MONTE CARLO TECHNIQUES IN DIAGNOSTIC AND THERAPEUTIC NUCLEAR MEDICINE

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Abstract

The use of the Monte Carlo method to simulate radiation transport has become the most accurate means of predicting absorbed dose distributions and other quantities of interest in radiation treatments of cancer patients using either external or radionuclide radiotherapy. This trend has continued for the estimation of the absorbed dose in diagnostic procedures using radionuclides as well as the assessment of image quality and the quantitative accuracy of radionuclide imaging. As a consequence of this generalized use, many questions are being raised, primarily about the need and potential of Monte Carlo techniques, but also about how accurate they really are, what would it take to apply them clinically and make them available widely to the nuclear medicine community at large. Many of these questions will be answered when Monte Carlo techniques are implemented and used for more routine calculations and for in-depth investigations. The conceptual role of the Monte Carlo method is briefly introduced in this paper, which is followed by a survey of its different applications in diagnostic and therapeutic nuclear medicine. Please note that due to limited space, the references contained herein are for illustrative purposes and are not inclusive; no implication that those chosen are better than others not mentioned is intended.

1. CONCEPTUAL ROLE OF MONTE CARLO SIMULATIONS

The Monte Carlo method describes a very broad area of science, in which many processes, physical systems and phenomena are simulated by statistical methods employing random numbers. The general idea of Monte Carlo analysis is to create a model, which is as similar as possible to the real physical system of interest, and to create interactions within that system based on known probabilities of occurrence, with random sampling of the probability density functions (PDFs). As the number of individual events (called histories) is increased, the quality of the reported average behaviour of the system improves, meaning that the statistical uncertainty decreases. Almost any complex system can in principle be modelled; perhaps there is a desire to model the number of cars passing a particular intersection during certain times of the day, to optimize traffic management, or to model the

number of people that will make transactions in a bank, to evaluate the advantages of different queuing systems. If the distribution of events that occur in a system is know from experience, a PDF can be generated and sampled randomly to simulate the real system. A detailed description of the general principles of the Monte Carlo method is given in Refs [1, 2].

In the specific application of interest in this paper, the transport of ionizing radiation particles is simulated by the creation of particles or rays from a defined source region, generally with a random initial orientation in space, with tracking of the particles as they travel through the system, sampling the probability PDFs for their interactions to evaluate their trajectories and energy deposition at different points in the system. The interactions determine the penetration and motion of particles, but, more importantly, the energy deposited during each interaction gives the radiation absorbed dose, when divided by the appropriate values of mass. With sufficient numbers of interactions the mean absorbed dose at points of interest will be given with acceptable uncertainties. The central issues include how well the real system of interest can be simulated by a geometrical model, how many histories (i.e. how much computer time) are needed to obtain acceptable uncertainties (usually around 5%, no more than 10%) and how can measured data be used to validate the theoretical calculations.

Monte Carlo techniques have become one of the most popular tools in different areas of medical physics following the development and subsequent implementation of powerful computing systems for clinical use [3]. In particular, they have been extensively applied to simulate processes involving random behaviour and to quantify physical parameters that are difficult or even impossible to calculate analytically or to determine by experimental measurements. The applications of the Monte Carlo method in medical physics cover almost all topics, including radiation protection, diagnostic radiology, radiotherapy and nuclear medicine, with an increasing interest in exotic and new applications, such as intravascular radiation therapy, boron neutron capture therapy and synovectomy. With the rapid development of computer technology, Monte Carlo based treatment planning for radiation therapy is becoming practicable.

This paper briefly reviews the conceptual role of the Monte Carlo method and summarizes its application in diagnostic and therapeutic nuclear medicine. Emphasis is given to applications in which photon and/or electron transport in matter are simulated. The historical developments and computational aspects of the Monte Carlo method, mainly related to random number generation, sampling and variance reduction, together with a description of widely used Monte Carlo codes in diagnostic and therapeutic

nuclear medicine, fall outside the scope of this paper and are discussed elsewhere [1–4].

