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A radionuclide dosimetry toolkit based on material-specific Monte Carlo dose kernels

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Objective **We sought to develop a user-friendly dosimetry toolkit that should aid the improvement of the quality of radionuclide therapy, which is critically dependent on patient-specific planning of each treatment.**

Methods **In this work, we present a new toolkit suitable for indicative radionuclide dose calculation. The software is built using open source tools and it uses dose kernels calculated using the Geant4 Application for Tomographic Emission simulation toolkit. In addition, a method that uses kernel data to extract a material-specific dose absorption factor is described and a proof of concept is given. In this work, time dependency and organ sensitivity are not modeled.**

Results **The developed software utilizes Monte Carlo calculated dose kernels and proposes a fast dose calculation method. Using computed tomography or magnetic resonance imaging it can provide a more accurate and personalized indicative dose map.**

Conclusion **Dosimetry based on quantitative three-dimensional data is more accurate and allows a more individualized approach in patient therapy. Moreover, the use of this toolkit with the standardization for data collection and processing will increase the accuracy as well as the compatibility of radiation dose.**
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Introduction

The biological responses of radionuclide therapy are mediated by a well-defined physical quantity, the absorbed dose, defined as the energy absorbed per unit mass of tissue [1]. This response and the prediction of toxicity are essential for rational implementation of cancer therapy. Nevertheless, to state that the absorbed dose alone would predict the radiobiological response of tissue is an oversimplification. It has already been recognized in radiotherapy that the response is affected by a number of parameters such as: the type of radiation, the rate at which absorbed dose is delivered, the radiobiological characteristics of the tumor or normal tissue etc. Moreover, the anatomical characteristics of the patients have to be taken into account, as the presence of different structures affects the distribution of radiation dose.

The system that defined medical internal dosimetry for many years is the system developed in 1988 by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine [2]. Absorbed dose values were initially calculated based on idealized models of human anatomy defined as a collection of appropriately placed distinct organ volumes with mass and composition that were selected to reflect a typical or standard human anatomy. These calculations were performed with very limited computational power, resulting in several simplifying assumptions. Therefore, the application of these values to real patient anatomies that deviate from the idealized model would certainly lead to errors.

MABDOSE [3] allows the user to place spherically shaped tumors within the simplified anatomic model originally described by the MIRD Committee. The most widely used was the MIRDOSE software with Versions 1, 2, 3, and 3.1 [4]. The code automated the calculation of the internal dose for a large number (>200) of radiopharmaceuticals in 10 different anthropomorphic models with great success, until it was replaced by a newer code called Organ Level Internal Dose Assessment with Exponential Modelling [4]. This software includes data for more than 800 radionuclides resulting in absorbed dose values specific to 10 phantoms and 5 organ models. The program also includes α-particle

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emitters and a pharmacokinetic module that may be used to determine organ-cumulated activities, as well as the ability to perform minor patient-specific adjustments to doses reported for the standard phantoms.

Several groups sought to contribute to the development of such software, including the following efforts: the three-dimensional internal dosimetry code [5], the RTDS code [6], the DOSE3D code [7], and the SIMDOS code [8]. The most fully developed and widely used software package until now is the three-dimensional internal dosimetry , which is able to perform both Monte Carlo and point-kernel-based calculations. This work introduced the concept of dose volume histograms for internally administered radionuclides in a clinical trial of ^{131}I-labeled anti-B1 antibody. Nevertheless, the analysis did not reveal a statistically significant dose–response relationship [9], but Koral *et al.* [10] were able to demonstrate a dose–response relationship, using a more robust and validated single photon emission computed tomography (SPECT) quantitation methodology in a selected subset of 15 patients with pelvic or abdominal tumors.

In this work, we present a new toolkit suitable for indicative radionuclide dose calculation. The software is built using open source tools and it uses dose kernels calculated using Geant4 Application for Tomographic Emission (GATE) [11] Monte Carlo simulation toolkit. In addition, a method that uses kernel data to extract a material-specific dose absorption factor is described and a proof of concept is given.

Materials and methods

The user environment includes tools for data import, image registration, contour selection, dose calculation and data storage, and export. Data are imported in digital imaging and communications in medicine format. The anatomic data set [computed tomography (CT) or MRI] is imported as the 'fixed' volume, whereas the nuclear medicine (NM) data set is imported as the 'moving' volume. The user can view all slices in both image sets. Tools are provided to adjust zoom, contrast, brightness, as well as image palettes in the functional image. Images and dose maps can be saved in various image formats, as well as exported as text files.

