Comparison of Different Cell-cluster Models for Cell-level Dosimetry

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An important factor in dose calculations for targeted radionuclide therapy is the cell-cluster model used. We developed a cell-cluster model based on optimization through mechanical hard-sphere collisions. The geometrical properties and the dosimetric effects of the new model were compared with those of two previous models, i.e. the traditional lattice model and our CellPacker model in which the cells are individually and systematically piled as a cluster. The choice of the cell-cluster model has an effect on the calculated mean absorbed doses in the cells. While CellPacker produces clusters with distinct tumour-healthy tissue interface, our new model is able to make the interface diffuse. Outside the interface the new model is capable to pack cells tighter than CellPacker enabling the description of tissues of higher cellular density. Our two cluster models make it possible to construct the cluster model according to the tissue in question.

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New promising methods like radioimmuno and neutron capture therapies provide new challenges to dosimetry. Contrary to the therapies exploiting external beam, radiation distributions in targeted radionuclidetherapies are generally highly non-uniform and large scale averaged doses do not make it possible to estimate the therapeutic effect (1). Since there exists at the moment no means to measure the patient absorbed doses from internally deposited radionuclides, the only way to proceed is to develop theoretical methods to estimate these absorbed doses. One remarkable, but mostly disregarded factor in analytical microdosimetry is the cell-cluster model to which the dosimetric calculation itself is applied.

Probably the most often used cell-cluster geometry is the close-packed cubic geometry, where each cell is in contact with 12 other cells forming a face-centred cubic lattice. Rassow et al. (2) had cells of two sizes in their tissue, the smaller spheres representing tumour cells and the larger ones describing healthy cells. Makrigiorgos et al. (3) and Kobayashi & Kanda (4) used the same geometry with only one cell size. For instance, macrophages in the mouse liver are positioned in a way that resembles the close-packed cubic geometry (3).

Another way to approach the cluster modelling is to exploit different kinds of optimization methods. Charlton & Utteridge (5) introduced a simple optimization method for constructing cell-clusters. They simulated cells and nuclei as concentric spheres and positioned them first randomly inside the cube, until it was 25% full. The diameters of the cells varied between chosen limits and overlapping spheres were rejected. The positioned spheres were then let to migrate towards the origin so that mutual overlapping was hindered. Fifty per cent of the volume was filled in this way. For example low-grade astrocytomas have a packing similar to the one used by Charlton & Utteridge (5).

The models have so far consisted of rather simple geometrical forms, but in some set-ups they have, as used with stochastic radiation transport simulation methods, proved to give correct results. The theoretically calculated mean specific energies and cell survival fractions were in good agreement with the experimental ones both in the study of

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Humm & Chin (6) and Verrijk et al. (7). Humm & Chin (6) simulated T-cell line HUT-102B2 cells with spheres and Verrijk et al. (7) described the V79 cells of Chinese hamsters as cubes.

In a previous study (8) we compared the close-packed cubic model with a new CellPacker model constructed by us. According to our knowledge, our study has so far been the only one presenting three-dimensional cluster models capable of describing both tumour and healthy tissue, i.e. to combine cells of different sizes. In our study we concluded that the CellPacker model does not have a gap in the tumour-healthy tissue interface as the close-packed cubic cluster model does. The close-packed cubic cluster may, however, be more tightly packed having the maximum cell density of 0.74 against 0.64 of the CellPacker's density. Futhermore, the cell density of the close-packed cubic cluster may easily be decreased, if needed.

In our previous study, in addition to a geometrical analysis, we also calculated the dosimetric relevance of the geometrical differences in the clusters using the indium isotope (^{111}In). The results showed that the gap at the interface of the tumour and healthy tissue increased the calculated tumour dose (i.e. the mean absorbed dose in tumour cells inside a fixed tumour diameter) to healthy tissue dose (i.e. the mean absorbed dose in healthy cells outside the tumour diameter and inside a fixed cluster diameter) ratio by the factor of 20 in the cluster set-up of smallest dimensions. In larger clusters the effect was smaller.

For this study our particular interest was to develop a model which would simulate the interface region even better than the CellPacker model and at the same time approach the maximum theoretical packing density of the close-packed cubic geometry.

In this work, we have developed a new cluster model based on optimization methods. The features of the new cluster model have been analysed against the close-packed and the CellPacker models and the dosimetric effects of the cluster models have been studied with three indium isotopes, ^{111}In, ^{113m}In and ^{114m1}In.

