuclear Medicine, its method of interaction in matter, and the means by which radiation is detected and stored for further analysis. Chapter 2 on Internal Dosimetry covers the fundamental basis (MIRD protocol) by which the absorbed dose is calculated. Two important factors for determining the absorbed dose are introduced: the MIRD S-factors and the cumulated activity \( \bar{A} \). This thesis focuses on improving the estimation of the cumulated activity in order to improve the absorbed dose estimates.

Measurement Techniques (Chapter 3) presents the imaging modalities available to acquire the patient images that are needed to perform dosimetry, namely planar and SPECT imaging, the limitations imposed on imaging by the attenuation of photons and how quantitation may be achieved by correcting for attenuation. Current methods
to perform dosimetry are included in this chapter along with the method proposed in this work. In Chapter 4, Simulations are described which quantify the shortcomings introduced by attenuation correction in planar imaging. The intent is to demonstrate why quantitative planar imaging is not sufficient as a complete method. And finally, Phantom Experiments presents some experimental results of the method proposed in this work and acknowledges two important factors that may affect quantitation in dosimetry, namely pixel saturation and dead-time.

1.3 Ionizing Radiation

It is important to understand the basic types of particles that are responsible for ionization in matter. The following is a brief summary of the origin of these particles and the way in which each behaves in matter. Only those particles of primary importance to internal dosimetry will be discussed further.

1.3.1 Ionizing Particles

Alpha Particles

Some atomic nuclei decay by the emission of an alpha particle. An alpha particle consists of two neutrons and two protons that are bound together. The alpha particle is a heavy particle and it is because of this, and its +2 charge, that it is highly interactive. These factors keep the alpha particle from travelling very far in any material, making it a non-penetrating radiation. Even alpha particles with energies as high as 5MeV have ranges of less than 0.04 millimetres in tissue [2]. Alpha particles lose energy by collisions with atomic electrons, causing ionizations to occur. Alpha particles are generally the result of nuclear decay in heavy elements. If ingested, these heavy elements have a tendency to deposit themselves in bone, usually interminably, thus increasing the radiation dose to
the bone marrow and impairing their usefulness in Nuclear Medicine applications.

**Beta Particles (Electron or Positron Emission)**

Nuclear decay can also result in the emission of electrons or positrons. Electrons are very light particles (7350 times less massive than an alpha particle) therefore less interactive, giving them a longer range in material [3]. Their paths through material also tend to be highly random. The electrons lose energy by collisions with atomic electrons (resulting in ionizations), by close encounters with an atom which can result in the excitation of the atom and/or by bremsstrahlung (which results in the emission of photons). Since bremsstrahlung is generally an effect of high energy (MeV range) electrons, which are far above the energies used in Nuclear Medicine, it is a process not of interest to this thesis. The range of an electron depends on its energy and the density of the material through which it travels. Its range tends to be longer than that of an alpha particle yet it is still considered a non-penetrating (short-ranged) radiation. As an example, the electrons produced by Hydrogen-3 and Sulphur-35 (having maximum electron energies of 18 keV and 167 keV respectively) have average ranges in unit-density material of 5.2 \( \mu \text{m} \) and 0.32 mm respectively [2].

**Photons**

The gamma photon, the vital component of Nuclear Medicine, is a result of interactions involving the atomic nucleus. Of the radionuclides used in Nuclear Medicine, the most abundantly used is Technetium-99m. Its mode of producing gamma rays will be discussed here. Technetium-99m is in a metastable state, as denoted by the ‘m’. The decay of a metastable state by the emission of a \( \gamma \) ray is called an isomeric transition. As is common to excited states, a Technetium-99m decay may also result in the emission of...
an orbital electron by a process called internal conversion. In this case, the nucleus decays by transferring energy to an orbital electron, resulting in the ejection of the electron instead of a gamma ray. Whether an electron or gamma ray is emitted is a study in probabilities but since the ratio of photons to electrons emitted is high, Tc-99m proves to be a definite advantage for studies requiring detection of $\gamma$ rays from internally administered radioactivity [4].

1.4 METHODS OF INTERACTION OF PHOTONS

At energies relevant to Nuclear Medicine (less than 511keV), gamma photons can interact with matter by means of the photoelectric effect, Rayleigh scattering, and Compton scattering (pair production cannot arise as it is only a factor at energies $\geq 1.022\text{MeV}$). These interactions can lead to ionizations, thus the emission of secondary electrons. The higher a photon's energy is, the greater its penetrating capabilities in matter.

1.4.1 THE PHOTOELECTRIC EFFECT

In the photoelectric effect the incident photon is completely absorbed by the atomic electron it collides with. This absorption of energy results in the emission of an orbital electron, known as a photoelectron. The kinetic energy of the emitted electron is the difference between the energy of the incident photon and the binding energy of the orbital electron. The short-ranged behavior of the electron, as mentioned earlier, results in the photoelectron depositing its energy close to the site of the photoelectric interaction. By definition, the photoelectric effect results in the total attenuation of the photon.
1.4.2 Rayleigh Scattering

Rayleigh scattering is an interaction between a photon and an atom whereby the photon is scattered by the atom as a whole. This type of elastic scattering results in essentially no energy being transferred to the atom. Given that there is no energy imparted to matter in this process, Rayleigh scattering is not a concern to Internal Dosimetry but the scattering itself may have an effect on the quality and quantitation of emission data.

1.4.3 Compton Scattering

In Compton scattering the interaction is between the incident photon and a loosely bound electron resulting in a transfer of energy to the electron. In this case, the incident photon energy greatly exceeds the binding energy of the electron. The photon, which has been scattered from its original path, may continue to interact by any of the methods mentioned here. Compton scattering, as its name suggests, contributes to the scatter of the photons.

The physical characteristics of radionuclides used in Nuclear Medicine are well known. The emissions that result from the decay of a particular radionuclide are important in determining its useful applications. Given the short range of the alpha and beta particles, they become useful tools in the applications of radionuclides in therapy – when the destruction of cells is important. The high penetrating power of gamma emissions makes them ideal in diagnostic imaging to provide functional information about a patients specific organ or body system, while simultaneously minimizing the dose to the patient. For therapeutic applications it is also useful to make use of a radionuclide, not only with short range radiation, but also with gamma emissions to aid in determining dose distributions within the body.
1.5 Attenuation of Photons

Quantification in SPECT requires that the image be corrected for the attenuation of gamma photons that are emitted during the nuclear decay of a radionuclide. These photons interact with tissues in the body. It is during these interactions that the photons may be deflected from their original path and lose some of their energy. Attenuation of photons will differ depending on the energy of the photon and the interacting medium i.e., bone, soft tissue, air, etc. A denser medium (e.g., lead, bone) will attenuate more photons than a less dense medium (e.g., air, soft tissue). Photons with higher energies will have a higher penetrating capability (less attenuation) than photons with lower energies (more attenuation) within the same medium.

1.6 Gamma Camera

Once a radiopharmaceutical has been administered, it is necessary to detect the gamma emissions in order to obtain the desired functional information. The instrument used in Nuclear Medicine for the detection of gamma rays is known as the Gamma camera. The Gamma camera is designed to have good detection efficiency of photons in the energy range relevant to the radionuclides used in Nuclear Medicine (80keV to 300keV) and its efficiency gets poor for energies above this. The components of the Gamma camera are the collimator (limits the acceptance angle of $\gamma$ rays onto the detector), the detector crystal (which produces visible photons from the interactions of the $\gamma$ rays with the crystal), and an array of photomultiplier tubes on the back surface of the crystal (to transform light into electric pulse and amplify the signal) and position logic circuits (to determine the location of each visible photon as it is produced within the crystal).
1.6.1 **Collimator**

The detector crystal lacks directional resolution thus a collimator is used to serve this purpose. The collimator is a pattern of holes through gamma ray absorbing material, usually lead or tungsten, which limits the passage of $\gamma$ rays to the detector crystal. The collimator achieves this by only allowing those $\gamma$ rays traveling within a small range of angles about the normal to the detector face to reach the detector crystal, absorbing those that exceed this angle of acceptance. The absorption of $\gamma$ rays in the collimator inherently reduces the sensitivity of the camera by several orders of magnitude. More lead
is used in the collimator for higher energies (to prevent septal penetration of high energy photons) or higher resolution but this reduces the sensitivity of the camera. Less lead can be used at the risk of septal penetration to give the advantage of better photon statistics. The most common collimator in Nuclear Medicine is the parallel hole collimator owing to its advantageous imaging properties in that it maintains object/image size.

Figure 1.2: Top and Side views of the parallel hole collimator frequently used in Nuclear Medicine. In the Side view it is apparent that γ rays having an incidence angle greater than the collimator acceptance angle will be absorbed by the collimator.
1.6.2 DETECTOR CRYSTAL

When a gamma photon interacts with the detector it does so by means of the Photoelectric Effect or Compton Scattering with the iodide ions of the crystal [5]. This interaction causes the release of electrons which in turn interact with the crystal lattice to produce light, a process known as scintillation. The amount of light produced is directly proportional to the energy lost by the incident photon.

A Thallium-activated Sodium Iodide [NaI(Tl)] detector crystal is generally used in Nuclear Medicine cameras owing to its good detection efficiency of photons. The thickness of the detector crystal is determined by the energy range for which it will be used, generally 3/8-1/2" for the 80-300keV photons in Nuclear Medicine. There is a delicate balance between the detection efficiency of photons and the spatial resolution of the crystal. Thicker crystals manage to detect more gamma rays thus increasing the detection efficiency of the crystal at the cost of decreased spatial resolution. Thinner crystals have poorer sensitivity but compensate with superior resolution. The NaI crystal has the capacity for energy discrimination. This allows data collection to be restricted to specific energy windows and also enables the user to collect data in scatter windows if a scatter correction is desired.

1.6.3 PHOTOMULTIPLIER TUBE ARRAY AND POSITION LOGIC CIRCUITS

A photomultiplier tube absorbs the light from the crystal on its photocathode and generates about 1 electron for every 7 to 10 scintillating photons absorbed [5]. Following the cathode is a series of dynodes that continually multiply the electrons upon colliding with each successive dynode resulting in a signal that is amplified by a factor of \( \sim 10^6 \). The output signal at the anode is proportional to the number of electrons that were incident at the cathode. Immediately following the photomultiplier tube array are position logic
circuits which determine the location of each scintillation event as it occurs in the crystal.

1.6.4 COMPUTER

The computer stores all detection, location, and energy information for each count as it occurs in real time. This information is stored in a predefined matrix size ranging from $64 \times 64$ (pixels) to $256 \times 256$ for SPECT projections and $256 \times 1024$ for a projection scan of the whole body. This projection information can then be displayed using image display software and/or the projections can be input into an image reconstruction software to produce a 3-dimensional representation of the object.
Once a radiopharmaceutical is administered to the patient it gets distributed throughout the body reflecting, it is hoped, the functioning of a particular organ or to seek out malignant cells for the purpose of therapy. When the affixed radionuclide decays, radiation specific to the particular radionuclide is emitted. The types of radiation of greatest interest in Nuclear Medicine were discussed in Chapter 1. Given that radiation is being emitted in a biological system, it is important to assess the effect to living tissue resulting from this radiation, in order to assess the risks to the patient, or the effectiveness of therapy, [6]. This is done by measuring the internal absorbed dose. Specifically, the internal absorbed dose is defined as the amount of energy deposited by ionizing radiation in tissue per unit mass of tissue.

