

## Calculating internal dose by convolution from SPECT/MR fusion images

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A new computer program was developed to calculate the absorbed dose. The program is based on the use of the convolution method and abdominal SPECT/MR fusion images. The applicability of the method was demonstrated by using data from  $^{111}\text{In}$ -labeled thrombocyte and  $^{99\text{m}}\text{Tc}$ -labeled colloid studies of three healthy volunteers. Dose distributions in the volunteers and the average absorbed doses in liver and spleen were calculated. The average doses for  $^{99\text{m}}\text{Tc}$ -labeled colloid study were  $0.07 \pm 0.02$  (liver) and  $0.046 \pm 0.005$  mGy/MBq (spleen). The results are in good agreement with a Monte Carlo (MC) based method (0.074 for liver and 0.077 mGy/MBq for spleen) used by the International Commission on Radiological Protection (ICRP). For  $^{111}\text{In}$ -labeled thrombocyte study the doses were  $0.33 \pm 0.05$  (liver) and  $8.9 \pm 1.2$  mGy/MBq (spleen) versus 0.730 and 7.50, respectively. The differences in dose estimates in the  $^{111}\text{In}$ -labeled thrombocyte study are mainly due to the approximation used in activity quantitation. Convolution of the activity distribution with a point dose kernel is an effective method for calculating absorbed dose distribution in a homogeneous media. Activity distribution must be aligned to anatomical data in order to utilize the calculated dose distribution. The program developed is applicable to and practical for clinical use provided that the input data needed are available.

**Key words:** internal dose, point dose kernels, convolution, SPECT/MRI fusion

### INTRODUCTION

METHODS for patient-specific dosimetry are needed both in radionuclide therapy and in diagnostics. In systemic radionuclide therapy, for example in radioimmunotherapy (RIT), the knowledge of the absorbed dose distribution in the tumor as well as in the neighboring healthy tissues is needed in order to optimize the treatment. In nuclear medical laboratories, where new isotope-antibody combinations for diagnostic use are studied, a practical method for dose distribution determination is needed.

The traditional method used for internal dose calculations is that developed by the Medical Internal Radiation Dose (MIRD) committee.<sup>1</sup> In the MIRD formalism a mathematical standard phantom with Monte Carlo (MC)

simulation methods is used to calculate the mean absorbed dose to each organ. The quantities used are S-values, where  $S(\text{Target-Source})$  [mGy/MBq·s] is the absorbed dose to the target organ from unit cumulative activity in a given source organ. The MIRD formalism assumes a uniformly distributed activity. There is a computer program, MIRDOSE3, for calculating the S-values for a large number of radioisotopes.<sup>2</sup>

In RIT the homogeneity of the activity distribution is determined by the kinetics of the isotope-antibody combination in that particular patient. The activity distribution is, therefore, always patient-specific. In RIT it is important to estimate heterogeneous distribution of the absorbed dose rather than to calculate the mean dose absorbed by the organ.<sup>3</sup> The dose calculation procedure should take both these facts into consideration. With these requirements, the MIRD formalism is not suitable for patient-specific dose assessment in RIT.

Patient-specific dose assessment methods developed to be used in RIT are based on point dose kernels<sup>4</sup> used either as lookup tables<sup>5</sup> or convoluted with activity distribution

Received July 7, 1997, revision accepted September 15, 1997.

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maps.<sup>3,6,7</sup> A patient-specific direct MC approach has also been suggested.<sup>8</sup> The convolution procedure is usually done by using a Fast Fourier transform (FFT) in 3 dimensions. The result of the convolution is the dose rate distribution. The point dose kernels are produced by MC simulations in homogeneous medium. The FFT procedure also assumes a homogeneous medium.