2. DEVELOPMENT OF ANTHROPOMORPHIC MATHEMATICAL AND VOXEL BASED PHANTOMS

Computerized anthropomorphic phantoms can either be defined by mathematical (analytical) functions or digital (voxel based) volume arrays [4]. Analytic phantoms consist of regularly shaped continuous objects defined by combinations of simple mathematical geometries, whereas voxel based phantoms are mainly derived from segmented tomographic images of the human anatomy obtained by either X ray computed tomography (CT) or magnetic resonance imaging (MRI). Any complex activity and corresponding attenuation distributions can therefore be modelled. Analytical phantoms, however, have the advantage of being able to model anatomical variability and dynamic organs easily. The mathematical specifications for phantoms that are available assume a specific age, height and weight. People, however, exhibit a variety of shapes and sizes. The first breakthrough in the use of Monte Carlo techniques was the development of the Fisher–Snyder heterogeneous, hermaphrodite, anthropomorphic model of the human body in the 1970s [5]. This phantom consisted of spheres, ellipsoids, cones, tori and subsections of such objects, combined to approximate the geometry of the body and its internal structures. The representation of internal organs with this mathematical phantom is very crude, since the simple equations can only capture the most general description of an organ's position and geometry. The original phantom developed was intended mainly to represent a healthy average adult male, which well characterized the working population of its time. The phantom did have both male and female organs, but most structures represented the organs of "Reference Man", as defined by the International Commission on Radiological Protection (ICRP) from an extensive review of medical and other literature, restricted primarily to European and North American populations. Both due to the makeup of the nuclear medicine population and the diversifying worker population, the need for other phantoms arose. In 1987 Cristy and Eckerman [6] of Oak Ridge National Laboratory (ORNL) developed a series of phantoms representing children of different ages, one of which (the 15 year old) also served as a model for the adult female. Bouchet and Bolch [7] developed a series of five dosimetric head and brain models to allow more precise dosimetry in paediatric neuroimaging procedures. More recently, a new rectal model and a dynamic urinary

bladder model have also been proposed. To develop more patient-specific dosimetry, new mathematical models for adults of different height have been developed using anthropometric data. Mathematical anthropomorphic phantoms are continuously being improved. Recent three and four dimensional computer phantoms seek a compromise between ease of use, flexibility and the accurate modelling of populations of patient anatomies, and attenuation and scatter properties as well as biodistributions of radiopharmaceuticals in patients. Current developments are aimed at computer phantoms that are flexible while providing the accurate modelling of patient populations. The use of dynamic anthropomorphic phantoms in Monte Carlo simulations is becoming possible, owing to the increasing availability of computing power. This includes the development of appropriate primitives that allow the accurate modelling of anatomical variations and patient motion, such as superquadrics and non-uniform rational B-spline surfaces [8].

Modelling for imaging and dosimetry applications is best done with phantom models that match the gross parameters of an individual patient. Anthropomorphic phantoms with internally segmented structures make clinically realistic Monte Carlo simulations possible. Zubal [9] developed a typical anthropomorphic voxel based adult phantom by the manual segmentation of CT transverse slices of a living human male performed by medical experts. A computerized three dimensional (3-D) volume array modelling all the major internal structures of the body was then created. Each voxel of the volume contains an index number designating it as belonging to a given organ or internal structure. These indexes can then be used to assign a value, corresponding to, for example, density or activity. The phantom data are available as a 128 × 128 × 246 matrix with a cubic resolution of 4 mm. The same group has also developed a high resolution brain phantom based on an MRI scan of a human volunteer, which can be used for detailed investigations in the head. The torso phantom was further improved by copying the arms and legs from the visible human (VH) and attaching them to the original torso phantom. However, the arms of the VH cadaver were positioned over the abdominal part, which limited the usefulness of the phantom for simulations of whole body scanning. This problem was tackled by mathematically straightening the arms out along the phantom's side [10]. More recently, a new voxel based whole body model, called VIP-Man, has been developed using high resolution transversal colour photographic images obtained from the National Library of Medicine's VH Project [11]. A group at the National Research Center for Environment and Health (GSF) in Germany has also been developing some voxel based phantoms. The GSF voxel phantoms family tends to cover persons of

individual anatomy and includes at the moment two paediatric and five adult phantoms of both sexes, different ages and stature, and several others are under construction [12].