Software tools and graphical user interface design

For user interface open source solutions were selected. The developed graphical user interface (GUI) was built using Qt software (Oslo, Norway) [12]. Qt is a cross-platform application development framework that is widely used for GUI programs as well as console tools and servers. It is a comprehensive development framework that includes a C++ class library, an extensive array of features, capabilities and tools that enable development of high-performance, cross-platform, rich-client, and server-side applications. Its main features are the (i) Modular Qt Class Library of over 400 classes, which encapsulates all infrastructure needed for end-to-end application development, (ii) Qt Designer, a powerful GUI layout and forms builder, (iii) Qt Linguist, a set of tools designed to smooth the internationalization workflow, and (iv) Qt Assistant, a fully customizable, redistributable help file/documentation browser that can be shipped with Qt-based applications.

Image registration algorithm

In combined SPECT/CT or PET/CT systems, anatomical and functional data are registered using systems software. However, registration is critical when data is obtained in separate systems, for example, simple SPECT or PET scanner, combined with CT or MRI data.

In the developed software, we have used multimodal registration with mutual information, as it is a robust method that can be used to align different modalities such as CT to MR-T1, MR-T1 to PET etc. [13]. Mutual information is a measure of how much information one random variable tells about another. For two images, the mutual information is computed from the joint probability distribution of the images' intensity or gray values. When two images are aligned, the joint probability distribution is 'peaky' resulting in a high mutual information value. Misregistration causes the distribution to disperse resulting in a low mutual information value. The program reads the fixed (target) volume and the moving (source) volume and then iteratively estimates the rigid transform that will align the moving onto the fixed volume.

The multimodal registration using mutual information implemented in Insight Segmentation and Registration Toolkit [14] has been integrated in the developed software. Both the fixed and moving volumes are transformed in binary format. The algorithm takes into account not only the dimensions of images in pixels, but also the physical dimensions in millimeters and distance in millimeters between slices. The differences in the patient orientation can be taken into account by specifying the permutation order and the axes that require flipping.

Dose calculation

Two approaches have been implemented. The first assumes that patient body is uniform. The second uses CT information to determine the material in each voxel and then selects the dose absorption factor. In this work, two materials are distinguished: water and bone. Dose kernels have been calculated using the GATE Monte Carlo toolkit and the results have been compared with the dose kernels published by Furhang *et al.* [15]. In all calculations, time dependency and organs sensitivity are not taken into account.

Without computed tomography information

Using published dose kernels: the kernels in Furhang's work have been calculated with Monte Carlo EGS4 photon transport code [16] assuming a point source in water. The kernel is given by the general expression:

$$k(r) = \sum_{i}^{i_{\max}} \left(\frac{a_{-2}}{r^2} + \frac{a_{-1}}{r} + a_0 + a_1 r + a_2 r^2 \right)_i e^{-m_i r} (cGy/Bq - s)$$

and depending on the isotope i can range between 1 and 3. Constants a_{-2}, a_{-1}, a_0, a_1, a_0 and m are derived from Monte Carlo simulations and they vary for different isotopes. For example, in ^{125}I those constants are a_{-2}=9909E-12, a_{-1}=5.767E-12, a_0=4.190E-14, a_1=2.626E-14, and a_0=0, m=0.45696. Dose is determined by convolving those kernels with the activity of the NM image. To calculate dose, convolution is carried out in three-dimensional space.

Using GATE dose kernels: GATE is a Geant4-based Monte Carlo toolkit, with wide use in NM applications. GATE has been designed to model PET and SPECT systems, as well as simulate NM experiments, by allowing the movement of both the detector system and/or the patient. In dosimetry, GATE can be used for dose calculation, given anatomical information, for example, CT images and the emission map [17].

In this work, we have used GATE for dose kernel calculation and not for total dose calculation. A point source is assumed in the center of a sphere with radius 40 cm. Each voxel has dimensions of $3.5 \times 3.5 \times 3.5\,mm^3$, as it is determined by SPECT input data. The simulated source was ^{153}Sm with 1 MBq activity and 100 s acquisition time. Dose kernels have been calculated for water and for bone. Simulations run on a 16-CPU cluster.

With computed tomography information

To have more accurate dose estimation, the structure of each patient has to be taken into account. This information can be obtained by analyzing the CT image, which provides accurate information about anatomy and tissue density. Image values in the CT image are scaled as Hounsfield units [18]. The conversion of Hounsfield units into attenuation coefficients that correspond to different materials is a complicated and challenging problem [19]. However, in our approach the CT image is descretized in only three levels that correspond to air, bone, and soft tissue. A threshold for differentiating bone from nonbone regions was selected to be 300 HU [20]. Air was set to –1000 and values between 0 and 300 were assumed as soft tissue. It must be noted that CT images are downsampled to match NM data resolution.