The patient-specific MC simulation is able to deal with body heterogeneities such as bones and lung tissue, so that accuracy is better than with the convolution method, but clinical applicability is restricted by the long computation time. A few additional problems limit the applicability of both methods, direct MC simulation and the convolution method. Aligning the calculated dose rate distribution with patient specific anatomical data is difficult. Another problem is how to quantitate the activity in the patient in absolute units, which are needed in order to calculate the dose in absolute units. Single photon emission computed tomography (SPECT) imaging provides only a count distribution and is affected by various sources of error. These errors have recently been discussed in detail by Sipilä et al.<sup>9</sup>

In this work we present a computer program which uses registered SPECT/MR images<sup>10,11</sup> to align patient specific anatomical data with the dose distribution calculated from the activity distribution by the convolution method. The capabilities of our program are demonstrated in <sup>111</sup>In-labeled thrombocyte and <sup>99m</sup>Tc-labeled colloid studies of healthy volunteers. The results provided by our program are compared with those of established methods. Comparison with a computer program based on the MIRD formalism, MIRDOSE3,<sup>2</sup> is made by using S-values. Another comparison is made with the results given in a report<sup>12</sup> from the International Commission on Radiological Protection (ICRP) in which a biokinetic model for each radiopharmaceutical has been used with the MIRD formalism.

## MATERIALS AND METHODS

### Structure of the program

The new program, later referred as *intdose*, is given three equally sized ( $N \times N \times N$ ) input matrices: point dose kernel, activity distribution and organ matrices. The first of these is generated once for each radionuclide from a known point dose kernel,  $K(r)$  [cGy/Bq·s] where  $r$  is the distance from the source. The two latter represent the data obtained from registered SPECT/MR images and they are presented in the same co-ordinate system. The use of Fourier transform limits the size of these matrices so that  $N$  must be a power of 2.<sup>13</sup>

The point dose kernel,  $K(r)$  describes how the absorbed dose distribution behaves per one decay of specific radionuclide in water. In the convolution procedure the point dose kernel is considered as a response function. The origin of the response function must be positioned in the origin of the co-ordinate system. Since the origin of a

matrix is in the corner and the response function is assumed to be periodic, the negative dimensions are mirrored on the other side of the matrix.<sup>13</sup> The dose contribution from the  $\beta$ -decays is assumed to be local in the scale of the size of the matrix voxel. The total  $\beta$ -energy per one decay<sup>14</sup> is therefore added in the origin of the point dose kernel matrix.

The activity distribution matrix  $A(r)$  represents the absolute activity [Bq] in each voxel of the phantom describing the patient. The absorbed dose rate distribution  $\dot{D}(r)$  is calculated by the convolution of the point dose kernel  $K(r)$  with the activity distribution  $A(r)$ <sup>7</sup>

$$\dot{D}(r) = \int_V A(r') \otimes K(r-r') \cdot dV' \quad (1)$$

The convolution is executed by 3 dimensional Fast Fourier transformations (FFT)<sup>7</sup>

$$\dot{D}(r) = FFT^{-1}[FFT\{A(r)\} \cdot FFT\{K(r)\}] \quad (2)$$

In order to calculate the dose distribution or the average dose in an organ or in another region of interest (ROI) the boundaries of that region are needed. The ROIs are segmented from MR images which are presented in the same co-ordinate system as the activity distribution. The result of the segmentation procedure is a ROI matrix filled with zeros (outside ROIs) or with ROI specific numbers (inside ROIs).

### Demonstrations

Abdominal SPECT/MR fusion images from three healthy volunteers were used. The volunteers are later referred to as 1, 2 and 3. Two different uptake studies were performed for each volunteer. For volunteer 3, however, data were available for only one study. The volunteers were first administered <sup>111</sup>In-oxine-labeled thrombocytes and two days later <sup>99m</sup>Tc-labeled tin colloids.<sup>11</sup> The study was approved by the local ethical committee and informed consent was obtained from all volunteers.

In the reconstruction of the transversal SPECT images only attenuation correction was performed. The imaging protocols and the registration technique were recently described in detail by Pohjonen et al.<sup>11</sup>