3. MONTE CARLO TECHNIQUES IN NUCLEAR MEDICINE DOSIMETRY

3.1. Calculation of absorbed fractions

There is broad consensus in accepting that the earliest Monte Carlo calculations in medical physics were made in the area of nuclear medicine, where the technique was used for dosimetry modelling and computations. Formalism and data based on Monte Carlo calculations, developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine, have been published as pamphlets in a series of supplements to the Journal of Nuclear Medicine, the first one being published in 1968 [13]. Some of these pamphlets made extensive use of Monte Carlo calculations to derive specific absorbed fractions (AFs) for photon sources uniformly distributed in organs of mathematical phantoms. This was extended later to electrons [14], beta particles and positron emitters [15].

Monte Carlo calculations for photons were performed using a computer code called ALGAM, which created photons at random positions within any source region (organ or tissue), gave these photons a random orientation in 4π space and then followed them through various Compton and photoelectric interactions (coherent scattering was neglect because of its low contribution to the total cross-section and pair productions events were quite rare, as starting energies did not exceed 4 MeV) until the photon reached a certain critical low cut-off energy and was assumed to be locally absorbed, or until it escaped the surface of the body (at which point the probability of scatter from an air molecule and redirection towards the body was assumed to be negligibly low). With repeated sampling of the source, which at this time generally involved only tens of thousands of trials (histories), a statistical average behaviour of particles originating in this source could be obtained for other regions of the body of interest to radiation dose assessment (target regions). This behaviour was reported as the fraction of energy emitted in the source that was absorbed in a target (AF), with an associated uncertainty (reported as the coefficient of variation). These AFs were thus a considerable improvement over the values given in ICRP Publication 2, as the organ geometries were more realistic, and, more importantly, the organs could

irradiate each other, whereas in the ICRP 2 model an organ could irradiate only itself. These AFs were used later by the ICRP in updated assessments for workers; of more interest for this paper is that they found a more immediate application in dose assessments for nuclear medicine patients, owing to the monumental efforts of the newly formed MIRD Committee. In a flurry of publications in its early years, this committee published decay data, methods for kinetic analyses, the AFs from the ALGAM calculations, dose conversion factors for over 100 nuclides of interest to nuclear medicine, dose calculations for various radiopharmaceuticals, methods for small scale dose calculations with electrons, and other interesting practical scientific documents. AFs for these phantoms were developed using the ALGAMP code (the P signifying a parameterized version of the code, allowing the substitution of parameters giving the radii and positions of the various organs at different ages). These values were published in an ORNL document, but never officially adopted in the MIRD or other peer reviewed literature. Nonetheless, they were widely accepted and used for dose calculations for individuals of different ages.