MATERIAL AND METHODS

In our new cluster model, we exploited an optimization method more complex than the one by Charlton & Utteridge (5). The migration was randomized by hard-sphere collisions of the cells and was accompanied with simultaneous increase of the cell size allowing the nearly optimal packing. The spherically organized small spheres in the middle of the spherical cluster were first packed in this way. After this, the large spheres around the small ones were packed. The initial state of both the small and large cells was a loose face-centred cubic lattice. The final diameters of the tumour and healthy cells were 12 and 30 μm, respectively. The selected sizes of the cells are generalizations corresponding to estimated averages of the spectrum of the size of the different cells according to Rassow et al. (2). In general, our new model is not limited to these cell sizes.

The CellPacker model (8) uses an algorithm which piles up spherical cells in a systematic way by stepping incrementally away from the origin in a spherical coordinate system and searching a vacant location as near to the origin as possible. The resulting asymmetric cluster consisted of cells of two sizes; the same used in this study.

The dose calculation methods applied to the clusters are similar to those given by Lampinen et al. (8) and are only briefly described here.

The electron decay radiation spectra of ^{111}In, ^{113m}In and ^{114m1}In were calculated using the program IMRDEC (9, 10), which considers all types of the decay processes and the radiation resulting from them (8). Dose kernels were calculated by the Monte Carlo method using the EGS4 code system (11) and applying the PRESTA algorithm (12). Dose kernel $F(r)$ is defined as the expectation value of the fractional energy deposition per decay of a radiation source at a certain distance r from the centre of the source:

$$F(r) = \frac{1}{T_0}\frac{\delta E(r)}{\delta r} \qquad [1]$$

where $\delta E(r)$ is the energy deposited into a spherical shell with a radius r and a thickness δr, T_0 is the mean total electron kinetic energy released in one decay. Note that in this case the radiation source is the whole cell containing activity, so kernels are not point kernels. The cut-off energies used in the simulation were 1.0 keV. Particles with a lower kinetic energy than this value were assumed to deposit their kinetic energy on-site. Particles with energies higher than the cut-off were divided into three categories, so three dose kernels were produced (8). The kernels were calculated assuming that the activity is homogeneously distributed in the tumour cells. Although EGS4 simulation results are expected to have inaccuracies below 10 keV electron energies, this should not pose any problem because the CSDA estimation of the range of 10-keV electrons is as small as 2.5 μm.

The procedure used for deriving the dose kernels in the dose calculations was verified against results reported by Simpkin & Mackie (13). Their results were compared with the simulations of kernels for electrons with energies of 50, 100 and 500 keV. The results were observed to agree with each other within statistical uncertainties of the simulations for 100 and 500 keV. For the case of 50 keV the kernel calculated in the current work extended approximately 1.5 μm deeper than that reported in the literature (13). This is probably due to the fact that Simpkin & Mackie (13) used a cut-off energy of 10 keV in their simulations. The CSDA estimation of the range of 10-keV electrons (2.5 μm) is not negligible compared to 43 μm, the maximum energy deposition depth of the 50-keV kernel.

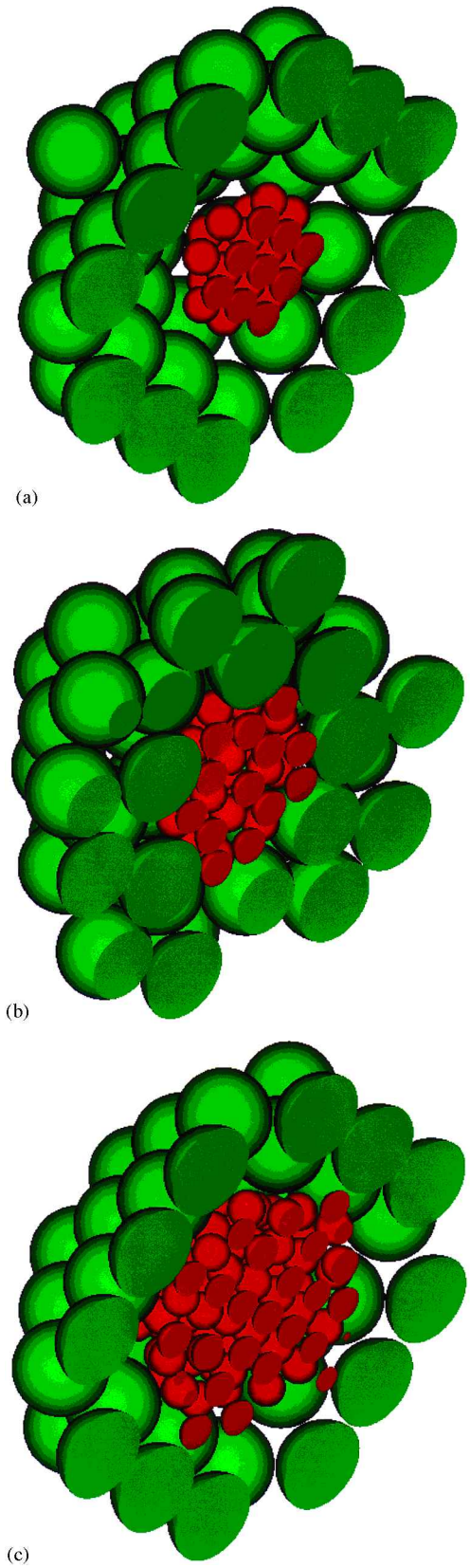

Fig. 1. Cross section of a cell-cluster based on the close-packed cubic geometry model (a), the CellPacker model (b), and the new optimization model (c).