Before an explanation can be made of how the absorbed dose is measured, it is worthwhile to describe the theory behind how it is calculated. The Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine set out to provide a means of accomplishing this calculation in 1968 [7], and has been improving upon it ever since.
2.1 THE MEDICAL INTERNAL RADIATION DOSE (MIRD) PROTOCOL

The Medical Internal Radiation Dose (MIRD) Committee developed a simple, yet useful, approach for estimating absorbed doses to normal organs and the whole body from radiopharmaceuticals [8]. This protocol has proven to be a valuable foundation in internal dosimetry. I will discuss the methods involved in estimating the internal absorbed dose by the MIRD protocol, the consequential limitations imposed by it, and recent research geared towards compensating for these faults.

In order for the absorbed dose to be calculated, two important factors must be determined: the amount of activity administered to the patient, and the length of time the radionuclide resides in a particular region of the body (in order to calculate the amount of radiation energy deposited at that site and delivered to neighbouring structures over the time that the radiation is present). The types of emissions for the particular radionuclide must be identified and, whenever possible, information on the metabolic response for the radiopharmaceutical should be considered. The MIRD Committee has attempted to address these issues thoroughly as they pertain to absorbed dose calculations and a description of their methods will ensue. The following information is derived from MIRD publications, specifically the MIRD Primer For Absorbed Dose Calculations[9], MIRD Pamphlets No.1 (Revised)[8], No.3[10], No.10[3], and No.11[11].

2.1.1 PHYSICAL AND BIOLOGICAL HALF-LIVES

The physical decay rates of radionuclides are constant and well known for commonly used isotopes [12] [13] [3]. When a radionuclide is introduced into the body, to estimate the total time it will remain in the body, we must also consider the biologic decay of the nuclide. This is because the radionuclide can be eliminated from the body by means of metabolic processes as well as physical decay.
Chapter 2. Internal Dosimetry

The effective decay constant is the total probability that a particular radionuclide will be eliminated, either through radioactive decay or metabolic processes, and is simply the sum of the physical and biological decay constants:

\[ \lambda_{eff} = \lambda_p + \lambda_b \]

where \( \lambda \) denotes the decay constant and the subscripts 'eff', 'p', and 'b' denote effective, physical, and biological, respectively.

A half-life can be introduced by:

\[ T_{\frac{1}{2}} = \frac{\ln 2}{\lambda} \]

where \( T_{\frac{1}{2}} \) = half-life, physical or biological.

Although the biologic half-life is not as well defined as the physical half-life, it is still possible to model a metabolic rate for a particular radiopharmaceutical [14]. The effective half-life of a radiopharmaceutical, \( T_{eff} \), in a living system can then be determined by combining the physical half-life with the biological half-life.

\[ \frac{1}{T_{eff}} = \frac{1}{T_p} + \frac{1}{T_b} \]

2.1.2 Source and Target Organs

Radiopharmaceuticals may deposit themselves in a number of organs. The organ (or region) of interest for which the absorbed dose is to be calculated is defined as the target organ. Organs containing radioactivity that contribute to the absorbed dose in the target organ are considered source organs. Specifically, all organs are considered to be source organs if they contain concentrations of radioactivity that exceed the average concentration in the body. The source and target may be the same organ and, frequently, the most important contributor to radiation dose is radioactivity contained within the target organ itself [4].
2.1.3 Calculating the Absorbed Dose

As mentioned previously, the radiation absorbed dose ($D$) is defined as the energy deposited by ionizing radiation ($\Delta E$) in a mass ($\Delta m$):

$$D = \frac{\Delta E}{\Delta m}$$

The energy released by the radionuclide in each decay is constant and has been well established. The total energy released in a target region is the product of the energy released per decay and the number of decays occurring within that target region.
Although this defines the amount of energy released by the isotope, this may be distinctly different from the energy deposited in the target region. This difference comes from the types of decay emissions, whether they be penetrating or non-penetrating emissions (as discussed in Chapter 1). The types of emissions determine if they will deposit their energy within the target region or escape and deposit their energy elsewhere. Hence, the total energy absorbed by the target region is the product of energy incident upon, or released in, the target region and the fraction that is absorbed [15].

The basic absorbed dose calculation, as derived by the MIRD Committee, provides the mean absorbed dose \( \overline{D}(r_k \leftarrow r_h) \) to the target region \( r_k \) from the uniformly distributed activity in the source region \( r_h \):

\[
\overline{D}(r_k \leftarrow r_h) = \frac{\tilde{A}_h \sum_i \Delta_i \phi_i(r_k \leftarrow r_h)}{M_k}
\]

where

- \( \tilde{A}_h \) = the cumulated activity in the source region \( r_h \) (in other words, the total number of nuclear decays occurring in the source region)
- \( M_k \) = the mass of the target region \( r_k \)
- \( \Delta_i \) = the radionuclide-specific equilibrium dose constant for radiation type \( i \) (or the average energy emitted per nuclear decay in the form of radiation \( i \))
- \( \phi_i(r_k \leftarrow r_h) \) = the absorbed fraction in target region \( r_k \) for radiation \( i \) emitted in source region \( r_h \) (or the fraction of energy of radiation \( i \) emitted in the source region \( r_h \) that is absorbed in the target region \( r_k \))

By the following definition—

- \( \Phi_i(r_k \leftarrow r_h) \) = the specific absorbed fraction in the target region \( r_k \) for radiation \( i \) emitted in the source region \( r_h \) (or the fraction of energy of radiation \( i \) emitted in the source region that is absorbed per unit mass in the target region);
the equation for the mean absorbed dose can be simplified to:

\[ \bar{D}(r_k \leftarrow r_h) = \tilde{A}_h \sum_i \Delta_i \Phi_i(r_k \leftarrow r_h) \]

The MIRD protocol has combined all physical factors necessary for dosimetry into a set of factors called the S-factors. The S-factor has a value for each source/target combination for the radionuclide of interest.

\[ S(r_k \leftarrow r_h) = \text{the radionuclide-specific S factor for the target region } r_k \text{ and source region } r_h, \]

or the absorbed dose to the target region per unit cumulated activity in the source region;

\[ S(r_k \leftarrow r_h) = \frac{\sum_i \Delta_i \phi_i(r_k \leftarrow r_h)}{M_k} \]

thus

\[ \bar{D}(r_k \leftarrow r_h) = \tilde{A}_h S(r_k \leftarrow r_h) \]

By summing all the absorbed dose contributions from all source regions \( r_h \), the total mean absorbed dose to the target region \( r_k \) can be estimated:

\[ \bar{D}(r_k) = \sum_h [\tilde{A}_h S(r_k \leftarrow r_h)] \]

This more condensed representation of the total mean absorbed dose \( \bar{D}(r_k) \) to the target region is expressed as a sum of the products of two important factors required for this calculation: the cumulated activity \( \tilde{A}_h \) from a potential source region, and the MIRD S-factor \( S(r_k \leftarrow r_h) \) which represents the absorbed dose to the target region per unit cumulated activity in the source region. Most of the biological information (e.g. uptake,
retention and washout) needed for dosimetry estimations is embodied in the quantity \( \tilde{A}_h \), while the physical and anatomical data is included in the S-factor \([16]\). Use of the S tables, along with knowledge of the cumulated activity, enables the straightforward calculation of the radiation absorbed dose.

**Cumulated Activity**

Once the activity \( A_o \) is administered to the patient, it is the effective decay constant \( \lambda_{eff} \) that characterizes the reduction of activity over time \( A(t) \) within a source region

\[
A(t) = A_o \exp^{-\lambda_{eff} \cdot t}
\]

The amount of activity in a source region changes with time and this trend can be portrayed on a Time-Activity curve where the activity in the region of interest \( A_h \) is plotted as a function of time. The *cumulated activity*, corresponding to a time period from \( t_1 \) to \( t_2 \), is determined by integration from time \( t_1 \) to time \( t_2 \) of the time-activity data \( A_h(t) \), as determined by serial measurements:

\[
\tilde{A}_h(t_1, t_2) \equiv \int_{t_1}^{t_2} A_h(t) dt
\]

To determine the *total* absorbed dose, however, it is necessary to integrate from time \( t_1 = 0 \) to time \( t_2 = \infty \):

\[
\tilde{A}_h = \int_0^\infty A_h(t) dt
\]

The cumulated activity is essentially a measure of the total number of radioactive disintegrations occurring during the time that the radioactivity is present in the source organ. The units of cumulated activity can be expressed in \( Bq \cdot s \) or in \( mCi \cdot hr \) where 1\( mCi \) is equal to \( 3.7 \times 10^7 \)\( Bq \).
MIRD S-factors

S-factors, or the absorbed dose per unit cumulated activity, depend on the mass of the target organ $M_k$, the mean energy emitted per disintegration $\Delta_i$, and the fraction of energy emitted from the source organ which is absorbed by the target organ $\phi_i$ [17].

Calculation of the radiation dose for non-penetrating radiations is relatively simple given that $\beta$ particles, $\alpha$ particles, conversion electrons and X and $\gamma$ rays of energies less than 11keV are absorbed in tissue within a volume of $\sim$1cm radius [18]. The calculation of radiation dose for penetrating radiations (i.e. higher energy photons) can get complicated. Estimates of the S-factors for photons have been calculated by means of Monte Carlo simulations [15] using a geometrical representation of the human body. The original 70kg "standard man" model, developed by Walter Snyder [19], defined the three-dimensional coordinates of the organs in this anthropomorphic phantom. The absorbed fractions for different sources and target organs were then calculated by Monte Carlo analysis of the trajectories of large numbers of photons of different energies [15] [20]. Since the original "standard man" model, the MIRD protocol has also developed S-factors based on pediatric phantoms for newborns and ages 1 year, 5 years, 10 years, and 15 years-old, the adult female phantom (based on the 15 year-old male phantom) [21], and the pregnant female at 3, 6, and 9 months gestation [22]. It is crucial to keep in mind that the shapes and proportions of the phantoms used to calculate S-factors only crudely approximate human anatomy. Actual patient values may vary considerably from model parameters, especially in the case of patients with various levels of disease.
In this chapter I will address the practical question of *How is the absorbed dose measured?* The S-factors have already been tabulated for all diagnostic and therapeutic radionuclides used in Nuclear Medicine. The majority of effort in dosimetry studies is spent determining the cumulated activity $A_h$ for each potential source organ. Although there is a common basis for all methods used to find the cumulated activities, a variety of approaches have been proposed in hopes of achieving more accurate results.

Before delving into the most common method for determining the cumulated activity, it is necessary to understand the imaging techniques available for data collection – specifically planar and SPECT imaging – and the effects of attenuation in imaging. Once this foundation is established, I will summarize the current methods used in dosimetry, how quantitation is achieved in planar and SPECT imaging and, finally, the dosimetry method proposed in this work.
Chapter 3. Measurement Techniques

3.1 IMAGING METHODS

3.1.1 PLANAR IMAGING

Planar imaging (represented in Figure 3.1 (a)) uses a stationary gamma camera, positioned close to the patient, to detect gamma emissions that originate within the patient. This type of imaging yields a two-dimensional representation of a three-dimensional activity distribution. The collimator, as described in Chapter 1, allows only photons travelling within a particular range of trajectories (the acceptance angle) to interact with the detector crystal, absorbing those photons that exceed the acceptance angle. The photon's direction of travel and its point of interaction within the detector crystal define a line somewhere along which the emission took place, therefore several layers of the body have their contributions superimposed. Planar imaging is limited by its lack of depth localization of the emission origins.