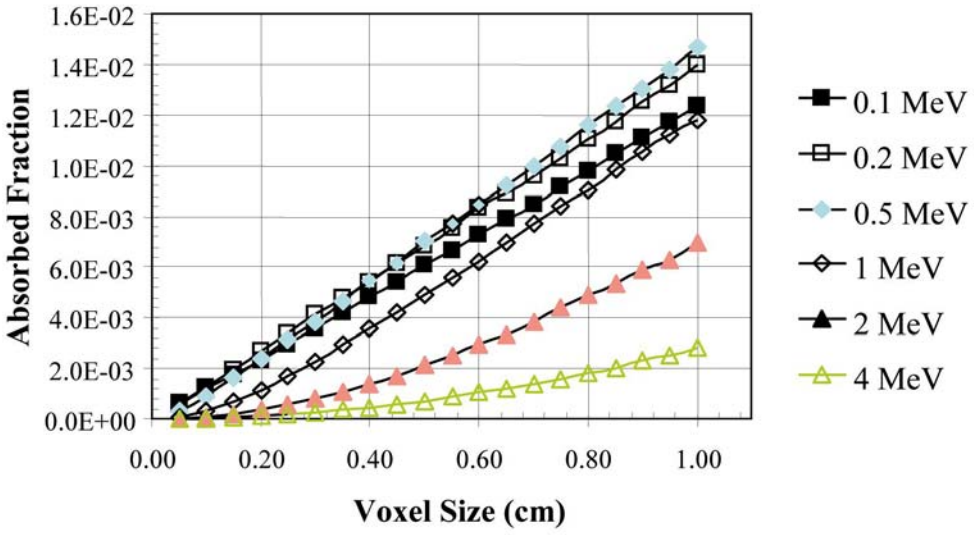

FIG. 1. AFs vs. voxel size for monoenergetic photons (source = target) calculated using the EGS4 Monte Carlo system. Linear interpolation was used to estimate intermediate AFs between different voxel sizes (courtesy of Dr. Bouchet).

Previously calculated AFs for unit density spheres in an infinite unit density medium for photon and electron emitters have been recently re-evaluated using both the EGS4 and MCNP-4B Monte Carlo codes.

Moreover, Stabin and Yoriyaz [16] used the MCNP-4B code to calculate AFs for photons in the voxel based phantom of Zubal et al. [9], and the results were compared with reference values from traditional MIRD and ORNL phantoms, while Chao and Xu used the EGS4 code to estimate specific AFs from internal electron emitters for the VIP-Man model with energies from 100 keV to 4 MeV [17].

The application of the Monte Carlo method to internal radiation dosimetry is further emphasized in two recent MIRD pamphlets. In MIRD Pamphlet No. 15 [18] the EGS4 Monte Carlo radiation transport code was used to revise substantially the dosimetric model of the adult head and brain originally published in MIRD Pamphlet No. 5 [5]. Pamphlet No. 17 [19] demonstrates the utility of the MIRD formalism for the calculation of the non-uniform distribution of radiation absorbed dose in different organs through the use of radionuclide specific *S* values defined at the voxel level. Figure 1 shows absorbed fractions for monoenergetic photons (the source and target are confounded) calculated using the EGS4 Monte Carlo system as a function of voxel size.

3.2. Derivation of dose point kernels

In most cases Monte Carlo calculations are used to simulate the random distribution of sources or targets, whereas the actual dosimetric calculation is performed using so called dose point kernels. Such kernels, usually spherical and calculated for monoenergetic sources, describe the pattern of energy deposited at various radial distances from photon and electron or beta point sources. Dose point kernels can be calculated using analytical or Monte Carlo methods. Hybrid approaches (analytical calculations using Monte Carlo data) have also been considered to decrease the computation time [20]. Three Monte Carlo systems have mainly been used for this purpose, namely ETRAN, the ACCEPT code of the ITS system and EGS4. Limitations and constraints of some of these codes have been reported in the literature, the impact of which on the calculated kernels is difficult to evaluate. ETRAN, for instance, had an incorrect sampling of the electron energy loss straggling, which has been corrected for in the ITS3 system (based on ETRAN). EGS4 did not include the accurate electron physics and transport algorithms, which have been incorporated in the recent EGSnrc system. Furhang [21] generated photon point dose kernels and absorbed fractions in water for the full photon emission spectrum of the radionuclides of interest in nuclear medicine, by simulating the transport of particles using Monte Carlo techniques. The kernels were then fitted to a mathematical expression.

A unified approach for photon and beta particle dosimetry has been proposed by Leichner [22] by fitting Berger's tables for photons and

electrons to generate an empirical function that is valid for both photons and beta particles. Both point kernel and Monte Carlo techniques can therefore be effectively employed to calculate absorbed dose to tissue from radionuclides that emit photons or electrons. The latter are computationally much more intensive; however, point kernel methods are restricted to homogeneous tissue regions that can be mathematically described by analytical geometries, whereas Monte Carlo methods have the advantage of being able to accommodate heterogeneous tissue regions with complex geometric shapes.