A computer program, later referred as *CellDose* (8), was used to calculate absorbed doses in a cell-cluster. The absorbed dose $\overline{D}(r_k \leftarrow r_h)$ to a target cell r_k from activity in a source cell r_h is given by MIRD schema (14):

$$\overline{D}(r_k \leftarrow r_h) = \tilde{A}_h \sum_i \Delta_i \phi_i (r_k \leftarrow r_h)/m_k \quad [2]$$

where $\tilde{A}_h$ is the cumulative activity of the source cell, Δ_i is the mean energy emitted per nuclear transition, $\phi_i(r_k \leftarrow r_h)$ is the fraction of the energy emitted from the source cell that is absorbed in the target cell for the ith radiation component and m_k is the mass of the target cell. $\phi_i(r_k \leftarrow r_h)$ values for those source-target combinations needed are calculated from the dose kernels (8).

To quantify the effect of the cluster model on absorbed doses, the ratio of the mean absorbed dose in tumour cells (normalized to unity) to the mean absorbed dose of the healthy cells in a cell-cluster inside radius r, $\overline{D}_{tumour}/\overline{D}(r)$, is used.

RESULTS

The constructed cell-cluster models are shown in Fig. 1. Diameters of 12 μm for tumour cells and 30 μm for healthy cells were used. The cell density of the new optimization model is 0.69. The graphic representation of the accumulation of the cells in different cell-cluster models is shown in Fig. 2.

The electron decay spectra of ^{111}In, ^{113m}In and ^{114m1}In are shown in Fig. 3. Dose kernels for electrons from different energy ranges of the indium-isotopes are given in Fig. 4.

The ratio of the mean absorbed dose in tumour cells (normalized to unity) to the dose of the healthy cells (inside variable radius r), of ^{111}In, for different cluster models (tumour radius 75 μm) in case of a homogeneous distribution of activity in the tumour cells, is given in Fig. 5.

The dose ratio (the same definition as in Fig. 5) as a function of radius r for different cluster models (tumour

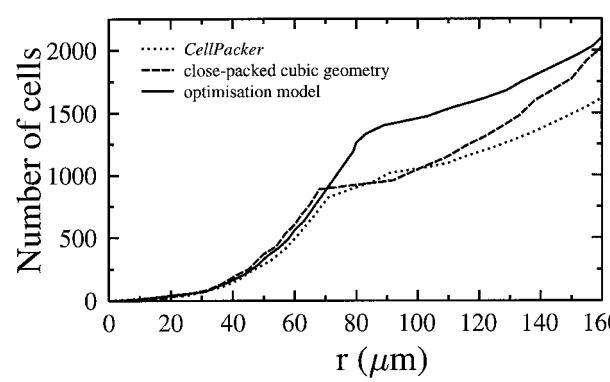

Fig. 2. The accumulation of the cells in different cell-cluster models as a function of cluster radius (r). The tumour radius was set to 75 μm.

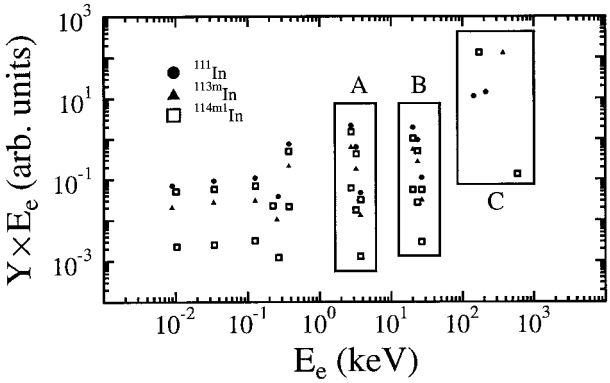

Fig. 3. The electron decay spectra of ^{111}In, ^{113m}In and ^{114m1}In. The spectra are divided in to three components denoted by A, B and C for which the dose kernels are generated. Radiation yield (Y) times the electron energy (E_e) is plotted as a function of electron energy for all conversion and Auger electrons emitted in the decay.

radius 15 μm) and isotopes, ^{111}In, ^{113m}In and ^{114m1}In, is given in Fig. 6.