3.1.2 SPECT IMAGING

Single Photon Emission Computed Tomography (SPECT), schematically represented in Figure 3.1 (b), acquires a set of 2-dimensional planar images (projections) by rotating the camera around the patient and acquiring data at a number of different angles (views). The multiple views around the patient allow for the reconstruction of a 3-dimensional representation of the activity distribution in the body.

3.1.3 ATTENUATION EFFECTS IN IMAGING

When the gamma ray photons travel through the patient, there is a probability that the photons will interact with the tissue, either by scattering or absorption, resulting in photon attenuation. The deeper in the patient the source of gamma rays is, the more those gamma rays are attenuated on the way to the detector. Attenuation is nonuniform
Figure 3.1: Schematic representation of (a)planar and (b)SPECT (2 detector heads) imaging and the projection profiles collected by the detectors. Planar and SPECT projections are 2-dimensional representations of a 3-dimensional object. The ability of SPECT to rotate around the object collecting multiple 2-D views enables the reconstruction of a 3-D image of the object.

Throughout the body since different tissues exhibit different aptitudes for attenuating photons (e.g. high attenuation in bone and low attenuation in the lungs).

Since attenuation will result in an image that misrepresents the real distribution of radiation within the body, data should be corrected for attenuation otherwise some areas of the patient will appear to be less radioactive than they really are.

**Linear Attenuation Coefficient**

When a number of photons $N$ passes through a material of thickness $\Delta x$, $n$ number of photons will interact with the attenuator and be removed from the initial flux of photons. This removal of photons can be represented by

$$n = \mu N \Delta x$$
The factor $\mu$ is the *Linear Attenuation Coefficient* and characterizes the attenuating properties of the material it represents. Specifically, $\mu$ is a constant that describes the number of photons attenuated per unit length of material for which the photons traverse. Not only does $\mu$ depend on the attenuating material it describes, but it also depends on the energy of the photons. The relationship between the number of incident photons $N_0$ on a material having a linear attenuation coefficient $\mu$ for that photon energy, traversing a thickness $x$ of the material and resulting in $N$ photons successfully transmitted through that thickness of material without being attenuated, is:

$$N = N_0 \exp^{-\mu x}$$

This equation describes the attenuation of photons by any thickness of material.

### 3.2 Current Methods for Dosimetry

The MIRD protocol has the limitation of basing its calculations on ‘standard’ anatomical geometries – ignoring the importance of individual patient differences along with anatomical mutations associated with some diseased states. Suggestions have been made, and protocols developed, in an effort to improve upon the MIRD protocol. Most of these techniques are supplements for improving the MIRD protocol rather than complete new protocols. It has to be recognized that the time and effort put into absorbed dose calculations by the MIRD committee would be difficult to surpass. It is therefore wise to take advantage of the insights the MIRD protocol can provide, limited as it may be.

With the introduction of new radiopharmaceuticals, specifically monoclonal antibodies (MABs) designed to target antigens generally associated with malignant cells, the activity is no longer localized in specific volumes. This activity spread, along with localized uptake in tumors, hinders the straightforward application of the MIRD protocol.
This is due to the fact that the S-factors have been designed for standard organ systems as sources/targets of radiation. Whether or not a tumor resides in a normal source region, it should be treated as a separate volume in dosimetry calculations. The most basic technique for tumor dosimetry is obtained by considering only the electron self-dose, or if the tumor is assumed to be a sphere or ellipsoid then the self-dose photon contributions can also be included by using the absorbed fractions listed in MIRD Pamphlet No.5 [15]. These techniques do not provide dose contributions to normal tissue from activity in the tumor nor do they include the tumor dose from activity in normal tissues. A software program MABDOS designed by Timothy Johnson [23] has overcome this predicament by recognizing non-standard volumes positioned in a non-standard geometry. MABDOS accomplishes this by performing on-the-fly Monte Carlo simulations to determine S-factors for tumors as source and target organs, whereby the tumor is treated as a spherical perturbation to the Standard Man geometry [23].

Patient-specific approaches to dosimetry generally require a 3-dimensional representation of patient anatomy (CT or MRI) as well as the radioactivity distribution within the patient (SPECT, PET, or biopsy samples). These patient-specific methods can be categorized as either Monte Carlo [24] [25] or point-kernel [26] [27] [28] [29] based. Monte Carlo methods provide simulation of particle transport and a tallying of energy deposited in target regions. The Monte Carlo code can use a SPECT or PET activity array to determine the number of radionuclide emissions at each array unit [26], while the emissions can be followed across a CT density array [25] to determine points of absorption in the patient or escape. Point-kernel consists of tables of absorbed doses versus the corresponding distances from a point source. It incorporates the emission spectrum of the radionuclide and its distribution (SPECT or PET) and the absorbing medium (CT or MRI). The distance between a given voxel inside an activity-containing source volume and a point
on the target plane is calculated, while always considering the traversing medium. The distance is then found in the lookup table of dose versus distance (point-kernel) to obtain the dose per unit cumulated activity [27].

The majority of these dosimetry revisions have focused on ways to improve absorbed fractions in the presence of tumors. Whether they were developed to be patient-specific or not, they have all focused on ways to improve the S-factors, or some component of the S-factors. Seldom is there a suggestion to improve upon methods used to measure the cumulated activity. Determining the cumulated activity via excreta counting (e.g. urine and feces) is not sufficient as the sole method of data collection and should only be used as a supplement to other methods. Tissue sampling (blood or biopsy) is usually not a viable option due to its invasive nature and may lack accuracy if used as a complete method. External non-imaging radiation monitoring (e.g. radiation counter) [30] is useful for determination of whole-body activity but lacks the capacity to deliver dose estimates for specific regions. Quantitative planar imaging makes possible the determination of organ and tumor activities but, due to its 2-D nature, can yield high errors in dose estimates not suitable for therapy.

The most notable recommendation to revise cumulated activity measurements has been the proposal of quantitative SPECT scans rather than planar scans [31]. This may be an attractive alternative in light of quantitative improvements in SPECT but it may not be realistic considering the time required for one SPECT scan, let alone the multiple scans necessary in dosimetry studies. It has also been proposed to implement only one SPECT scan and use this as a constraint for the planar scans [32]. A slight modification to this proposal is the inspiration for this thesis. Because this thesis attempts to improve upon the determination of the cumulated activity $\hat{A}_h$, it may be complemented by the above attempts to include S-factors by non-standard regions. Together these methods
could have the potential to generate more accurate estimates of the absorbed dose.

### 3.3 Quantitative Planar and SPECT Imaging

#### 3.3.1 Attenuation Correction in Planar Imaging

The conventional manner in which attenuation correction is carried out in planar imaging is invariably crude yet swift. The general protocol in internal dosimetry involves whole body planar scans of the patient from both anterior and posterior views. Since the data in both the anterior $I_A$ and posterior $I_P$ projections are less than the unattenuated data they do not accurately represent the unattenuated activity distributions. However, a mean image may be modified by a correction factor to compensate for the attenuation.

By assuming a constant attenuation coefficient in a region, a hyperbolic sine correction can be used [33]. Figure 3.2 represents the source distribution within an attenuating region to supplement the proof for the hyperbolic sine correction.

The anterior $I_A$ and posterior $I_P$ projections can be represented by:

$$I_A = \int_{m-fL/2}^{m+fL/2} K \cdot e^{-\mu(L-l)} \, dl$$

$$I_P = \int_{m-fL/2}^{m+fL/2} K \cdot e^{-\mu} \, dl$$

where

- $K$ = the linear concentration of the isotope activity in the source region, assumed constant
- $f$ = the linear fraction of the thickness in which the isotope is distributed
- $m$ = the mean depth of the source distribution
- $L$ = the total thickness through which the ray passes
Figure 3.2: The anterior and posterior projections from a constant source distribution $K$ (shaded object) at a mean depth $m$ within the constant attenuator $\mu$.

$\mu = \text{the linear attenuation coefficient for the attenuating object}$

Integrating a projection (posterior, for example) over the source region:

$$\int_{m-L/2}^{m+L/2} e^{-\mu l} \, dl = \frac{-1}{\mu} [e^{-\mu (m+L/2)} - e^{-\mu (m-L/2)}]$$

$$= \frac{-1}{\mu} [e^{-\mu (m+L/2)} - e^{-\mu (m-L/2)}] = \frac{e^{-\mu m}}{\mu} (e^{\frac{\mu L}{2}} - e^{-\frac{\mu L}{2}})$$

From the definition $\sinh A = \frac{1}{2} (e^A - e^{-A})$ the integrated posterior projection can be simplified to:

$$I_P = \frac{2Ke^{-\mu m}}{\mu} \sinh\left(\frac{\mu fL}{2}\right)$$

Likewise for the anterior projection:
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\[ I_A = \frac{2Ke^{-\mu(L-m)}}{\mu} \sinh(\frac{\mu f L}{2}) \]

The geometric mean of these two projections yields:

\[ \sqrt{I_A I_P} = \frac{2Ke^{-\frac{\mu L}{2}}}{\mu} \sinh(\frac{\mu f L}{2}) \]

Since the unattenuated projection data \( P \) is simply \( P = K f L \), rearranging and substituting for \( K \) gives an expression for the corrected projection:

\[ P = \frac{\mu f L e^{\frac{\mu L}{2}}}{2} \sqrt{I_A I_P} \frac{\sinh(\frac{\mu f L}{2})}{\sinh(\frac{\mu L}{2})} \]

It is important to note that this correction is independent of source depth \( m \). A similar process for an arithmetic mean yields the following:

\[ P = \frac{\mu f L e^{\frac{\mu L}{2}}}{4} \frac{(I_A + I_P)}{\sinh(\frac{\mu f L}{2}) \cosh(\mu(\frac{L}{2} - m))} \]

The corrected projection using an arithmetic mean is dependent on source depth. The extra factors required to complete the calculation, generally accompanied by a lack of knowledge of the source depth, makes using an arithmetic mean misguided and undesirable.

To apply theory to practice, the expression for the corrected projection is simplified by combining \( \frac{\mu f L}{\sinh(\frac{\mu L}{2})} \) into a factor \( F_j \). \( F_j \) is a correction for the source region attenuation coefficient \( (\mu_j) \) and source thickness \( (fL) \) [34] and will not deviate significantly from 1.0 until \( \mu_j \) or \( fL \) becomes large (unlikely for most source regions unless a significant background of activity is present). A calibration source of known activity \( C \) must be placed in the field of view for each scan in order to convert image counts to activity.

In a typical dosimetry (imaging) study, the first set of scans is taken immediately post-injection and the following scans are taken over time until the activity in the body has
dropped to no more than 10% of the initial activity. From these scans a region of interest (ROI) is drawn around any region that contains a concentration of activity (counts) that exceeds the average concentration in the body. The anterior, $I_A$, and posterior, $I_P$, counts are then averaged to attain a mean count for that ROI. This method then takes the patient's anterior/posterior thickness $L$ (at the waist or chest) and assumes this as the attenuating thickness. The attenuating medium is generally assumed comparable to that of water. Using half of the anterior/posterior thickness, $\frac{L}{2}$, and an effective attenuation coefficient equal to that of water, $\mu$, for the $\gamma$ ray energy of interest (and energy window), a correction is then made to increase the counts by a factor of $e^{\frac{\mu L}{2}}$. The counts are then converted to activity by means of the calibration source ROI in the image. For a geometric mean, the planar attenuation correction can be represented by the following equation [34]:

$$A_j = \frac{F_j}{C} \sqrt{\frac{I_A I_P}{e^{-\mu L}}}$$

where

$A_j$ = the attenuation corrected activity in the source region

$C$ = calibration factor (count rate per unit activity)

The planar attenuation correction using an arithmetic mean is represented by:

$$A_j = \frac{F_j}{C} \left( \frac{I_A + I_P}{2} \right) \frac{e^{\frac{\mu L}{2}}}{e^{\frac{\mu L}{2}}}$$

These corrections consistently overestimate the counts in the thinner regions of the patient and ignore the important contributions of differing tissue densities within the patient. This over-correction obviously has the safety of the patient in mind but, as we will see later, such an overestimation could prevent effective therapy from being administered.
When all the activities are determined for a particular ROI, they can then be plotted as a function of time (post-injection) on a Time-Activity curve. Figure 3.3 is an example of a Time-Activity curve.