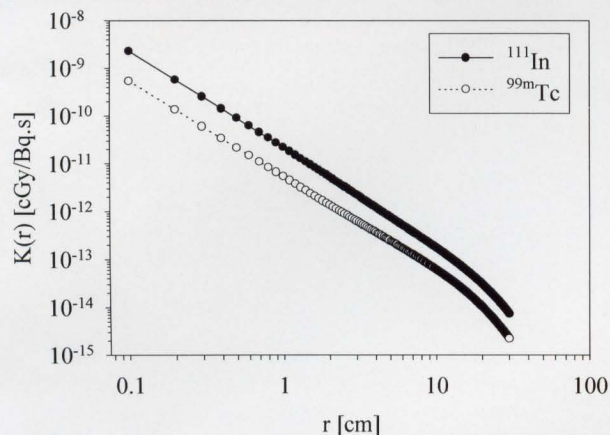
The program was given as an input registered SPECT and MR image sets, each of which consisted of 128\*128\*128 images. Each dimension of a voxel was 2.88 mm. The point dose kernel was also calculated for a similar matrix. The photon point dose kernels used in the demonstrations, for <sup>99m</sup>Tc and <sup>111</sup>In isotopes, were taken from Furhang et al.<sup>4</sup> in which a mathematical fit is given for several isotopes. The general expression given for the fit is<sup>4</sup>

$$K(r) = \sum_i^{i_{\max}} \left( \frac{a_{-2}}{r^2} + \frac{a_{-1}}{r} + a_0 + a_1 \cdot r + a_2 \cdot r^2 \right)_i e^{-m_i \cdot r} \times (\text{cGy/Bq} \cdot \text{s}) \quad (3)$$

The total (with both  $\beta$ - and  $\gamma$ -contribution) point dose kernels used in this work are presented in Figure 1.

Each set of registered MR images was manually segmented to identify liver and spleen. Two kinds of calculations were performed with *intdose*. First, patient-specific dose distributions were calculated for each study performed. From these distributions mean absorbed doses to liver and spleen were calculated. Here we assumed that the relative activity distribution does not change and the activities in each voxel decay as predicted by the physical half-life  $T_{1/2}$  for that nuclide.

The activity distributions  $A(r)$  were calculated from the SPECT images by assuming that all of the activity is present in the volume given by these images. The activity



**Fig. 1** The point dose kernels  $K(r)$  [cGy/Bq·s] as a function of distance  $r$  [cm] for the isotopes used in the demonstrations of this work.<sup>4</sup>

(A) vs. counts ( $c$ ) ratio [Bq/counts] was calculated as

$$\frac{A}{c} = \frac{A_{\text{tot}}}{c_{\text{tot}}} \quad (4)$$

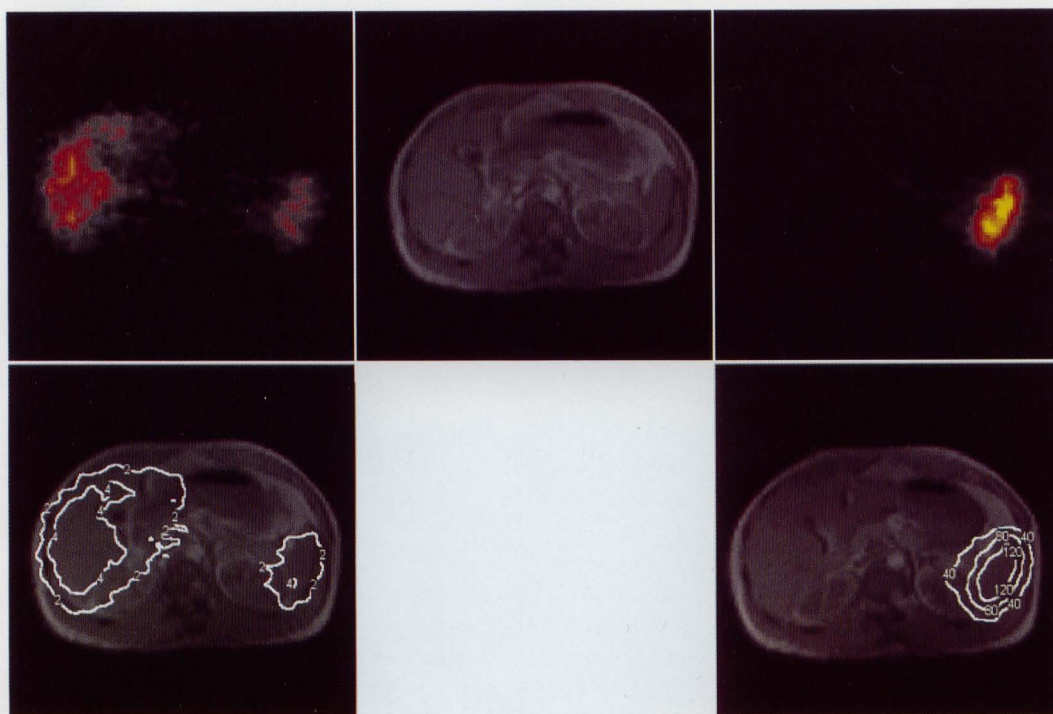
where  $A_{\text{tot}}$  is the total activity administered and  $c_{\text{tot}}$  is the number of total counts in the SPECT images. The activity distribution matrix  $A(r)$  was then calculated by multiplying the counts (from SPECT image) by the activity vs. the counts ratio. The mean doses to liver and spleen calculated this way were compared to doses given by ICRP.<sup>12</sup>