3.3. Patient-specific dosimetry and treatment planning

To perform real patient specific dose calculations, a patient specific physical model to be used with patient specific biokinetic data is required. Individual patients not only have significantly different uptake and retention half-lives of activity of the radioactive agent, but also have significantly different physical characteristics and radiosensitivities. If our goal is to optimize patient therapies, their individual parameters should be accounted for as much as possible during treatment planning. Currently, the preferred strategy with radiolabelled antibodies is to use personalized patient dosimetry, and this approach may become routinely employed clinically. The dose distribution pattern is often calculated by generalizing a point source dose distribution [23], but direct calculation by Monte Carlo techniques is also frequently reported, since it allows media of inhomogeneous density to be considered [24].

The development of a 3-D treatment planner based on nuclear imaging is an area of considerable research interest, and several dose calculation algorithms have been developed [2]. Figure 2 lists the essential steps required in developing a 3-D treatment planning program for radioimmunotherapy (RIT). Projection data acquired from an emission tomographic imaging system are processed to reconstruct transverse section images, which yields a count density map of source regions in the body. This count density is converted to an activity map using the sensitivity derived from a calibration phantom. In the final step this activity distribution is converted to a dose rate or dose map, either by convolving the activity distribution with dose point kernels or by direct Monte Carlo calculations. To elaborate a treatment plan for an individual patient, prospective dose estimates can be made by using a tracer activity of radiolabelled antibody to obtain biodistribution information prior to the administration of a larger therapeutic activity. The clinical implementability of treatment planning

algorithms will depend to a significant extent on the time required to generate absorbed dose estimates for a particular patient.

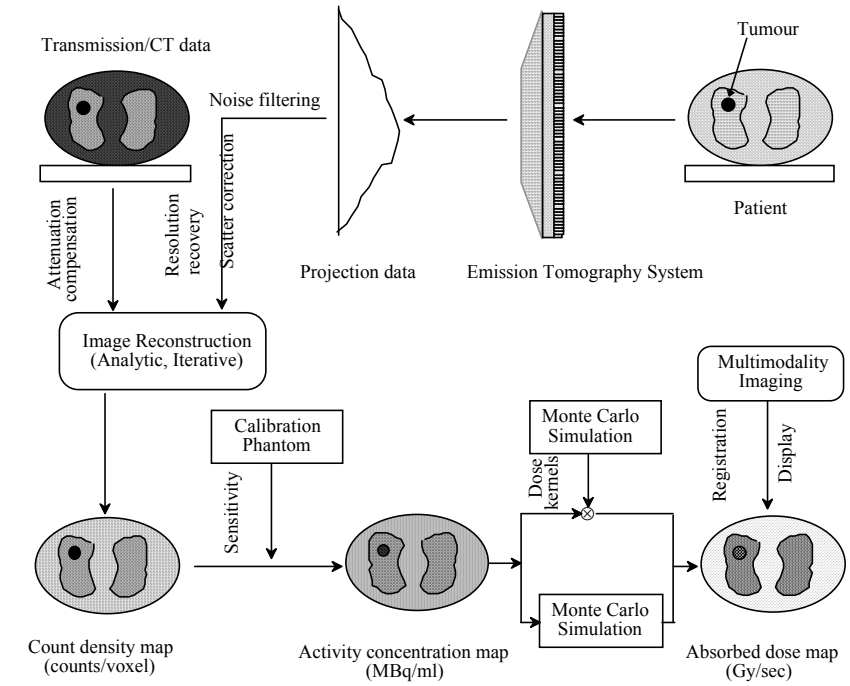

FIG. 2. Essential steps required in developing a 3-D internal dosimetry program for treatment planning with RIT based on quantitative nuclear medical imaging, for which Monte Carlo simulations play a crucial role.