![Sample Time-Activity Curve](image)

Figure 3.3: Sample Time-Activity curve as used to determine the cumulated activity.

A function can then be mathematically fit to the data points, generally described by a mono-exponential (general clearance of the radiopharmaceutical), bi-exponential (slow and fast clearance rates), uptake-clearance bi-exponential (uptake and clearance rates), among others. The fit depends on the behavior of the radiopharmaceutical within the patient and the source region. Once this function is attained it is possible to extrapolate the behavior of the radiopharmaceutical to time $t = \infty$. If the scans are taken short of
Chapter 3. Measurement Techniques

the radiopharmaceutical decaying to 10% of its original activity, then more error may be introduced when calculating a fit to the data. Unless the behavior of the radiopharmaceutical has been well established then it is common protocol to continue scanning the patient until this 10% mark has been achieved.

The area under the time-activity curve (function fit to the data points) yields the cumulated activity \( \bar{A}_h \) necessary to complete the absorbed dose calculation. Recalling from the previous chapter, this area is determined by integration of the function \( A_h \) from time \( t = 0 \) to \( t = \infty \):

\[
\bar{A}_h = \int_0^\infty A_h(t) dt
\]

3.3.2 Attenuation Correction in SPECT

From no attenuation correction at all to the crude method of approximating the patient as an ellipse of uniform attenuation [35] to the refined methods of today – attenuation correction in SPECT has evolved greatly. Patient-specific methods of attenuation correction generally make use of a point, line, or flood transmission source to determine the patient's internal density distribution. The method of attenuation correction that will be discussed in this thesis makes use of a Multiple Line Array (MLA) transmission source developed by the Medical Imaging Research Group (MIRG) [36] at Vancouver Hospital & Health Sciences Centre in collaboration with Siemens. This transmission source is made up of a series of parallel collimated Gadolinium-153 line sources. The sources are placed in a manner whereby the strongest sources are placed in the middle and each successive source has reduced activity. The ratio between each neighbouring pair is constant throughout the array (from the middle outwards). Figure 3.4 depicts the concept behind the MLA transmission source.

The MLA is mounted opposite the detector head and undergoes the same rotation,
Figure 3.4: MLA transmission source and resulting profiles (a) without and (b) with the attenuating object.

always keeping its face to the detector. The Gd-153 line sources in the MLA decay by means of electron capture, resulting in the emission of $\gamma$ rays. The fundamental emissions from the Gd-153 source are 97KeV and 103KeV $\gamma$ rays producing a peak emission profile centered about 100keV. At each projection, emission data from within the patient are acquired into one energy window (e.g. centered around 140keV for Technetium-99m) simultaneously with transmission data collected into the 100keV transmission window. Simulated emission/transmission data is represented in Figure 3.5.

A scan is taken of the Gd-153 transmission source without attenuating objects in the field of view in order to compare these to patient-inclusive projections. The ratio between the transmission projection without (3.4 (a)) and with (3.4 (b)) the attenuating object is used to reveal the effects of the attenuation for each projection. The transmission data for all projections can then be reconstructed to yield a 3-dimensional attenuation map of the patient.
3.4 Dosimetry Method Proposed in This Work

This thesis proposes a protocol that builds on the quantitative planar protocol commonly used today. Like the planar protocol, multiple anterior and posterior planar scans (with the presence of a calibration source) are taken at regular intervals until the activity has sufficiently decayed (i.e., where the errors introduced by extrapolation of the decay function can be minimized). Once the counts for the ROI in the anterior view $I_A$ and posterior view $I_P$ are averaged by a geometric mean, and converted from counts to activity by means of the calibration source $C$, the $e^{\frac{t}{T_d}}$ attenuation correction is applied. The attenuation corrected activities $A_j$ for the source region $j$ are plotted on a time-activity curve and an appropriate function is fit to the line.

In addition to the quantitative planar protocol, a minimum of two quantitative SPECT scans are acquired with the source region of interest in the field of view of
the camera. By quantitative SPECT I imply a simultaneous emission/transmission scan using the Siemens MLA transmission source [36]. The presence of a calibration source is also required in order to convert counts to activity. Siemens Profile software uses the patient-specific attenuation map to iteratively reconstruct a 3-dimensional attenuation corrected image of the activity distribution within the patient. This 3-D image can then be imported into Display software, produced by Christine Dykstra [37], whereby contiguous volume analysis is performed on the data to seek out 3-D regions of interest. The counts in the 3-D source ROI's can then be compared to the counts in the 3-D calibration ROI to make the conversion from counts to activity.

More than one SPECT scan is preferential in the protocol, not only to ensure that no gross errors have occurred during one of the scans, but to maximize the benefits of SPECT quantitation. The 3-D source region activity, determined from the SPECT image, is accepted as the true activity in the region, hence it is used to constrain the planar data points. The term constrain refers to a normalization factor applied to the planar data. A normalization factor $N$, specific to each region, is determined by the ratio of what the planar function $A(t)$ would yield as an activity for the time the SPECT image was acquired ($A(t=SPECT)$) to the true activity in the 3-D source region $A(t_{true})$ as determined by the SPECT image.

$$N = \frac{A(t=SPECT)}{A_{true}}$$

A normalization factor can be calculated for every SPECT scan. A mean normalization factor can then be used to constrain the planar data.

All planar data points are then divided by the normalization factor $N$ (ie. constrained), to yield the SPECT-corrected data. A function is fit to the new data points so that the cumulated activity $\tilde{A}$ can be determined by integrating the function from $t = 0$ to $t = \infty$. Once the cumulated activities are calculated for all potential source organs, the absorbed
dose can be calculated by using the MIRD S-factors, or some other proposed method for determining S-factors as suggested earlier in this chapter.
Mathematical simulations were performed in order to evaluate the errors introduced by different methods of image averaging and attenuation correction in planar imaging techniques. The first technique, performed using Matlab, was simplistic in nature, lacking a realistic portrayal of photons in matter, yet not completely devoid of useful information. Even though the trajectories of the photons are not representative of their true behavior (i.e. interactions on the path to the detector are ignored), the calculations performed on the collected photons are realistic in the systematic errors they reveal. The second technique, performed using SimSET or Simulation System for Emission Tomography (a Monte Carlo photon history generator), realistically portrays the interactions of photons through the attenuating material, any absorptions or energy losses of the photons, the collimation and detection system, and the energy window employed to detect the photons. Again, these simulations are used to assess the errors incurred by planar attenuation correction.
4.1 MATLAB SIMULATIONS

To describe the attenuating object, the Matlab simulations utilized a single slice of an elliptical object (diameters of 20cm by 40cm) to model a cross-sectional view through a patient's mid-section.

![Pixelized representation of the attenuating ellipse used in Matlab simulations.](image)

Figure 4.1: Pixelized representation of the attenuating ellipse used in Matlab simulations.

Different combinations of one, two, or three spherical activity sources (each of 4cm diameter) were placed within this slice for the case of no background activity as well as for the case of a uniformly distributed background of activity within the ellipse.

The 1, 2, 3, 4, and 5 notations on the activity sources in Figure 4.2 denote the activity coordinates of (0,0), (0,6), (-16,0), (8,0), and (-8,3) respectively where the origin (0,0)
Figure 4.2: Locations of the activity sources and background activity within the Matlab object.

is defined as the centre of the attenuating ellipse (coordinates are expressed in cm).

Outside the attenuating ellipse there was assumed to be a non-attenuating medium, approximating that of air. Three separate matrices (each 64 × 64) were created, one to describe the activity indexes per pixel, and the other two to describe the anterior and posterior attenuation indexes for each pixel. A representation of the attenuating matrices is shown in Figure 4.3. Each pixel in the activity spheres was specified to have 10000 starting photons and if a background was used then the background pixels were specified as having 100 starting photons per pixel. The attenuating matrix defined a weighting for each pixel (based on $\mu = 0.12 cm^{-1}$ assuming water equivalency for a photon energy window of 126-154keV to simulate the most frequently used radionuclide in Nuclear Medicine, Technetium-99m) depending on the pixel’s depth within the ellipse relative
to where the detector head would be positioned. The cumulative pixel weightings along
the path from the photon’s origin to the detector face determines whether the radiation
arising in the pixel will be absorbed within the attenuating ellipse or penetrate the ellipse
to be counted by the detector. Again, the pixels outside the ellipse did not contribute
any attenuation.

Figure 4.3: Anterior and posterior attenuating matrices. Actual matrices are 64 x 64.
Each pixel has an attenuation weighting defined by its depth within the attenuating
ellipse as measured from the detector head.

The simulations exclude any possible scatter of the photons, assuming that if they are
not completely absorbed on their path to the detector (depending on the pixel weightings
along the way) they are collected as a photon count on the detector bin that is in a direct
line from the point of the photon’s origin. Photons originating within a given pixel are
defined as originating in the centre of that pixel. By definition this means that the photon
is only attenuated by half of the originating pixel (ie. half of the pixel weighting).
Depending on the activity arrangement defined for each simulation, the activity matrix would then be multiplied pixel-by-pixel by the attenuating matrix and the resulting counts placed in 64 detector bins (for the single slice simulated). The attenuating matrix would obviously be equal but opposite for the anterior and posterior projections. Once the binning was done, the anterior $I_A$ and posterior $I_P$ projections were then averaged, either by an arithmetic or geometric mean, and multiplied by a factor for attenuation correction. This procedure is outlined by the following equation:

$$C_{\text{corr}} = \sqrt{I_A I_P} \exp^{\frac{\mu L}{2}}$$

for a geometric mean and

$$C_{\text{corr}} = \frac{(I_A + I_P)}{2} \exp^{\frac{\mu L}{2}}$$

for an arithmetic mean.

Where $C_{\text{corr}}$ represents the attenuation corrected counts in the projection, $\mu$ is assumed to be the linear attenuation coefficient of water over a photon energy window of 126-154keV, centered about 140keV (simulating Tc-99m), and $L$ denotes the attenuating ellipse’s anterior/posterior thickness.

The linear attenuation coefficient $\mu$ for Tc-99m 140keV $\gamma$ rays has a table value of 0.15$cm^{-1}$. This tabulated value fails to account for the fact that in Nuclear Medicine studies photons are accepted over a range of energies (ie. 126-154keV rather than only 140keV). A tabulated value of $\mu = 0.15cm^{-1}$ for 140keV in water indicates that 15% of the monoenergetic photons will be attenuated in 1cm of water. Obviously the value of 0.15$cm^{-1}$ fails to account for the possibility that some of the attenuated (scattered) photons may still be collected by the detector, therefore the tabulated value must be appropriately adjusted. The value is often adjusted to a lesser value generally near
Matlab simulations were carried out for the two cases where $\mu = 0.15 cm^{-1}$ and $\mu = 0.12 cm^{-1}$ to demonstrate the typical errors that can arise.