Dose calculation is carried out using a modification of the point kernel convolution method. It is not possible to use convolution of NM image with both the water and the bone kernel. Between the source and the target voxel there are voxels of different materials. The dose kernel gives the absorbed dose as a function of the distance from the source voxel, assuming that particles travel in the same material. Thus, we are using a dose absorption factor, which is derived from the calculated dose kernels. This dose absorption factor depends on the material and gives the average dose decrease when particles travel through a voxel of a specific material. This simple technique allows the use of the CT image to calculate dose absorption in a specific voxel.

For dose map calculation, the NM data set is read (or the voxels that are within the selected volume of interest). The value of each voxel of the dose map is calculated using the following algorithm:

(1) Step 1: Read the intensity of the NM voxel.
(2) Step 2: Find the corresponding voxel in the dose map (source voxel).
(3) Step 3: For all voxels of the dose map (target voxels) calculate the distance between the source voxel and the target voxel.
(4) Step 4: Find all voxels between the source voxel and the target voxel.
(5) Step 5: For each voxel read the corresponding voxel in the CT data set and identify material.
(6) Step 6: Select the proper energy loss factor.
(7) Step 7: The dose in this voxel equals the product of the intensity in the previous voxel multiplied by the selected energy loss factor (bone or soft tissue).

To speed up calculations, three approximations can be done and the user can turn these options 'on' and 'off'; (i) In step 3, if the distance between the source and the target voxel is more than 45 cm, dose is not calculated. This is acceptable because published dose kernels are approximately zero, in distances more than 30 cm. (ii) In step 7, if the dose in a voxel is less than a low threshold (set by the user) dose is assumed zero and calculations in the remaining voxels are not carried out. (iii) If the CT value of a voxel is outside body contour, dose is not calculated.

The method is applied in PET/CT data using Biograph 2 scanner (Siemens; Siemens Medical Solutions Inc., Pennsylvania, USA). A tumor is visible in the lower region of the head. For proof of concept, dose calculation using ^{153}Sm has been carried out.

Results

Data import

In Fig. 1, the developed GUI is shown a CT image, a PET image, as well as the respective fused image. In the main form there are three windows showing the CT data set, NM data set, and the fused image. On the left toolbar there are tools for image contrast, brightness, zoom, and

coloring. There are three basic menus for navigation, registration, and dosimetry.

Calculation of dose kernels using Geant4 Application for Tomographic Emission

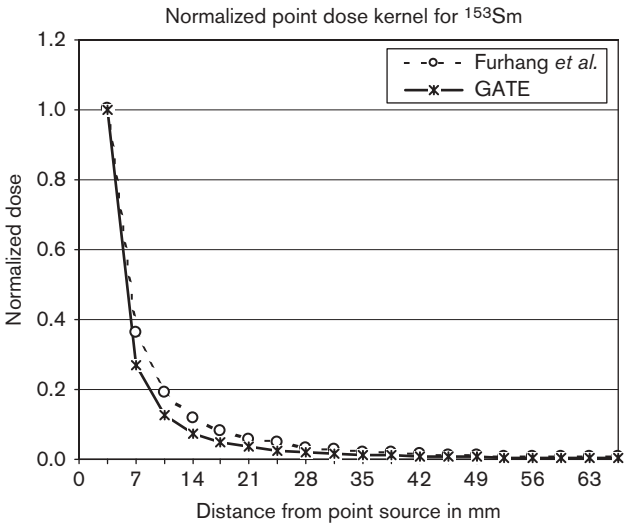
Dose kernels for water

A comparison of GATE and Furhang's dose kernels for ^{153}Sm is shown in Fig. 2. Points in distances up to 6.3 cm from the point source are plotted.

In Fig. 3 the value of (dose kernel) $\times r^2$ is plotted for the first 22 cm.