Many specially designed software packages have been developed for patient specific dosimetry and treatment planning. The MABDOSE and DOSE3D computer codes adapt the standard geometrical phantoms, allowing the placement of a single or multiple tumours in various locations to estimate dose contributions from these tumours to normal organs, but do not at present use patient images. These codes work with stylized representations of average individuals, and give the average dose to whole organs. The RTDS code employs either the standard MIRDOSE phantom set or its own transport algorithms in a limited body space, based on voxel source kernels to produce average organ doses or dose distributions within specified organs or tissues of the body. More sophisticated approaches combine anatomical (CT or MRI) and functional radionuclide (single photon

emission computed tomography (SPECT) and positron emission tomography (PET)) images to compute patient specific absorbed dose distributions and dose–volume histograms similar to the treatment planning programs used in external beam radiotherapy. Several software packages have been devised and validated by different research groups, including the 3D-ID code, SIMDOS and its more recent version based on the EGS4 system, the RMDP package, and the SCMS code. A detailed description of some of these tools is provided in Ref. [2]. It is worth emphasizing that, with some exceptions; very few have been used in clinical environments.

4. MONTE CARLO TECHNIQUES IN NUCLEAR MEDICINE IMAGING

There has been an enormous increase and interest in the use of Monte Carlo techniques in all aspects of nuclear imaging, including planar imaging, SPECT, PET and multimodality imaging devices [1, 4]. However, due to computer limitations, the method has not yet fully lived up to its potential. With the advent of high speed supercomputers the field has received increased attention, particularly with parallel algorithms, which have much higher execution rates. Figure 3 illustrates the principles and main components of Monte Carlo or statistical simulation as applied to a cylindrical PET imaging system [25]. Assuming that the behaviour of the imaging system can be described by PDFs, then the Monte Carlo simulation can proceed by sampling from these PDFs, which necessitates a fast and effective way to generate uniformly distributed random numbers. Photon emissions are generated within the phantom and are transported by sampling from PDFs through the scattering medium (transmission image) and detection system until they are absorbed or escape the volume of interest without hitting the crystal matrices. The outcomes of these random samplings, or trials, must be accumulated or tallied in an appropriate manner to produce the desired result, but the essential characteristic of the Monte Carlo method is the use of random sampling techniques to arrive at a solution of the physical problem.

4.1. Applications in diagnostic nuclear medicine imaging

The Monte Carlo method is a widely used research tool for different areas of diagnostic nuclear imaging, such as detector modelling and systems design, image correction and reconstruction techniques, internal dosimetry and pharmacokinetic modelling. The method has proven to be very useful for solving complex problems that cannot be modelled by computer codes using deterministic methods or when experimental measurements may be

impracticable [4]. The design of SPECT and PET systems using the Monte Carlo method has received considerable attention, and a large number of applications were the result of such investigations. During the past two decades the simulation of scintillation camera imaging using both deterministic and Monte Carlo methods has been developed to assess qualitatively and quantitatively the image formation process and interpretation and to assist in the development of collimators. Several researchers have also used Monte Carlo simulation methods to study potential designs of dedicated small animal positron tomographs.