To calculate the percent error resulting from this method of attenuation correction, the following equation was used:

$$\%Error = \frac{C_{corr} - C_{true}}{C_{true}} \times 100$$

where $C_{true}$ represents the true activity originating from within the object.

### 4.1.1 RESULTS

Results of the Matlab simulations for $\mu = 0.15 cm^{-1}$ and $\mu = 0.12 cm^{-1}$ are summarized in Table 4.1 and Table 4.2 respectively. The most conspicuous difference between Tables 4.1 and 4.2 is the magnitude of the errors. Table 4.1 clearly shows larger errors for all cases in comparison to Table 4.2. This is simply due to the larger linear attenuation coefficient of $\mu = 0.15 cm^{-1}$ rather than $\mu = 0.12 cm^{-1}$. In all cases, the presence of background radiation introduces more error when correcting for attenuation (with the exception of activity source 3). Any peripheral (off-centre) activity will always be over-corrected due to the fact that the attenuating thickness used to correct for attenuation is selected as half of the thickest width of the patient (in this case, half of the thickest part of the ellipse, $\frac{b}{2} = 10 cm$). This correctly estimates the thickness at the centre of the patient (ellipse) but over-estimates the thickness at the periphery.

These results indicate that a tabulated value of the linear attenuation coefficient $\mu$ clearly produces an overestimation of the true counts in the object. An overestimation of this magnitude would translate into a gross overestimate of the cumulated activity (hence absorbed dose) in the region, potentially preventing adequate therapy from being administered.
Table 4.1: Matlab results of attenuation correction using planar techniques with $\mu = 0.15cm^{-1}$ (Activity Source Combinations are labeled in Figure 4.2).

<table>
<thead>
<tr>
<th>Activity</th>
<th>Arithmetic</th>
<th>Geometric</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent Error (%)</td>
<td>Percent Error (%)</td>
</tr>
<tr>
<td>Combination</td>
<td>No Background</td>
<td>W/Background</td>
</tr>
<tr>
<td>NONE</td>
<td>94.1</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>35.9</td>
<td>56.0</td>
</tr>
<tr>
<td>2</td>
<td>72.6</td>
<td>80.1</td>
</tr>
<tr>
<td>3</td>
<td>120.1</td>
<td>111.2</td>
</tr>
<tr>
<td>4</td>
<td>53.2</td>
<td>67.3</td>
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<td>5</td>
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<td>73.9</td>
</tr>
<tr>
<td>1+2</td>
<td>54.3</td>
<td>62.6</td>
</tr>
<tr>
<td>1+3</td>
<td>78.0</td>
<td>81.4</td>
</tr>
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<td>1+5</td>
<td>49.6</td>
<td>58.9</td>
</tr>
<tr>
<td>2+3</td>
<td>96.4</td>
<td>95.9</td>
</tr>
<tr>
<td>2+5</td>
<td>67.9</td>
<td>73.4</td>
</tr>
<tr>
<td>3+4</td>
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<td>73.4</td>
</tr>
<tr>
<td>1+2+3</td>
<td>-</td>
<td>78.9</td>
</tr>
<tr>
<td>1+3+5</td>
<td>-</td>
<td>76.2</td>
</tr>
<tr>
<td>2+3+4</td>
<td>-</td>
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</tr>
<tr>
<td>2+3+5</td>
<td>-</td>
<td>86.6</td>
</tr>
<tr>
<td>2+4+5</td>
<td>-</td>
<td>67.7</td>
</tr>
<tr>
<td>3+4+5</td>
<td>-</td>
<td>81.1</td>
</tr>
</tbody>
</table>
Table 4.2: Matlab results of attenuation correction using planar techniques with $\mu = 0.12\text{cm}^{-1}$ (Activity Source Combinations are labeled in Figure 4.2).

<table>
<thead>
<tr>
<th>Activity Source Combination</th>
<th>Arithmetic Percent Error (%)</th>
<th>Geometric Percent Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Background</td>
<td>W/Background</td>
<td>No Background</td>
</tr>
<tr>
<td>NONE</td>
<td>-</td>
<td>43.8</td>
</tr>
<tr>
<td>1</td>
<td>0.7</td>
<td>15.6</td>
</tr>
<tr>
<td>2</td>
<td>27.9</td>
<td>33.4</td>
</tr>
<tr>
<td>3</td>
<td>63.1</td>
<td>56.4</td>
</tr>
<tr>
<td>4</td>
<td>13.5</td>
<td>24.0</td>
</tr>
<tr>
<td>5</td>
<td>20.9</td>
<td>28.8</td>
</tr>
<tr>
<td>1+2</td>
<td>14.3</td>
<td>20.4</td>
</tr>
<tr>
<td>1+3</td>
<td>31.9</td>
<td>34.4</td>
</tr>
<tr>
<td>1+5</td>
<td>10.8</td>
<td>17.7</td>
</tr>
<tr>
<td>2+3</td>
<td>45.5</td>
<td>45.1</td>
</tr>
<tr>
<td>2+5</td>
<td>24.4</td>
<td>28.5</td>
</tr>
<tr>
<td>3+4</td>
<td>38.3</td>
<td>39.4</td>
</tr>
<tr>
<td>3+5</td>
<td>42.0</td>
<td>42.4</td>
</tr>
<tr>
<td>4+5</td>
<td>17.2</td>
<td>22.8</td>
</tr>
<tr>
<td>1+3+4</td>
<td>-</td>
<td>28.4</td>
</tr>
<tr>
<td>1+2+3</td>
<td>-</td>
<td>32.5</td>
</tr>
<tr>
<td>1+3+5</td>
<td>-</td>
<td>30.5</td>
</tr>
<tr>
<td>2+3+4</td>
<td>-</td>
<td>36.2</td>
</tr>
<tr>
<td>2+3+5</td>
<td>-</td>
<td>38.3</td>
</tr>
<tr>
<td>2+4+5</td>
<td>-</td>
<td>24.2</td>
</tr>
<tr>
<td>3+4+5</td>
<td>-</td>
<td>34.2</td>
</tr>
</tbody>
</table>
Chapter 4. Simulations

For all cases in Tables 4.1 and 4.2, the errors produced by the use of an arithmetic mean were either equal to or greater than the errors produced by a geometric mean. It is plausible to explain this difference by the proof in Chapter 3, whereby attenuation correction by a geometric mean is independent of source depth and the correction by an arithmetic mean is dependent of source depth. These preliminary results tend to favor the use of a geometric mean. A further inquiry into the question of an arithmetic vs geometric mean is presented in the following set of simulations using SimSET.

4.2 SimSET Simulations

This Simulation System for Emission Tomography uses Monte Carlo techniques to accurately model photon interactions with the attenuating object. The attenuating object was defined to be a circular cylinder of 20cm radius (x- and y-axis planes) with a length of 24cm (along the z-axis). The length of the cylinder was comprised of 12 slices (2cm each). Each simulation was set to track $10^7$ photons (designated as Tc-99m $\gamma$ rays of 140keV) through their interactions, escapes, and/or detection. To model a planar scan, detection was performed by simulating detectors at 0° (anterior) and 180° (posterior), with the data for each projection binned into a $128 \times 128$ matrix. Like the Matlab simulations, an energy window from 126-154keV was used to allow for some scattered radiation – as this 20% energy window is often used in Nuclear Medicine. These $10^7$ photons were distributed corresponding to the defined activity geometry for each simulation, and each photon was emitted randomly in a $4\pi$ solid angle. Each simulation for a particular activity distribution was performed twice – once with the attenuating cylinder in the simulation and once without the attenuating cylinder (in order to estimate the true activity to compare with the attenuated case). The purpose of these simulations is to compare the results of attenuation corrected data to the unattenuated true data.
Once the anterior and posterior projections were simulated, ROI's were drawn around activity regions and the counts from these ROI's were noted. The count total in a particular ROI was averaged with its opposing projection counterpart (ROI count total), either by an arithmetic or geometric mean, then an attenuation correction factor was applied to obtain the \textit{corrected counts} for that ROI. Rather than using a tabulated $\mu$, an \textit{effective $\mu$} was used that incorporated the effects of the energy window and also the attenuating medium (water). This \textit{effective $\mu$}, evaluated as $0.127 \text{cm}^{-1}$, was determined by comparing the mean counts in the attenuated run to the mean counts in the unattenuated run for the case where there was one activity sphere directly in the centre of the attenuating cylinder.

Simulations were carried out using either one, two, or three activity spheres in a uniform background of activity or no background activity. The positions of the spheres
in the central slice of the object are illustrated in Figure 4.5. This representation lacks any depth element in the z-direction, although it is implied. Each activity source is 4cm in diameter, spanning over the two central slices. If a background of activity is included in the simulation then this activity spans uniformly over the entire cylinder (all 12 slices). Each activity source was given an activity of 0.255$mCi$ per voxel (a voxel being $1cm^3$) and if a background of radiation was included in the simulation then all regions in the cylinder (excluding sphere regions) were given an activity of $0.001mCi$ per voxel. To clarify the units, a $mCi$ is equal to $3.7 \times 10^7 Bq$ (bequerels) where a bequerel is one disintegration of radioactive material per second.

\[
\text{Figure 4.5: Activity positions as viewed in the central slice of the attenuating cylinder used in SimSET simulations.}
\]

The 1, 2, and 3 notations on the activity sources in Figure 4.5 denote the activity coordinates of $(0,0,0)$, $(0,10,0)$, and $(10,0,0)$ respectively where the origin $(0,0,0)$ is defined to be the centre of the attenuating cylinder (coordinates are in $cm$). In the case of a single activity source there is only one ROI to consider in the projections. For
multiple activity sources (2 or 3) there may be one or two ROI's (as there is overlap of the 1 and 3 activity positions). The ROI#1 refers to the central region of interest and the ROI#2 refers to the region offset in the y-direction. These results are summarized in Table 4.3.

Table 4.3: SimSET results of attenuation correction using planar techniques.

<table>
<thead>
<tr>
<th>Activity Source</th>
<th>Arithmetic</th>
<th>Geometric</th>
<th>ROI#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination</td>
<td>No BKG</td>
<td>W/BKG</td>
<td>No BKG</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>58</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>125</td>
<td>135</td>
<td>-1</td>
</tr>
<tr>
<td>1+2</td>
<td>5</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>1+3</td>
<td>26</td>
<td>45</td>
<td>26</td>
</tr>
<tr>
<td>1+2+3</td>
<td>66</td>
<td>65</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>51</td>
<td>38</td>
</tr>
</tbody>
</table>

To demonstrate the results of differing levels of background, another set of simulations was carried out using all three activity spheres whereby the activity per voxel in the activity spheres was reduced from 0.255mCi to 0.150mCi to 0.075mCi, hence increasing the background contribution (of the total activity) from 54% to 67% to 80% respectively. Again, an effective $\mu$ of 0.127cm$^{-1}$ was used in the attenuation correction calculations. These results are summarized in Table 4.4.

4.2.1 RESULTS

Like the previous Matlab simulations, the results presented in Table 4.3 demonstrate that the errors produced by the use of an arithmetic mean are either equal to, or greater than, the errors produced by use of a geometric mean. For this reason, in the next
Table 4.4: SimSET investigation of the effects of different levels of background radiation on attenuation correction in planar techniques.