Other kinds of calculations were used to compare the S-values from MIRDOSE3 with the corresponding values from *intdose*. The S-values  $S(\text{liver-spleen})$ ,  $S(\text{liver-liver})$ ,  $S(\text{spleen-liver})$  and  $S(\text{spleen-spleen})$  were calculated by considering only the activity in one source organ (liver or spleen) at a time.

In the program each voxel occupies 2 bytes, so the memory taken by each matrix is about 8 megabytes. During the FFT procedure, both the activity distribution and the point dose kernel must be in the computer's memory. *Intdose* was programmed with C-language under the Linux operating system.

## RESULTS

Figure 2 shows registered SPECT and MR images and calculated dose distributions for both  $^{99\text{m}}\text{Tc}$ -colloid and  $^{111}\text{In}$ -thrombocyte studies of one volunteer. The calculated average absorbed doses to each patient's liver and



**Fig. 2** Registered SPECT/MR images of volunteer 1 (top row) and corresponding calculated dose distributions (second row).  $^{99\text{m}}\text{Tc}$ -labeled colloids are shown in the left column and  $^{111}\text{In}$ -labeled thrombocytes are shown in the right column.

**Table 1** Average absorbed doses per activity administered to liver and spleen. Values for volunteers 1, 2 and 3 are calculated by *intdose*, values for ICRP<sup>12</sup>

study	volunteer	A [MBq]	$D_{liver}/A$ [mGy/MBq]	$D_{spleen}/A$ [mGy/MBq]
<sup>99m</sup> Tc-colloids	1	29.3	0.075	0.049
	2	37.0	0.046	0.049
	3	37.0	0.084	0.041
	ICRP		0.074	0.077
<sup>111</sup> In-platelets	1	7.70	0.364	9.84
	2	5.64	0.287	8.11
	3	nd	nd	nd
	ICRP		0.730	7.50

**Table 2** S-values for <sup>99m</sup>Tc and <sup>111</sup>In isotopes as calculated by *intdose* for volunteers 1, 2 and 3 and by MIRDOSE3<sup>2</sup>

isotope	volunteer	source	$D_{liver}/A$ [mGy/MBq]	$D_{spleen}/A$ [mGy/MBq]
<sup>99m</sup> Tc	1	liver	0.118	6.27e-3
			0.075	7.17e-3
			0.130	6.90e-3
			MIRD	2.25e-3
	2	spleen	6.42e-3	0.645
			6.17e-3	0.412
			6.95e-3	1.190
			MIRD	0.727
<sup>111</sup> In	1	liver	3.955	0.218
			2.936	0.212
			nd	nd
			MIRD	0.078
	2	spleen	0.207	20.5
			0.197	14.5
			nd	nd
			MIRD	23.2

spleen as well as the results from ICRP<sup>12</sup> are summarized in Table 1. The calculated S-values and values from MIRDOSE3<sup>2</sup> are presented in Table 2.

## DISCUSSION

A new computer program was developed to calculate the absorbed dose in any isotope study. The program is based on a combination of the convolution of activity distribution and point dose kernel and SPECT/MR fusion imaging.