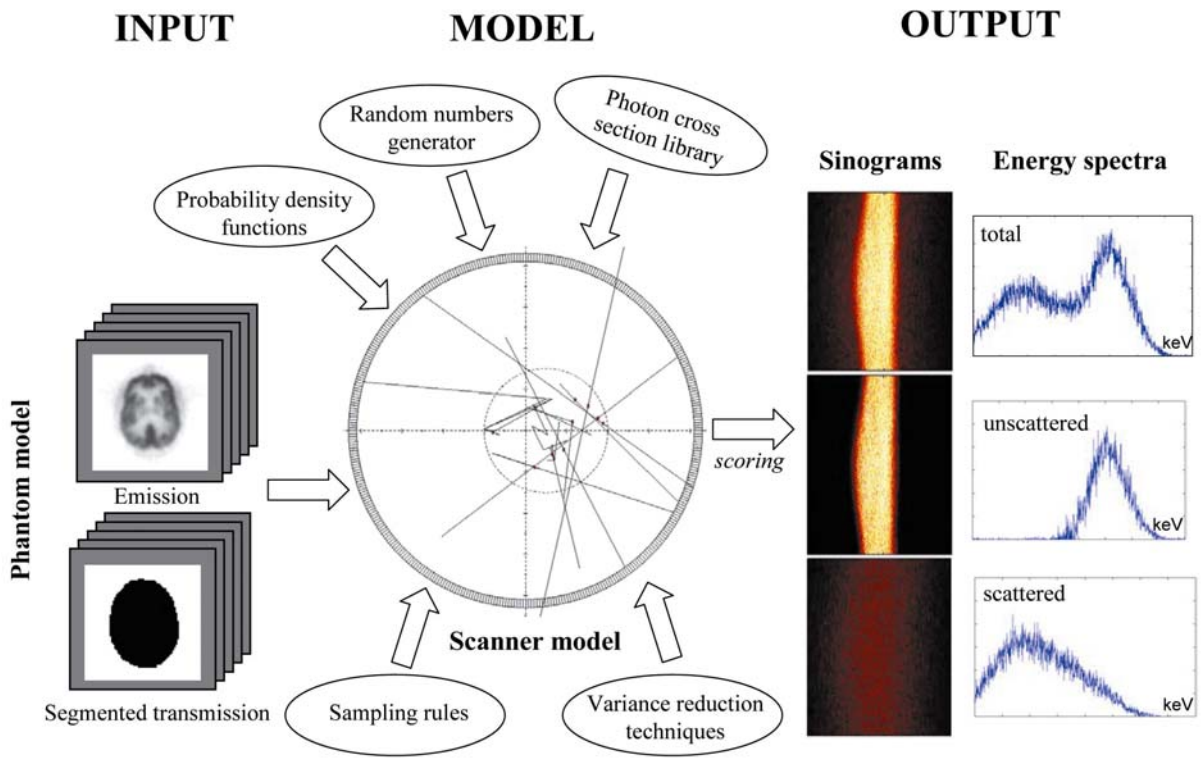

FIG. 3. Principles and main components of a Monte Carlo simulation environment for a cylindrical multiring PET imaging system.

Another promising application of Monte Carlo calculations is the development and evaluation of image reconstruction algorithms and correction methods for photon attenuation and scattering in nuclear medicine imaging, since the user has the ability to separate the detected photons into

their components: primary events, scatter events, contribution of downscatter events, etc. Monte Carlo modelling thus allows a detailed investigation of the spatial and energy distribution of Compton scatter, which would be difficult to perform using present experimental techniques, even with very good energy resolution detectors. A Monte Carlo study of the acceptance of scattered events in a depth encoding large aperture camera made of position encoding blocks modified to resolve the depth of interaction through a variation in the photopeak pulse height has been performed by Moison et al. [26]. The contribution of scatter from outside the field of view is a challenging issue, especially with the current large axial field of view 3-D PET scanners. Several researchers used Monte Carlo simulations to study scatter contribution from outside the field of view and the spatial characteristics of scatter for various phantoms. It was concluded that the spatial distribution of multiple scatter is quite different from the simple scatter component, which might preclude the rescaling of the latter to take into account the effect of the former for scatter correction purposes. Monte Carlo simulations have also been extensively used to evaluate and compare scatter correction schemes in both SPECT and PET [27]. The simulation of transmission scanning allowed the study of the effect of downscatter from the emission (^{99m}Tc) photons into the transmission (^{153}Gd) energy window in SPECT and the investigation of detected scattered photons in single-photon transmission measurements using ^{137}Cs single photons sources for PET [4].