<table>
<thead>
<tr>
<th>Activity Per Voxel</th>
<th>Arithmetic</th>
<th>Geometric</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the Activity</td>
<td>No BKG</td>
<td>W/BKG</td>
</tr>
<tr>
<td>Spheres (mCi)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.255</td>
<td>67</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>57</td>
</tr>
<tr>
<td>0.150</td>
<td>58</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>70</td>
</tr>
<tr>
<td>0.075</td>
<td>65</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>108</td>
</tr>
</tbody>
</table>

Chapter on Phantom Experiments, a geometric mean is employed when performing planar attenuation correction. The presence of background radiation also contributes to an increased error in the estimate of the activity in the source region. As Table 4.4 illustrates, increasing the background level from 54% to 80% has increased the error in the activity estimate from 44% to 72% in ROI#1 and from 57% to 107% in ROI#2 (values are quoted for a geometric mean).
Phantom experiments were performed with the intention of obtaining time-activity curves for regions of interest so that the cumulated activity could be calculated and compared to the known cumulated activity. The known activity in the phantom was determined by the accurate calibration of the activity-containing syringes both before and after the contents were injected into specific regions in the phantom. No biological decay exists in the phantom hence only the known physical decay constant $\lambda_p$ of the radionuclide is needed to calculate the cumulated activity $\bar{A}$ in each ROI.

The phantom employed in these experiments was a thorax phantom, simulating the chest of a patient. This phantom has dimensions of 32.0cm by 23.5cm (diameters), and contains two low-attenuating inserts (to simulate lungs), a high-attenuating insert 37mm in diameter (to simulate the spinal cord), and a water/activity fillable insert (to simulate the heart). The body of the phantom could also be filled with activity to replicate a background of activity within the body. The second experiment also made use of 2 activity filled tumor inserts within the phantom.
5.1 TECHNETIUM-99m PHANTOM EXPERIMENT # 1

The radionuclide used in this experiment was Technetium-99m since it is relatively cheap, easily accessible in the Department of Nuclear Medicine, and a $\gamma$ emitter at an energy of 140keV which is ideal for the efficiency of the NaI[Tl] detector crystal. The heart insert of the thorax phantom was filled with 18.84MBq of calibrated activity at the initial time $t_0$. The body of the phantom (excluding lung and spinal cord inserts) was filled with 177.5MBq of activity at time $t_0$. The Siemens e.cam (dual-head) camera was used for acquisitions, along with low energy, high resolution collimators. Each scan (both planar and SPECT) was taken with the presence of a calibration source (contained in a syringe) with an activity of 10.46MBq at time $t_0$.

5.1.1 ACQUISITION PROTOCOLS

Five planar scans were acquired, each over a period of 5 minutes. This time interval was intended to resemble that of a patient whole body scan which acquires data over a period of 4.88 minutes in any particular region. Because the phantom dimensions easily fit within the field of view of the detector, a static planar scan rather than a moving whole-body scan was used. Simultaneous anterior/posterior scans were acquired with the phantom and calibration source in the field of view of the detectors. Figure 5.1 shows the phantom and detector orientation used in all the planar scans. The energy window used to accept/reject photons was a 20% window centered at 140keV – meaning that photons in the range of 126-154keV as detected by the detector crystal were counted as emission data. The data from each detector was acquired in a 128 x 128 matrix for later analysis.

The SPECT scans were acquired with the two detector heads in a 90° configuration with respect to one another. Two sets of MLA Gadolinium-153 transmission sources
Figure 5.1: Planar imaging of a phantom by two detector heads in a 180° configuration were placed opposite each detector head so that the transmission data could be collected simultaneous with the emission data. The SPECT detector and transmission source orientation is represented in Figure 5.2 as used for all SPECT scans. The scan covered a 180° rotation about the phantom (90° for each detector head) with 64 projections acquired (again, 32 per head). Data collection for each projection lasted 30 seconds and was binned into a 128 × 128 matrix. The accepted photons were collected from four possible energy windows, rather than one window as was used in planar studies. The first was a 15% window centered about 140keV (emission window), the second a 20% window centered about 100keV (transmission window), and the third and fourth are
scatter windows on both sides of the emission and transmission windows. The presence of these scatter windows enables a scatter correction to be performed on the projections, if so desired. The third scatter window allows a correction for the Technetium photons that scatter and result in being collected into the lower energy Gadolinium window. The transmission window enables attenuation correction to be performed on the data.

Figure 5.2: SPECT imaging of a phantom by two detector heads in a 90° configuration

5.1.2 Scan Schedule

Phantom activities and scan times were normalized so that the first scan time represented time $t = 0$ (true activities were decay corrected accordingly). Scans 1, 2, 3, 5 and 7 were
planar scans acquired at \( t = 0, 87, 214, 352, \) and 393 minutes and intervening scans \( 4 \) and \( 6 \) were SPECT scans acquired at \( t = 249 \) and 364 minutes.

5.1.3 REGION OF INTEREST (ROI) ANALYSIS

In the planar anterior/posterior projections, elliptical ROI's (2-dimensional) were drawn around the heart and calibration source regions to obtain the anterior/posterior counts in the regions. The anterior and posterior counts were then averaged by a geometric mean and, for the heart region, corrected for attenuation by using an effective \( \mu \) of \( 0.12\text{cm}^{-1} \). The averaged counts in the calibration ROI, when divided by the known activity in the calibration source (at the time of the scan), yielded a conversion factor from counts to activity in MBq. This conversion factor is used to convert the attenuation corrected counts in the heart region into an activity in MBq. Once this procedure is carried out for all planar scans, a time-activity curve could be plotted for the heart region. Table 5.1 contains the planar attenuation corrected activities for the heart ROI (and their subsequent errors from the true activity).

<table>
<thead>
<tr>
<th>Scan Number</th>
<th>Measured Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Percent Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56.55</td>
<td>17.45</td>
<td>224</td>
</tr>
<tr>
<td>2</td>
<td>47.83</td>
<td>14.77</td>
<td>224</td>
</tr>
<tr>
<td>3</td>
<td>38.56</td>
<td>11.57</td>
<td>233</td>
</tr>
<tr>
<td>5</td>
<td>28.93</td>
<td>8.88</td>
<td>226</td>
</tr>
<tr>
<td>7</td>
<td>26.63</td>
<td>8.21</td>
<td>224</td>
</tr>
</tbody>
</table>

The curve fit to the planar attenuation corrected data yields an equation to represent the activity in the heart as a function of time:
Figure 5.3 displays the curve fit to the planar attenuation corrected data (+). The cumulated activity is determined by integration:

\[
\tilde{A} = \int_0^\infty 56.81 \cdot e^{-0.0019t} dt = \left[ \frac{-56.81}{0.0019} e^{-0.0019t} \right]_0^\infty
\]

\[
= \frac{56.81}{0.0019} = 29900 \text{ MBq} \cdot \text{min}
\]
thus

\[ \bar{A} = 1.794 \times 10^6 \text{MBq} \cdot s \]

Likewise for the true activity (also represented in Figure 5.3 (·)):

\[ A(t) = 17.45 \cdot e^{-0.0019\cdot t} \]

\[ \bar{A} = 5.511 \times 10^5 \text{MBq} \cdot s \]

\[ \%\text{Error} = \frac{(1.794 \times 10^6 - 5.511 \times 10^5)}{5.511 \times 10^5} \times 100 = 225\% \]

The cumulated activity using the planar attenuation corrected data gives an estimate that is 225\% larger than the truth.

**5.1.4 SPECT Constraint**

SPECT scans were reconstructed using an iterative technique developed by Siemens known as Iterative W. The images were reconstructed using 10 iterations and a Butterworth filter with a cut-off of 0.35. SPECT scans 4 and 6, acquired at \( t = 249\text{min} \) and 364\text{min}, were used to constrain the planar data. From the 3-dimensional iteratively reconstructed image, and using the Display software to determine the counts in the heart and calibration ROI's, the activity of the heart was determined as 11.84\text{MBq} at \( t = 249\text{min} \) and 9.27\text{MBq} at \( t = 364\text{min} \). Table 5.2 illustrates the difference between the SPECT values and the truth, giving an idea of how well SPECT performs quantitatively.

The planar curve, at \( t = 249\text{min} \), produces an activity of

\[ A(t = 249) = 56.81 \cdot e^{-0.0019\cdot 249} = 35.40\text{MBq} \]
Chapter 5. Phantom Experiments

Table 5.2: Heart data from SPECT scans (Experiment #1).

<table>
<thead>
<tr>
<th>Number</th>
<th>Measured Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Error Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>11.84</td>
<td>10.87</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>9.27</td>
<td>8.74</td>
<td>6</td>
</tr>
</tbody>
</table>

Likewise for \( t = 364 \text{min} \), \( A(t = 364) = 28.45 MBq \). The ratio of the planar value (at \( t = 249 \text{min} \) and \( 364 \text{min} \)) to the SPECT value (at \( t = 249 \text{min} \) and \( 364 \text{min} \)) yields the normalization factors used to constrain the planar data.

\[
N_1 = \frac{35.40 MBq}{11.84 MBq} = 2.99
\]

\[
N_1 = \frac{28.45 MBq}{9.27 MBq} = 3.07
\]

A normalization factor \( N_j \) can be determined for each SPECT scan \( j \) that is acquired. An average \( \bar{N} \) is taken of all the normalization factors then all planar data is divided by the mean normalization factor to achieve the SPECT constrained data.

\[
\bar{N} = \frac{N_1 + N_2}{2} = \frac{2.99 + 3.07}{2} = 3.03
\]

Table 5.3 displays the results of dividing all of the planar activities by the normalization factor.

The SPECT constraint yields a new curve fit to the data (represented in Figure 5.3 (x)):

\[
A(t) = 18.80 \cdot e^{-0.0019 \cdot t}
\]

And the cumulated activity is:
Table 5.3: Planar data re-normalized using the SPECT Constraint for the Heart ROI (Experiment # 1).

<table>
<thead>
<tr>
<th>Scan Number</th>
<th>Constrained Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.66</td>
<td>17.45</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>15.79</td>
<td>14.77</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>12.73</td>
<td>11.57</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>9.55</td>
<td>8.88</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>8.79</td>
<td>8.21</td>
<td>7</td>
</tr>
</tbody>
</table>

\[ A = 5.937 \times 10^5 MBq \cdot s \]

The SPECT constraint has brought the cumulated activity estimate to within 8% of the true cumulated activity within the heart region of the phantom.

5.2 **Technetium-99m Phantom Experiment # 2**

The same thorax phantom was used for this experiment with the addition of two spherical tumor inserts. One tumor (2.54cm diameter) insert was placed under the right lung and the other (1.86cm diameter) was placed on the lateral surface of the left lung. The heart was injected with an activity of 20.4MBq, the body with 127.2MBq, the right-lung tumor (Tumor # 1) with 8.87MBq, and the left-lung tumor (Tumor # 2) with 8.99MBq. The calibration source used in the planar scans had an initial activity of 9.41MBq and an additional calibration source (on the surface of the phantom) was used in the SPECT scans (10.21MBq) in order to test the effects of attenuation on the calibration source. All of the quoted activities are decay corrected so that the first scan coincides with time.
$t_0$. Figure 5.4 illustrates the thorax phantom and the two tumor inserts used in the experiment.

![Figure 5.4: Thorax phantom with two spherical tumor inserts - one underneath the right lung and one on the lateral side of the left lung.](image)

5.2.1 ACQUISITION PROTOCOLS

The planar and SPECT acquisition protocols are identical to those described in Technetium-99m Phantom Experiment #1.