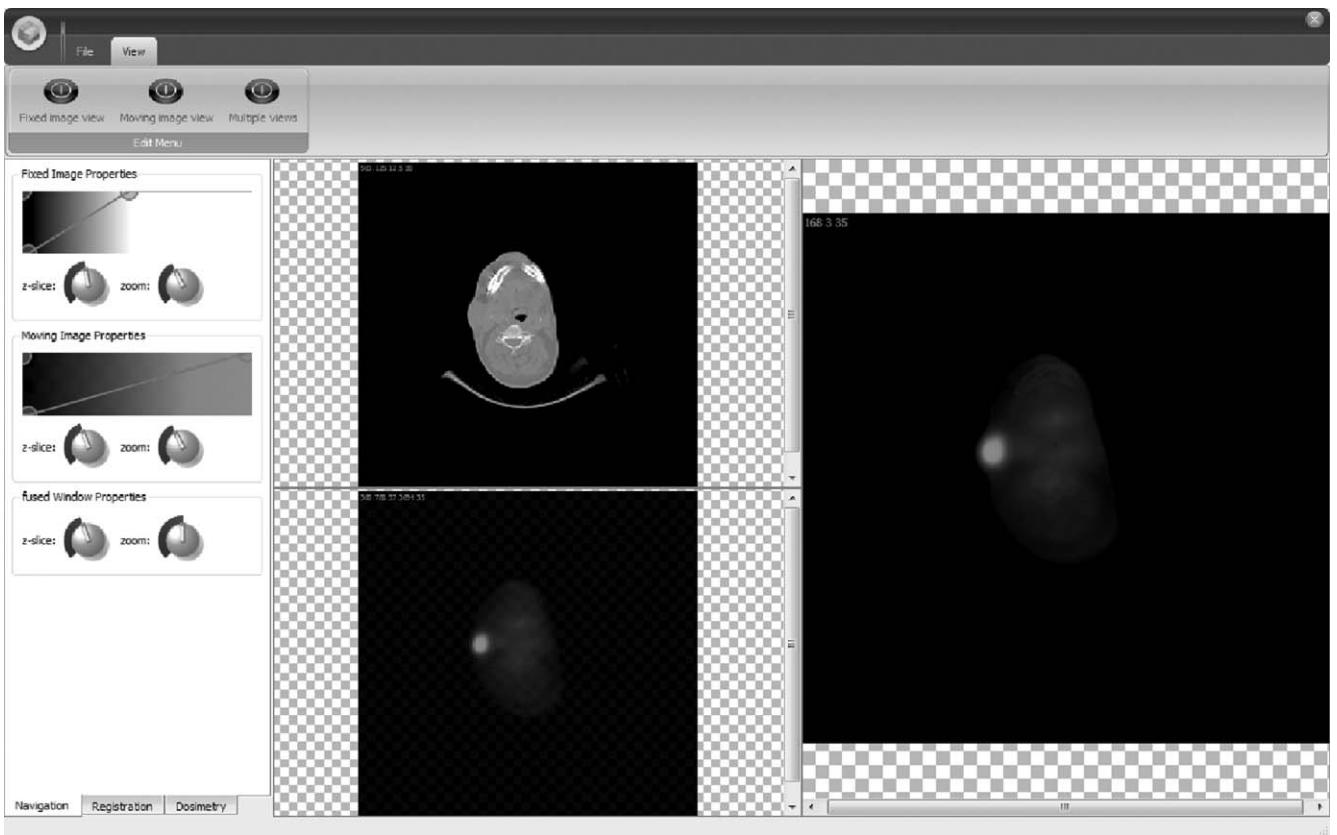
GATE provides satisfactory agreement with already published data. There are two important reasons that explain the observed differences. The first has to do with the selected voxel size, which in this work was selected to be of size $3.5 \times 3.5 \times 3.5\,\text{mm}^3$, to speed up simulations. When a point source is used for the calculation of the dose kernel, one makes the assumption that the sizes of the source and target voxels are much smaller than their distance. However, when dose is calculated in

Fig. 2



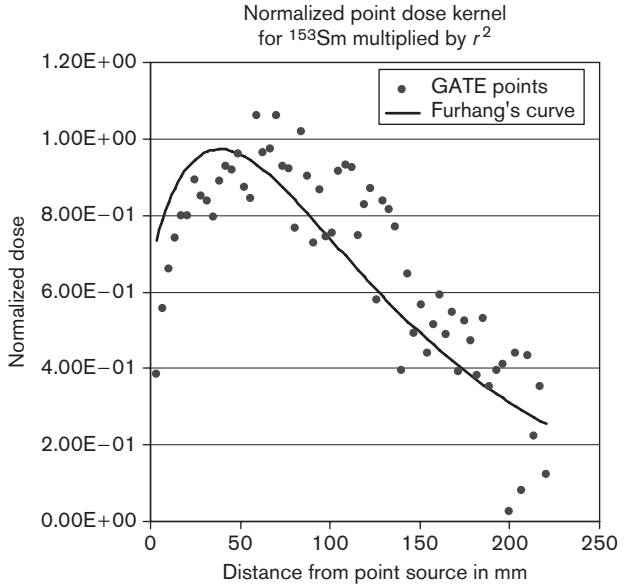
Normalized dose kernels using Monte Carlo simulations for a point ^{153}Sm source in water. Geant4 Application for Tomographic Emission (GATE) results are compared with reproduced data, published by Furhang *et al.* [15].

Fig. 1



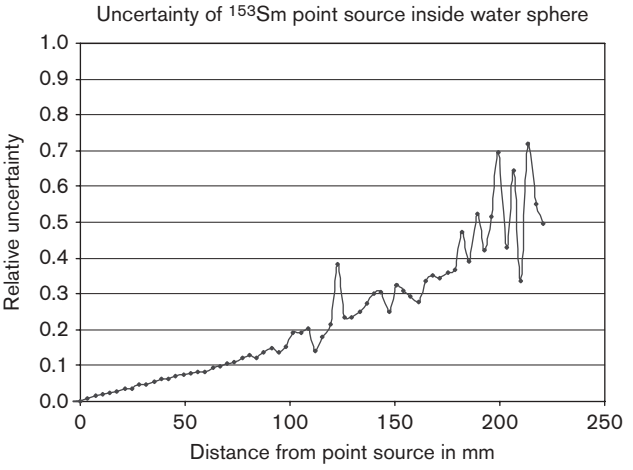
The developed graphical user interface is shown.