Monte Carlo simulations have been shown to be very useful for the validation and comparative evaluation of image reconstruction techniques. Smith et al. [28] used Monte Carlo modelling to study photon detection kernels, which characterize the probabilities that photons emitted by radioisotopes in different parts of the source region will be detected at particular projection pixels of the projection images for the case of parallel hole collimators. The authors also proposed a reconstruction method using 3-D kernels, in which projection measurements in three adjacent planes are used simultaneously to estimate the source activity of the centre plane. The search for unified reconstruction algorithms led to the development of inverse Monte Carlo (IMC) reconstruction techniques. The principal merits of IMC are that, like direct Monte Carlo methods, the method can be applied to complex and multivariable problems, and variance reduction procedures can be applied. Floyd et al. [29] used IMC to perform tomographic reconstruction for SPECT with simultaneous compensation for attenuation, scatter and distance dependent collimator resolution. More recently, direct fully 3-D Monte Carlo based statistical reconstruction proved to be feasible within clinically acceptable computation times [30].

4.2. Applications in therapeutic nuclear medicine imaging

For internal radiation dose estimates, the biodistribution of a trace ^{131}I labelled monoclonal antibody is generally used to predict the biodistribution of a high-dose administration for therapy. Imaging therapeutic doses would further confirm the hypothesis that the biodistribution is similar; however, current generation scintillation cameras are unable to handle accurately the corresponding high counting rate. Monte Carlo calculations have been used in the development of a method for imaging therapeutic doses of ^{131}I by using thick lead sheets placed on the front surface of a high-energy parallel hole collimator [31]. Huili et al. [32] simulated point response functions for pinhole apertures with various aperture span angles, hole sizes and materials. The point responses have been parameterized using radially circular symmetric 2-D exponential functions, which can be incorporated into image reconstruction algorithms that compensate for the penetration effect. The effect of pinhole aperture design parameters on angle dependent sensitivity for high-resolution pinhole imaging has been also investigated using Monte Carlo modelling.

The accuracy of ^{131}I tumour quantification after RIT has been further investigated with an ultra-high energy collimator designed for imaging 511 keV photons. It has been shown that the difference in tumour size, relative to the size of a calibration sphere, has the biggest effect on accuracy, and recovery coefficients are needed to improve the quantification of small tumours. Different strategies are being developed to improve image quality and quantitative accuracy in tumour SPECT imaging, including collimator detector response compensation and high energy scatter correction techniques. In an elegant study by Dewaraja et al. [33], Monte Carlo simulations have been used to evaluate how object shape influences spill out and spill in, which are major sources of quantification errors associated with the poor spatial resolution of ^{131}I SPECT, and to characterize energy and the spatial distributions of scatter and penetration.

5. FUTURE APPLICATIONS OF MONTE CARLO TECHNIQUES

The On-line monitoring of the positron emitting activity created in patient tissues undergoing radiotherapy treatment has been a goal pursued by several investigators since the 1990s. Whereas the clinical application of on-line PET monitoring in photon radiotherapy has so far been limited by the reduced activity produced in a patient using today's clinical accelerators, its use in heavy particle radiotherapy has become a useful technique to visualize the β^+ activity distributions that help to determine the effective range of heavy particles in the patient, as well as to evaluate blood flow in some

organs. Several groups have reported the applicability of PET to in vivo dosimetry in radiotherapy treatments with photons, protons and light and heavy ions using different Monte Carlo codes to investigate this challenging field [34].

It is clear that a new generation of dose modelling tools needs to be developed for use with internal emitter therapy in nuclear medicine. It is unacceptable to use standardized, geometrical phantoms to perform dose calculations for individual patients if the physician is asking for meaningful information to be used in planning patient therapy. The evolution of the methodology that was followed for external beam radiotherapy treatment planning must be followed for internal emitter therapy. The technology now exists to develop patient specific 3-D dose distributions, based on a fusion of anatomical (CT or MRI) and functional (SPECT or PET) data, with individualized Monte Carlo calculations done in a reasonable amount of time using high powered computing workstations or distributed computing networks. The combination of realistic computer phantoms and accurate models of the imaging process allows the simulation of nuclear medicine data that are ever closer to actual patient data. Simulation techniques will find an increasingly important role in the future of nuclear medicine in light of the further development of realistic computer phantoms, the accurate modelling of projection data and computer hardware. However, caution must be taken to avoid errors in the simulation process, and verification via comparison with experimental and patient data is essential.

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