5.2.2 SCAN SCHEDULE

Scans 1, 2, 4, 6 and 7 were planar scans acquired at $t = 0, 92, 215, 353$, and 381 minutes and scans 3 and 5 were SPECT scans acquired at $t = 103$ and 326 minutes.
5.2.3 **REGION OF INTEREST (ROI) ANALYSIS**

Region of interest analysis was performed as described in the previous experiment. Again the planar attenuation correction was performed using an *effective* $\mu$ of 0.12$cm^{-1}$. Tables 5.4, 5.5, and 5.6 contain the planar attenuation corrected activities for the heart, tumor 1, and tumor 2, respectively.

<table>
<thead>
<tr>
<th>Scan Number</th>
<th>Measured Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Error Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46.11</td>
<td>20.4</td>
<td>126</td>
</tr>
<tr>
<td>2</td>
<td>39.22</td>
<td>17.1</td>
<td>129</td>
</tr>
<tr>
<td>4</td>
<td>31.51</td>
<td>13.6</td>
<td>132</td>
</tr>
<tr>
<td>6</td>
<td>24.13</td>
<td>10.4</td>
<td>132</td>
</tr>
<tr>
<td>7</td>
<td>22.84</td>
<td>9.89</td>
<td>131</td>
</tr>
</tbody>
</table>

Table 5.4: Heart data from planar scans (Experiment # 2).

<table>
<thead>
<tr>
<th>Scan Number</th>
<th>Measured Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Error Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.21</td>
<td>8.87</td>
<td>105</td>
</tr>
<tr>
<td>2</td>
<td>15.39</td>
<td>7.45</td>
<td>107</td>
</tr>
<tr>
<td>4</td>
<td>12.12</td>
<td>5.90</td>
<td>105</td>
</tr>
<tr>
<td>6</td>
<td>9.41</td>
<td>4.54</td>
<td>107</td>
</tr>
<tr>
<td>7</td>
<td>8.92</td>
<td>4.30</td>
<td>107</td>
</tr>
</tbody>
</table>

Table 5.5: Tumor 1 data from planar scans (Experiment #2).

**HEART**

The curve fit to the planar attenuation corrected data yields the following:
Table 5.6: Tumor 2 data from planar scans (Experiment # 2).

<table>
<thead>
<tr>
<th>Scan Number</th>
<th>Measured Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Percent Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23.96</td>
<td>8.99</td>
<td>167</td>
</tr>
<tr>
<td>2</td>
<td>20.11</td>
<td>7.55</td>
<td>166</td>
</tr>
<tr>
<td>4</td>
<td>16.02</td>
<td>5.98</td>
<td>168</td>
</tr>
<tr>
<td>6</td>
<td>12.11</td>
<td>4.60</td>
<td>163</td>
</tr>
<tr>
<td>7</td>
<td>11.80</td>
<td>4.36</td>
<td>171</td>
</tr>
</tbody>
</table>

\[ A(t) = 46.40 \cdot e^{-0.0018t} \]

Figure 5.5 displays the curve fit to the planar attenuation corrected data (+). From this fit, the cumulated activity is \( \tilde{A} = 1.547 \times 10^6 MBq \cdot s \).

The true activity (also represented in Figure 5.5(·)) and the resulting cumulated activity are:

\[ A(t) = 20.4 \cdot e^{-0.0019t} \]

\[ \tilde{A} = 6.442 \times 10^5 MBq \cdot s \]

The cumulated activity using the planar attenuation corrected data gives an estimate that is 140% larger than the truth.

**TUMOR 1**

The curve fit to the planar attenuation corrected data yields the following:

\[ A(t) = 18.2 \cdot e^{-0.0019t} \]
Figure 5.5: Heart Time-Activity curve for the thorax phantom in Experiment # 2.

Figure 5.6 displays the curve fit to the planar attenuation corrected data (+). From this fit, the cumulated activity is $\bar{A} = 5.747 \times 10^5 \text{MBq} \cdot \text{s}$.

The true activity (also represented in Figure 5.6(·)) and the resulting cumulated activity are:

$$A(t) = 8.87 \cdot e^{-0.0019t}$$

$$\bar{A} = 2.801 \times 10^5 \text{MBq} \cdot \text{s}$$

The cumulated activity using the planar attenuation corrected data gives an estimate that is 105% larger than the truth.
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Figure 5.6: Tumor 1 Time-Activity curve for the thorax phantom in Experiment # 2.

TUMOR 2

The curve fit to the planar attenuation corrected data yields the following:

\[ A(t) = 24.0 \cdot e^{-0.0019t} \]

Figure 5.7 displays the curve fit to the planar attenuation corrected data (+). From this fit, the cumulated activity is \( \tilde{A} = 7.579 \times 10^5 MBq \cdot s \).

The true activity (also represented in Figure 5.7(\( \cdot \))) and the resulting cumulated activity are:

\[ A(t) = 8.99 \cdot e^{-0.0019t} \]
Figure 5.7: Tumor 2 Time-Activity curve for the thorax phantom in Experiment # 2.

$\tilde{A} = 2.839 \times 10^5 MBq \cdot s$

The cumulated activity using the planar attenuation corrected data gives an estimate that is 167% larger than the truth.

5.2.4 SPECT CONSTRAINT

Image reconstruction using the Iterative $W$ method resulted in strong artifacts in the image, likely due to the high activities in the tumors. For this reason the SPECT scans
were reconstructed using another iterative technique known as OSEM or Ordered Subset Expectation Maximization. The images were reconstructed over 15 iterations using a Butterworth filter with a cut-off of 0.35. The OSEM method returned a cleaner image with less artifacts. Scans 3 and 5, acquired at t = 103\,min and 326\,min, were SPECT scans and were used to constrain the planar data. From the 3-dimensional iteratively reconstructed image, the Display software determined the counts in the heart, tumor 1, tumor 2, and calibration ROI's. Tables 5.7, 5.9 and 5.11 illustrate the difference of the SPECT values from the truth, demonstrating how SPECT performs quantitatively.

**Heart**

Table 5.7: Heart data from SPECT scans (Experiment # 2).

<table>
<thead>
<tr>
<th>Scan Number</th>
<th>Measured Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Percent Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>19.02</td>
<td>16.77</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>10.10</td>
<td>10.98</td>
<td>-8</td>
</tr>
</tbody>
</table>

At times t = 103\,min and 326\,min, the planar curve yields activities of 38.55\,MBq and 25.80\,MBq respectively. Determining the normalization factors:

\[
N_1 = \frac{38.55}{19.02} = 2.03
\]

and

\[
N_2 = \frac{25.80}{10.10} = 2.55
\]

\[
\tilde{N} = \frac{2.03 + 2.55}{2} = 2.29
\]
Table 5.8: Planar data re-normalized using the SPECT Constraint for the Heart ROI (Experiment # 2).

<table>
<thead>
<tr>
<th>Scan Number</th>
<th>Constrained Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Percent Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.14</td>
<td>20.4</td>
<td>-1</td>
</tr>
<tr>
<td>2</td>
<td>17.13</td>
<td>17.13</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>13.76</td>
<td>13.56</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>10.54</td>
<td>10.43</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>9.97</td>
<td>9.89</td>
<td>1</td>
</tr>
</tbody>
</table>

The results of using the above normalization factor to constrain the planar data are summarized in Table 5.8.

The new fit to the SPECT constrained data (represented in Figure 5.5 (*) is:

\[
A(t) = 21.16 \cdot e^{-0.0020 \cdot t}
\]

giving a cumulated activity \tilde{A} of \(6.348 \times 10^5\) MBq·s which is \(-1\)% from the true cumulated activity.

TUMOR 1

Table 5.9: Tumor 1 data from SPECT scans (Experiment # 2).

<table>
<thead>
<tr>
<th>Scan Number</th>
<th>Measured Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Percent Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>6.35</td>
<td>7.29</td>
<td>-13</td>
</tr>
<tr>
<td>5</td>
<td>5.07</td>
<td>4.77</td>
<td>6</td>
</tr>
</tbody>
</table>

At times \(t = 103\text{min}\) and \(326\text{min}\), the planar curve yields activities of \(14.97MBq\) and \(9.80MBq\) respectively. Determining the normalization factors:
Chapter 5. Phantom Experiments

\[ N_1 = \frac{14.97}{6.35} = 2.36 \]

and

\[ N_2 = \frac{9.80}{5.07} = 1.93 \]

\[ \bar{N} = \frac{2.36 + 1.93}{2} = 2.15 \]

The results of using this normalization factor to constrain the planar data are summarized in Table 5.10.

Table 5.10: Planar data re-normalized using the SPECT Constraint for the Tumor 1 ROI (Experiment # 2).

<table>
<thead>
<tr>
<th>Number</th>
<th>Scan Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.47</td>
<td>8.87</td>
<td>-5</td>
</tr>
<tr>
<td>2</td>
<td>7.16</td>
<td>7.45</td>
<td>-4</td>
</tr>
<tr>
<td>4</td>
<td>5.64</td>
<td>5.90</td>
<td>-4</td>
</tr>
<tr>
<td>6</td>
<td>4.38</td>
<td>4.54</td>
<td>-4</td>
</tr>
<tr>
<td>7</td>
<td>4.15</td>
<td>4.30</td>
<td>-3</td>
</tr>
</tbody>
</table>

The new fit to the SPECT constrained data (represented in Figure 5.6 (*)) is:

\[ A(t) = 8.20 \cdot e^{-0.0017 \cdot t} \]

giving a cumulated activity \( \bar{A} \) of \( 2.894 \times 10^5 MBq \cdot s \) which is 3% from the true cumulated activity.
Table 5.11: Tumor 2 data from SPECT scans (Experiment # 2).

<table>
<thead>
<tr>
<th>Scan Number</th>
<th>Measured Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Error Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>9.18</td>
<td>7.39</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>7.32</td>
<td>4.84</td>
<td>51</td>
</tr>
</tbody>
</table>

**Tumor 2**

At times $t = 103\text{min}$ and $326\text{min}$, the planar curve yields activities of $19.73\text{MBq}$ and $12.92\text{MBq}$ respectively. Determining the normalization factors:

$$N_1 = \frac{19.73}{9.18} = 2.15$$

and

$$N_2 = \frac{12.92}{7.32} = 1.77$$

$$\bar{N} = \frac{2.15 + 1.77}{2} = 1.96$$

The results of using this normalization factor to constrain the planar data are summarized in Table 5.12.

The new fit to the SPECT constrained data (represented in Figure 5.7 (*) is:

$$A(t) = 11.82 \cdot e^{-0.0917t}$$

giving a cumulated activity $\bar{A}$ of $4.172 \times 10^5\text{MBq} \cdot \text{s}$ which is 47% from the true cumulated activity.
Table 5.12: Planar data re-normalized using the SPECT Constraint for the Tumor 2 ROI (Experiment # 2).