Fig. 3



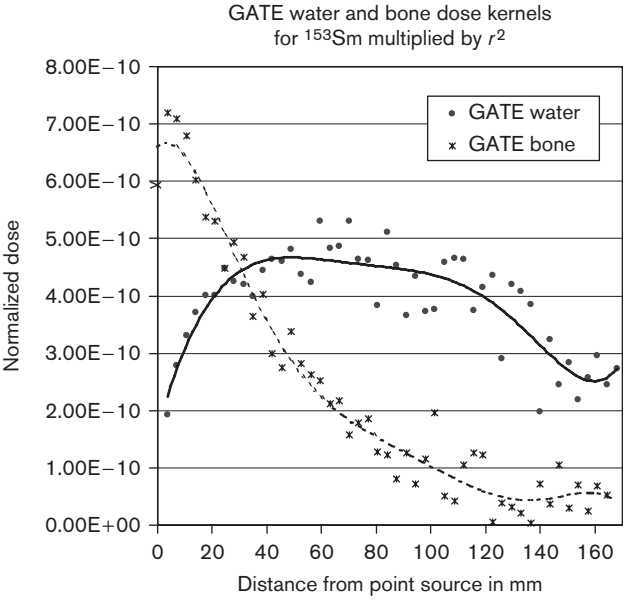
Normalized plot of dose kernels multiplied by the square of the distance from a ^{153}Sm point source in water. Geant4 Application for Tomographic Emission (GATE) results are compared with reproduced data, published by Furhang *et al.* [15]

Fig. 4



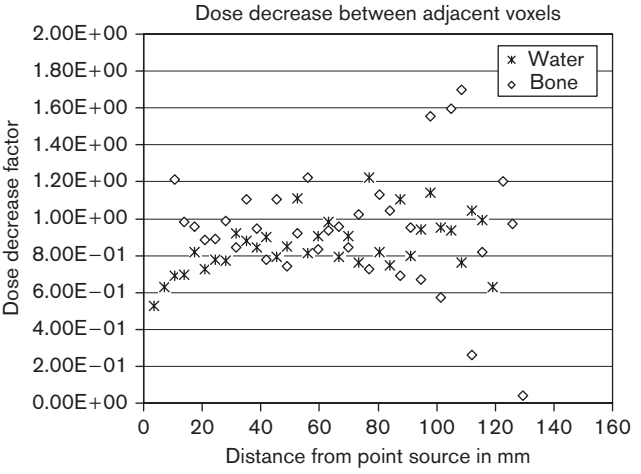
Relative uncertainty of the calculated dose kernel for a point ^{153}Sm source in water, using Geant4 Application for Tomographic Emission (GATE).

Fig. 5



Absolute dose kernels multiplied by the square of the distance from a ^{153}Sm point source in water and bone respectively. Polynomial fit lines are drawn.

Fig. 6



Ratio of successive dose kernel points for an ^{153}Sm point source in water and bone respectively.

the neighboring area to the source pixels, the distance is comparable with the voxel size. For more accurate results the simulation space should be divided in smaller pixels ($< 1 \times 1 \times 1\,\text{mm}^3$).

The second has to do with the fact that the number of simulated events is relatively small for the given problem. Given a $3.5 \times 3.5 \times 3.5\,\text{mm}^3$ voxel and a sphere of 40 cm, there are $230 \times 230 \times 230 \approx 12\,000\,000$ voxels. For larger distances from the source voxel, the number of 'target' voxels increases. Thus, the uncertainty in dose estimation for the given simulated activity becomes significant. This can be seen in Fig. 4 where the measured uncertainty is plotted as a function of the distance from the point source.

Dose kernels for bone

In Fig. 5, the comparison of (dose kernel) $\times r^2$ for water and bone are shown. Data are plotted in distance up to 17 cm from the source (where uncertainty is acceptable).