The convolution theorem takes the duration of the response to be the same as the period of the data.<sup>13</sup> This means that if the dose distribution from a source voxel would in fact exit the calculation matrix, the convolution procedure folds the dose distribution to the other side of it. Calculational error in dose distribution caused by this phenomenon is determined by the distance between source voxels and the matrix border and by the gradient of the response function (point dose kernel). In practice, the error caused by the folding phenomenon in the convolution procedure is insignificant since the point dose kernels for the isotopes used have large gradients, as can be seen

in Figure 1.

The use of convolution for calculating the dose rate distribution from the activity distribution with the point dose kernel has been validated by Giap et al.<sup>7</sup> According to them the calculated absorbed dose agreed well inside the phantom but outside of it the calculation overestimates the dose because the convolution method assumes homogeneous media, water in this case.<sup>7</sup>

The calculation time for one dose distribution was about 105 s when a Pentium 200 MHz computer with the Linux operating system was used. The calculation time is short considering that the matrix size used in the demonstrations was 128\*128\*128.

The doses calculated by the program agreed reasonably well with those given in the ICRP publication,<sup>12</sup> Table 1. The results in the ICRP report are based on a standard biokinetic model, which ignores any patient-specific fluctuations in relative organ uptakes. On the other hand, in the demonstrations of this work, activity changes in time were ignored. We also assumed that all the activity administered is present in the volume covered by SPECT images. The activity per count calculated this way is the maximum possible. According to the biokinetic model

used by ICRP,<sup>12</sup> fractions of 0.30 and 0.10 of <sup>111</sup>In-labeled thrombocytes are immediately deposited in spleen and liver. The remaining fraction (0.60) is cleared from the blood (0.25 to red bone marrow, 0.2 to liver and 0.05 to spleen) with a half-time of 4 d. For <sup>99m</sup>Tc-labeled colloids, fractions of 0.70 and 0.10 are deposited in liver and spleen and no redistribution or excretion occurs.<sup>12</sup> In our program the activity is assumed to decay as predicted by its physical half-life  $T_{1/2}$ . This is valid in the case of <sup>99m</sup>Tc-labeled colloids. In the case of <sup>111</sup>In-labeled thrombocytes, the half-life assumption is justified since spleen/liver activity ratios in <sup>111</sup>In-labeled thrombocyte studies did not change remarkably after 1 hour, as can be seen in Figure 3 in Pohjonen et al.,<sup>11</sup> even though the major fraction of the <sup>111</sup>In activity is still circulating with the blood. The quantity of activity obtained by one SPECT imaging, especially in liver, is however underestimated in the case of <sup>111</sup>In-labeled thrombocytes because activity is cleared from the blood to liver and spleen. Doses calculated for liver in Table 1 are smaller than those given by ICRP<sup>12</sup> as expected. Because of these facts, doses calculated for <sup>99m</sup>Tc studies are to be considered more accurate. This is emphasized by the superior imaging characteristics of <sup>99m</sup>Tc compared to <sup>111</sup>In.<sup>11</sup>

Because the self dose to each organ is the main contributor, the effect of patient size (in terms of organ distances) on the average doses to organs with the isotopes used is not significant. The size of the source organ is here the most important factor. Since the total activity is constant, a large organ has a lower activity concentration [Bq/ml] than a small organ. As can be seen in Table 2, the S-values for cases where the target equals the source calculated by the *intdose* agree with MIRDOSE3. The differences between S-values calculated by the *intdose* and MIRDOSE3 can be explained by comparing the organ volumes. According to Pohjonen et al.,<sup>11</sup> the liver sizes as estimated from MRI were 1.70, 2.63 and 1.43 liters for volunteers 1, 2 and 3. The volume of the liver in the MIRD phantom is 1.83 liters.<sup>15</sup> Correspondingly, the spleen sizes of the volunteers were 196 ml, 302 ml and 106 ml<sup>11</sup> while the volume of the spleen in the MIRD phantom is 176 ml.<sup>15</sup> As can be seen, the ratio of organ volumes of two individual male adults may be as high as 2.8 (spleen volume ratio of volunteers 2 and 3).

Our results are in good agreement with previous data. The program developed is applicable and practical for clinical use providing that registered absolute activity distribution and segmentation data are available.

#### ACKNOWLEDGMENTS

The authors thank Mr. Eero Salli M. Sc. (Eng.) for assisting with the image manipulation.

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