<table>
<thead>
<tr>
<th>Scan Number</th>
<th>Activity (MBq)</th>
<th>True Activity (MBq)</th>
<th>Error Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.22</td>
<td>8.99</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>10.26</td>
<td>7.55</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>8.17</td>
<td>5.98</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>6.18</td>
<td>4.60</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>6.02</td>
<td>4.36</td>
<td>38</td>
</tr>
</tbody>
</table>

5.3 · DISCUSSION

Results from the planar studies compiled in Tables 5.1, 5.4, 5.5 and 5.6, and the SPECT studies compiled in Tables 5.2, 5.7, 5.9 and 5.11 demonstrate how planar and SPECT data compare quantitatively once corrected for attenuation. In experiment #1, by using a SPECT constraint, the cumulated activity in the heart improved from a 225% overestimate of the truth (planar attenuation correction) to an 8% overestimate of the truth using the SPECT attenuation correction. Likewise, in experiment #2, the heart activity improved from 140% error to −1% error, the tumor #1 from 105% error to 3% error, and the tumor #2 from 167% error to 47% error — all the result of using a SPECT constraint rather than planar data alone. Although tumor #2 experienced a drastic improvement in the estimate of \( \tilde{A} \), the resulting error of 47% is potentially due to persistent artifacts in the image around tumor #2. Tumor #2 was more susceptible to reconstruction artifacts due to its high activity contained in a small volume, along with its placement near the edge of the phantom.

The method selected to reconstruct the SPECT data should not be carelessly chosen. Improper reconstruction will result in image artifacts that will carry over to the 3-D ROI.
software thus affecting the activity estimates in the source regions. It is wise to be most cautious when dealing with regions of high activity, as these regions are most prone to reconstruction artifacts. For the levels of activity used in Experiment #1, reconstruction by Iterative $W$ did not produce any noticeable artifacts. However, at the high tumor activities used in Experiment #2, Iterative $W$ did produce noticeable artifacts, prompting the decision to try another reconstruction method. OSEM improved the image quality sufficiently to consider it a worthy option when dealing with high activities.

5.4 OTHER FACTORS AFFECTING QUANTITATION

Some factors are often overlooked when considering quantitation in imaging. Camera systems are generally designed to cope with matters affecting image quality in diagnostic applications but quantitation may break down when most needed – at the high levels of activity necessary for therapeutic applications. The two factors considered here, namely Pixel Saturation and Dead-Time, were investigated as to their effect on image quantitation.

5.4.1 PIXEL SATURATION

When the computer stores photon counts into the specified matrix, each pixel in that matrix is designated to hold a specific data type. In most cases this data type is unsigned integer, also known as unsigned short integer. This data type allows for numbers 0 to 65535 to represent the counts collected in that particular pixel. The purpose of assigning a specific data type to hold the data is for the sake of memory storage requirements. An unsigned integer only requires 2 bytes of memory space for storage whereas an unsigned long integer (from 0 to 4,294,967,295) requires 4 bytes of memory space for storage. Saving all image matrices with a data type of unsigned long integer would seem excessive.
and a waste of memory since most pixel counts would rarely exceed 65535. This is the valid justification of why most imaging software will store the data as unsigned integer.

This justification is perfectly warranted for most needs of a Nuclear Medicine department as most applications are diagnostic in nature. But with the increasing interest in therapeutic applications, the justification may no longer be valid. To investigate potential pixel saturation, an experiment was performed with a syringe initially containing 16.34 MBq of Tc-99m, scanned over a period of 5 minutes (simulating a whole body planar scan), and the data was acquired in a $64 \times 64$ matrix. Analysis of the image proved that quantitation was lost as some of the pixels were saturating (i.e. no longer acquiring counts) after they reached a count of 65535. Once pixels stop acquiring data, when data is still present to be counted, accurate quantitation of the data is no longer possible.

Another experiment was performed using a syringe of 13.23 MBq of Tc-99m, scanned over a period of 1 minute, and the data was acquired in a $256 \times 256$ matrix. It was concluded that no pixel saturation was present in this case. The effects of pixel saturation can be overcome by increasing the size of the acquisition matrix, reducing the acquisition time, decreasing the activity or increasing the size of the activity source (same activity but in a larger volume). When considering therapy, some of these factors are controllable and others are beyond our control.

5.4.2 Dead-Time

When counts (scintillation events) are collected by the gamma camera at rapid acquisition rates, the gamma camera may fail to detect some scintillation events that interact with the detector crystal. The loss of counts is due to the dead-time of the electronics of the detection and computer instrumentation. Dead-time is defined as the period of time after acquisition of a scintillation during which the gamma camera and computer electronics
are unable to respond to another scintillation [38]. When the source activity is increased (increasing the scintillation events) the number of counts lost will increase as well. In regions of high count rates, dead-time results in a loss of quantitation of the data. The effects of dead-time will be more pronounced in the case of high levels of activity.

Two experiments were performed to investigate the effects of dead-time. The first experiment coincided with one of the pixel-saturation experiments described above. The experiment was performed using a syringe of 13.23 MBq of Tc-99m, scanned over a period of 1 minute, and the data was acquired in a 256 x 256 matrix. Six scans were acquired over a period of 5 hours with the scan times accurately recorded. The total counts in each of scans 2 through 6 were corrected for physical decay in order to normalize each scan to Scan # 1. Performing this normalization allows us to see any effects of dead-time since a horizontal plot (Counts vs. Scan) is free of significant dead-time whereas a plot that deviates from the horizontal reveals the influence of dead-time. The results for this experiment are plotted in Figure 5.8.

Taking statistical errors into account the plot in Figure 5.8 proves to be a horizontal line, suggesting that there is no significant dead-time present. In other words, quantitation is not lost by potential dead-time effects. To explore this further, another experiment was performed – this time using both detectors 1 and 2 of the Siemens MultiSPECT2 (MS2) and detector 2 of the Siemens e.cam. To simulate an extended source, like the area of a kidney, a petri dish of diameter 8.88 cm (61.9 cm² area) was used. An activity of 347 MBq was distributed over the bottom of the petri dish with minimal liquid (to minimize attenuation). Four 5 minute scans were acquired (in 128 x 128 matrices) on both the e.cam and the MS2 over a period of 5 hours. The first scan on the e.cam was plagued by pixel saturation, thus the e.cam scan time was reduced to 3 minutes. The
Figure 5.8: Results of the Dead-Time investigation for detector 1 of the Siemens e.cam camera.

MS2 data did not have any pixel saturation, likely due to the fact that the MS2 camera had ultra-high resolution collimators with less sensitivity than the high resolution collimators used on the e.cam.

After all scans were normalized (decay corrected) to the first scan, they were plotted on a Counts vs. Scan plot. Results are summarized in Figure 5.9. Taking statistical errors into account, all three plots display a non-horizontal trend. The e.cam detector 2 is most noticeably impacted by the effects of dead-time. This is likely due to the collimator difference between the e.cam and the MS2. Quantitation will be restored when the activity has decayed to a manageable level. These results demonstrate a necessary concern over dead-time in image quantitation. Although this experiment may prove to be an extreme case (ie. high activity over a small region with little attenuation), it also
proves that dead-time cannot be ignored as a factor affecting quantitation – especially at therapeutic levels of activity. When quantitation is important, as it is in dosimetry, protocols need to be established for particular cameras regarding dead-time limitations (ie. activities, matrix sizes, collimators, scan times), or dead-time needs to be measured and accounted for.
CHAPTER 6

CONCLUSIONS

This thesis proposes a method for Internal Dosimetry that implements patient-specific SPECT scans that are corrected for attenuation. To conclude this thesis, I will briefly summarize the work that has been presented and suggest an extension of this work for clinical applications.

6.1 SUMMARY OF THE WORK

In order to form an understanding of dosimetry, it is fundamental to be familiar with radiations relevant to Nuclear Medicine, how these radiations interact with tissue, and how it is possible to detect where radiation originates from within a patient. The introductory chapter built the foundation of this understanding by introducing emissions involving $\alpha$ and $\beta$ particles and $\gamma$ photons – discussing how these particles can be absorbed or scattered in matter – and how the gamma camera is used to detect the $\gamma$ emissions emanating from a patient.

Chapter 2 went on to describe how the effect of radiation on tissue must be quantified by estimating the internal absorbed dose. This is the goal of Internal Dosimetry. The primary method to estimate the absorbed dose is known as the MIRD Protocol. A
comprehension of the MIRD protocol is vital as all current methods have derived from it in one form or another.

The MIRD protocol explains how the absorbed dose is calculated but Chapter 3 goes on to detail how the absorbed dose is measured. To do this, the two primary modalities used to perform measurements are explained, namely planar and SPECT imaging. In order to quantify planar and SPECT data, a correction for attenuation must be performed. This chapter outlines current methods in dosimetry that arose from the need to improve absorbed dose estimates, hence the proposal of this thesis is included here. By keeping most scans planar, yet implementing at least 2 SPECT scans, we have gained the benefits of 3-D information, not to mention a promising technique for attenuation correction. I have put forth a method to provide higher accuracy than planar methods alone.

Simulations were performed to give an idea of the errors incurred by planar methods of attenuation correction. The high errors that stem from planar attenuation correction justify the motivation to improve this favored method somehow. For averaging anterior and posterior image ROI's, it was determined that a geometric mean demonstrated more quantitative accuracy than an arithmetic mean – suggesting that if planar methods are the sole method available, a geometric mean should be used when processing the data.

Phantom experiments were carried out, not only to describe in detail the protocol presented here, but also to illustrate the results of this protocol. Estimates of the cumulated activity by using a SPECT constraint demonstrates that the method shows much promise. A good method of attenuation correction (the MLA transmission source) is crucial to this method, not to mention an appropriate reconstruction method. For all regions, the cumulated activity estimates improved from an average error of 159% to an average error of 14% when using a SPECT constraint over planar exclusively. These
results are especially promising in light of the need for improvements in dosimetry for therapeutic applications. To date, quantitative planar methods have maintained their popularity by their simplicity and clinically practical time requirements. Never has there been as much of a push to improve planar estimates as now, with the promise of new therapeutic possibilities looming on the horizon. With the high levels of activity required for therapy, it is no longer sufficient to settle for dose estimates that exceed 100% error. At this level of uncertainty, either patient's lives could be at risk or adequate therapy may not be provided. Implementing a dosimetry protocol that maintains the majority of scans as planar yet incorporates regional SPECT scans would reduce the need to re-train staff on a completely new protocol while also producing more accurate dose estimates. If patients can be successfully treated with new radiopharmaceuticals, the extra clinical time needed to perform two or more regional SPECT scans should be considered worthwhile.

Other factors that are often taken for granted but may affect quantitation have also been covered, namely pixel saturation and dead-time. Quantitation of the data is lost if pixels begin to saturate at high levels of activity. Pixel saturation does not pose much of a problem for the short SPECT acquisitions but planar scans can prove vulnerable to saturation over a 4.88min whole-body acquisition. Dead-time effects are potentially significant at therapeutic levels of activity but quantitation may be restored if these effects are measured and accounted for.

6.2 SUGGESTIONS FOR CLINICAL APPLICATIONS

Although these results may be impressive for a phantom study, reality dictates that a proposed method must be practical for use on patients. To accurately produce time-activity curves, SPECT scans would have to be performed over any region containing
significant uptakes of activity. This may or may not prove to be time consuming for some radiopharmaceutical distributions. Ideally, this potential setback could be overcome by using a transmission source on a camera that is capable of performing helical SPECT. Instead of a regional SPECT scan, a whole-body SPECT scan could be performed. Again, with the aid of a good reconstruction method, all significant regions in the whole-body SPECT image could be used to constrain the corresponding planar images.

The development of a superior reconstruction method that is capable of producing high-activity images free of artifacts would also be a worthwhile pursuit. An effective means of attenuation correction in SPECT (perhaps transmission helical SPECT), along with improved reconstruction methods, would certainly help pave the way for a growing interest in therapeutic applications in Nuclear Medicine.