Data are fitted using polynomial functions. Uncertainty in bone dose kernel calculation is smaller as it can be derived by fitting parameters ($R^{w} = 0.7581$ and $R^{b}=0.9669$) and is observed in Fig. 4. The polynomial expressions for water and bone are respectively:

$$R^{w}(x) = 5E^{-22}x^6 - 2E^{-19}x^5 + 1E^{-17}x^4 + 2E^{-15}x^3 - 3E^{-13}x^2 + 2E^{-11}x + 2E^{-10}$$

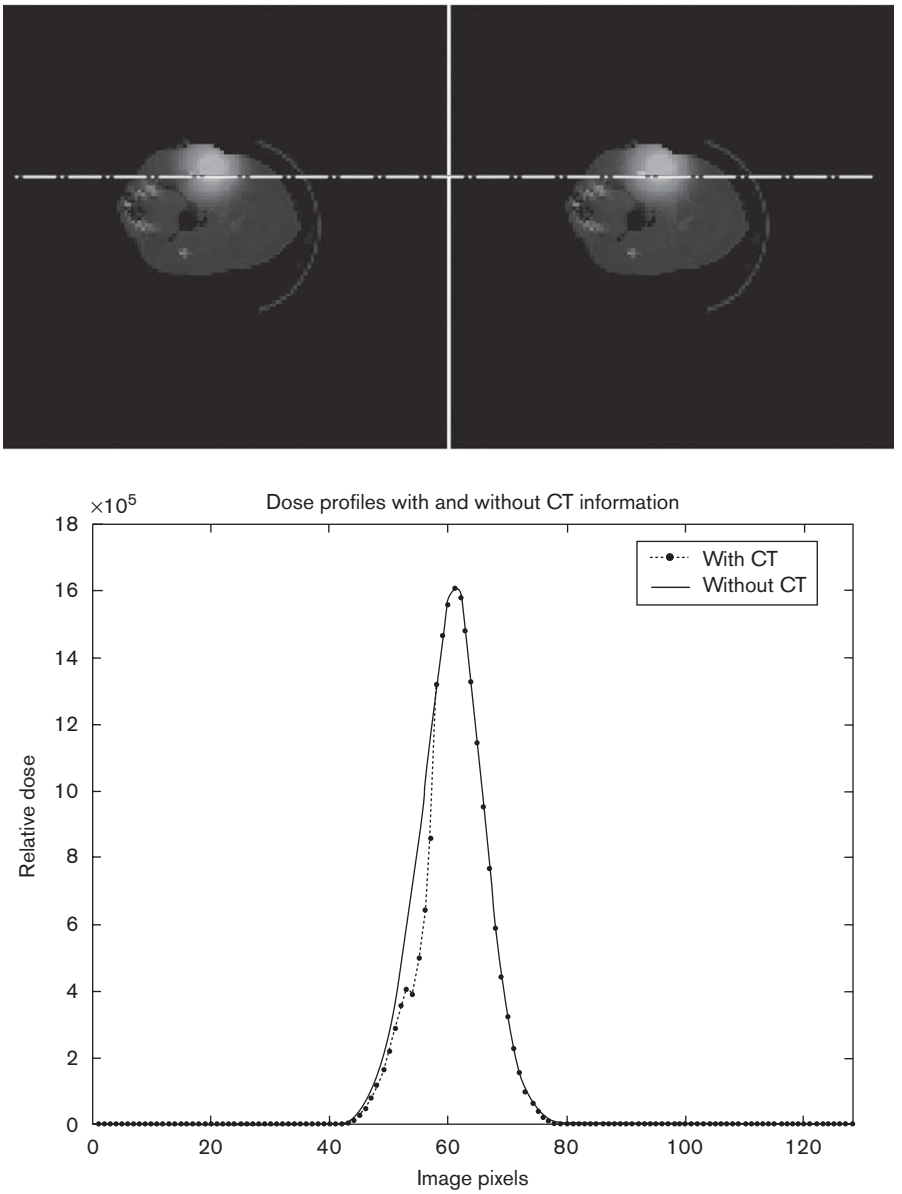
and

$$R^{b}(x) = -1E^{-21}x^6 + 8E^{-19}x^5 - 2E^{-16}x^4 + 2E^{-14}x^3 - 7E^{-13}x^2 + 4E^{-12}x + 7E^{-10}$$

Dose calculation

To estimate dose decrease from voxel to voxel, the ratio of the dose kernel value between two successive distance

Fig. 7



Dose calculation for a tumor located at the lower part of a patient's head. Computed tomography (CT) and PET data have been used. Dose map is fused on the CT image using the assumption that CT information is used (upper left) and patient body is approximated by water (upper right). Corresponding line profiles are drawn (down).

steps is calculated. This decrease factor is derived by calculating the factor (current voxel dose)/(previous voxel dose), using the dose kernel values. The resulting values are plotted in Fig. 6 and the average values for water and bone are derived.

In our dataset, these values were found to be 0.94 for water and 0.84 for bone. It can be observed that data points have a wider distribution when the distance from the source voxel increases. This is because of the higher uncertainty in larger distances, as is it has been shown in Fig. 4. Longer simulations are expected to decrease this uncertainty. When fewer data pits were used for dose decrease factors calculation, the mean value did not significantly change. Thus they were used in dose calculations.

Dose calculation uses a data set of $128 \times 128 \times 30$ slices for PET and $128 \times 128 \times 30$ slices for CT. Downsampling of CT images has been done. Dose calculation takes only 2 min when executed on a simple laptop (1.6 GHz, 2 GB memory).

In Fig. 7, the absorbed dose is fused on the CT image using either the assumption that CT information is used (left) or that the patient body is approximated by water material (right). Corresponding line profiles have been drawn. Data are given for a slice that is not in the tumor region. From the drawn profiles it is observed that the calculated dose differs because of the higher absorption by bones of the skull.

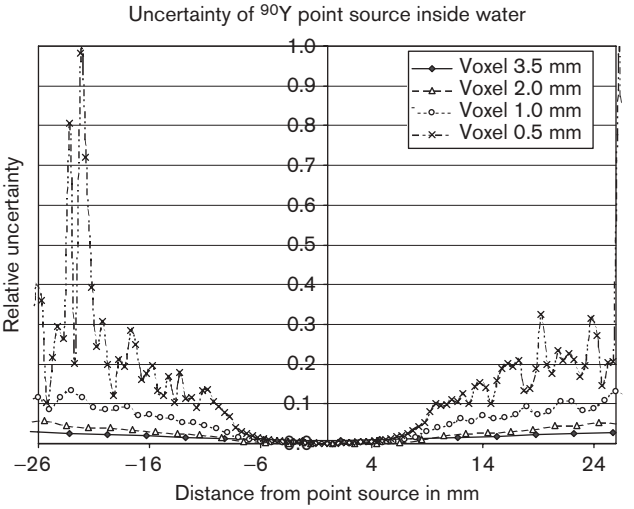
Effect of voxel size

A critical parameter when calculating dose kernels is the voxel size in Monte Carlo simulation. The smaller the voxels, the better the accuracy is expected to be. However, longer simulations are required to acquire a satisfactory number of events in each voxel. Otherwise, the uncertainty in voxels that are located away from the point source is expected to increase, as the same number of events has to be distributed in a larger number of voxels.

To study the effect of voxel size, two sets of four simulations were designed (i) a sphere of radius 26 mm filled with water was assumed and voxel size was set to $0.5 \times 0.5 \times 0.5\,mm^3$, $1.0 \times 1.0 \times 1.0\,mm^3$, $2.0 \times 2.0 \times 2.0\,mm^3$, and $3.5 \times 3.5 \times 3.5\,mm^3$ and (ii) a sphere of radius 26 mm filled with bone was assumed, and voxel size was set again to $0.5 \times 0.5 \times 0.5\,mm^3$, $1.0 \times 1.0 \times 1.0\,mm^3$, $2.0 \times 2.0 \times 2.0\,mm^3$, and $3.5 \times 3.5 \times 3.5\,mm^3$. A ^{90}Y point source was placed in the center of the spheres. The radius of both spheres was limited to 26 mm, as simulation time significantly increased, especially when voxel size was set to $0.5 \times 0.5 \times 0.5\,mm^3$ and $1.0 \times 1.0 \times 1.0\,mm^3$ and execution was rather small even to the 16-CPU cluster, mainly because of memory limitation.

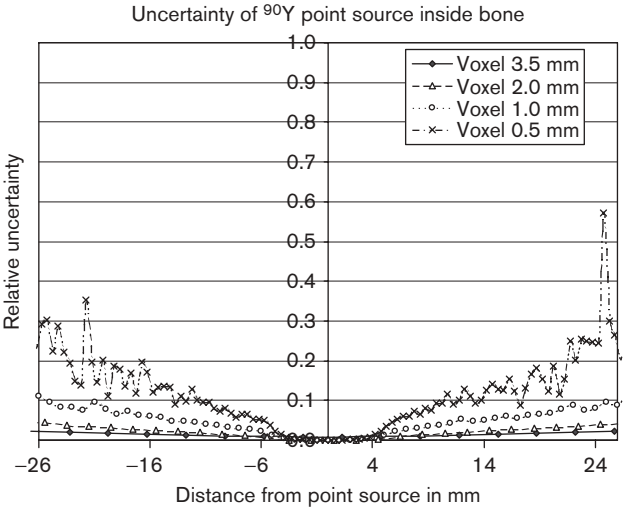
In Fig. 8, the relative uncertainty in water is plotted as a function of the distance from the source for the four voxel sizes. As can be seen, the uncertainty increases for the smallest voxel sizes. This can be explained, as the

Fig. 8



Relative uncertainty of the calculated dose kernel for a point ^{90}Y source in water, using Geant4 Application for Tomographic Emission (GATE). The radius of the water sphere is 26 mm and four voxel sizes are used: $0.5 \times 0.5 \times 0.5\,mm^3$, $1.0 \times 1.0 \times 1.0\,mm^3$, $2.0 \times 2.0 \times 2.0\,mm^3$, and $3.5 \times 3.5 \times 3.5\,mm^3$.

Fig. 9



Relative uncertainty of the calculated dose kernel for a point ^{90}Y source in bone, using Geant4 Application for Tomographic Emission (GATE). The radius of the bone sphere is 26 mm and four voxel sizes are used: $0.5 \times 0.5 \times 0.5\,mm^3$, $1.0 \times 1.0 \times 1.0\,mm^3$, $2.0 \times 2.0 \times 2.0\,mm^3$, and $3.5 \times 3.5 \times 3.5\,mm^3$.

same number of events was calculated in all simulations. Thus, distant voxels have lower statistics. In Fig. 9, the relative uncertainty in bone is plotted as a function of the distance from the source for the four voxel sizes.

Again, the uncertainty increases for the smallest voxel sizes. However, it is noticed that uncertainty is lower in bone. This can be explained, as bone attenuates particles and most events are calculated closer to the source; thus statistics are improved. A good compromise between simulation time and uncertainty is a voxel size of $2.0 \times 2.0 \times 2.0\,\text{mm}^3$.

Discussion

Nuclear medical imaging (PET, SPECT) plays a continuously increasing role in radionuclide dosimetry. The established method for dosimetry is based on the measurement of the biokinetics by serial gamma camera scans, followed by calculations comprising three steps. First, the percentage of administered activity of the radiopharmaceutical is determined for the accumulating organs for several scan times. Second, these biokinetic data are integrated to obtain the percentage of the number of decays in the source organs, that is, the residence times. Third, the radiation-absorbed doses of critical organs must be determined.

However, the quantification of the activity in different organs from planar data is hampered by inaccurate attenuation and scatter correction as well as because of background and organ overlay. Dosimetry based on quantitative three-dimensional data is more accurate, provided that all effects that degrade the quantitative content of the images have been corrected for, and allows a more individualized approach. In addition, inhomogeneous organ accumulation of the radionuclide can be detected and possibly taken into account.

The challenge in radionuclide dosimetry is personalized dose calculation. Thus, it is important to have an accurate description of patient anatomy, as well as tumor size and radionuclide concentration. The use of pure Monte Carlo simulations for dose calculation has the disadvantage of long computational time; thus it cannot be used in clinical practice.

The developed software uses Monte-Carlo-calculated dose kernels and proposes a fast dose calculation method. CT or MRI imaging can provide an accurate and personalized dose map. NM information provides spatial and quantitative information for radionuclide's concentration. When patient body is assumed homogeneous the dose kernels calculated by Furhang *et al.* [15] are used. When anatomical information is used, it is necessary to calculate dose kernels for several tissue materials. In this work only a proof of concept is given. However, time dependency and organ sensitivity are not yet taken into account, thus an indication of dose distribution is given. More detailed studies are now being carried out using the experience and the results of this work.

More specifically, the initial comparison of GATE dose kernels with the ones published has shown good agreement. It is important though, to carry out simulations using a larger space and smaller voxels, to fulfill the hypothesis that the sizes of the source and target voxels are much smaller than their distance; however, this requires advanced computer resources or code optimization.

Dose kernels for more materials will be calculated. In GATE it is possible to use a number of predefined materials such as bone, air, lung, soft tissue etc or even define new materials by providing their composition, elements' atomic number, and density. In addition, all those kernels will be calculated for a number of radionuclides that are used in NM. The result will be a set of equations similar to those presented in Calculation of dose kernels using GATE, with modified constants.

The use of a more sophisticated approach to calculate dose absorption step is being investigated. When more materials are taken into account, the results of dose calculation using the suggested approach will be compared with dose curves provided by full Monte Carlo simulations with GATE.

There are improvements that can be made in the developed toolkit, as this is the first version. More features can be added and new methods for image manipulation can be incorporated, as it is built using open source tools and Insight Segmentation and Registration Toolkit libraries are continuously updated. One important feature that will be added is time dependency of absorbed dose. This step requires the kinetic properties of the used radionuclides, as well as dynamic NM images. Finally, through national collaborations the software is being validated by physicians, so that users' feedback is collected for future improvements.

Conclusion

Patient-specific treatment planning should substantially improve the quality of radionuclide therapy, especially in a curative setting. It is already stated that more refinement in dosimetry techniques as well as standardization for data collection and processing will increase the accuracy as well as the compatibility of radiation dose [21,22]. Towards that direction, this PC-based software includes tools for data import, image registration, contour selection, data storage, and export, and is suitable for radionuclide dose calculation using open source tools with Monte Carlo and material-specific calculated dose kernels.

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