DISCUSSION

In this work we compared the dosimetric effects of electrons from ^{111}In, ^{113m}In and ^{114m1}In isotopes when calculated in three different cell-cluster models.

Our new optimization model exceeds close-packed cubic geometry model and even the CellPacker model in density at the tumour-healthy tissue interface region (Fig. 2), because of the small cells' tendency to migrate partly to the healthy tissue side. In the CellPacker cluster model the interface line is more distinct. The optimization model is thus better suited to model systems with diffuse tumour-healthy tissue interface region while the CellPacker model is more appropriate for cases of rigid tumours. As the cluster grows beyond the tumour and healthy tissue interface, the cell density of a cluster based on the optimization model is between that of the close-packed cubic model's and CellPacker's.

The cluster model properties in the tumour-healthy tissue interface influence greatly the calculated tumour to healthy tissue dose ratio, especially when small tumours are modelled. In the case of the close-packed cubic geometry, the gap eliminates most of the category A and B components (see Fig. 4) of the radiation from the outermost tumour cells to the innermost healthy cells. In the CellPacker and the optimization model some tumour cells have always a direct contact with healthy cells, which allows radiation from all energy groups to be absorbed in the healthy cells. Since a tumour cell in the optimization model based cluster may be surrounded by healthy cells,

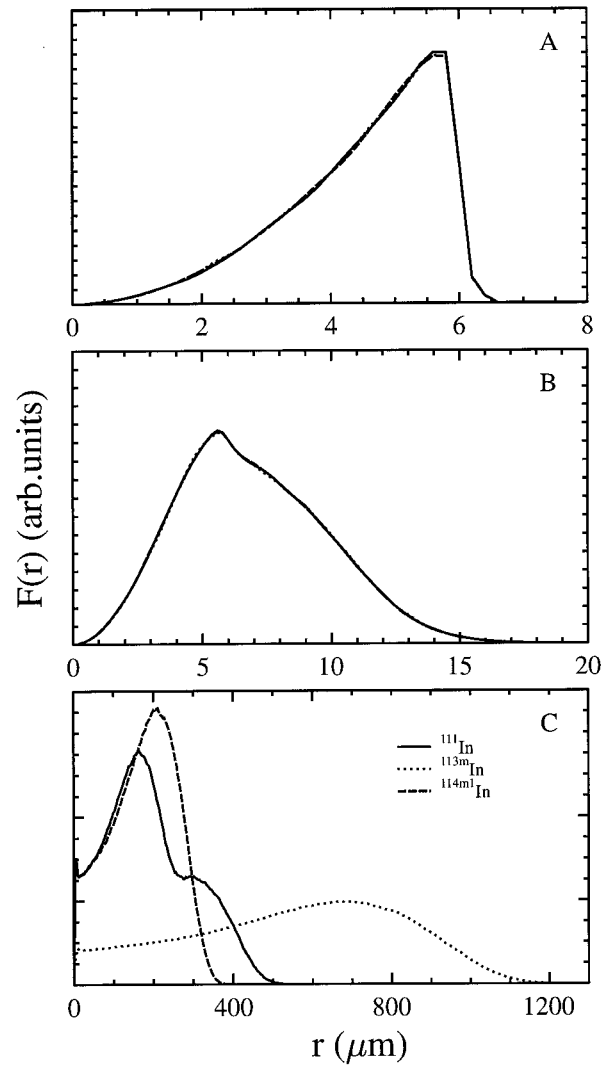

Fig. 4. Dose kernels ($F(r)$, Equation [1]) for electrons from different energy ranges of the indium-isotopes as function of distance (r) from the centre of the source. Kernel components A, B and C correspond to the electron decays shown in the Fig. 3.

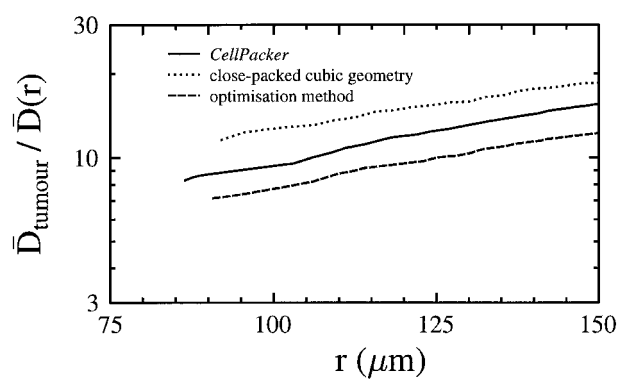

Fig. 5. The ratio of the mean absorbed dose in tumour cells, $\bar{D}_{tumour}$ (normalized to unity), to the mean absorbed dose of the healthy cells inside radius r, $\bar{D}(r)$, for different cluster models (tumour radius 75 μm) in case of ^{111}In.

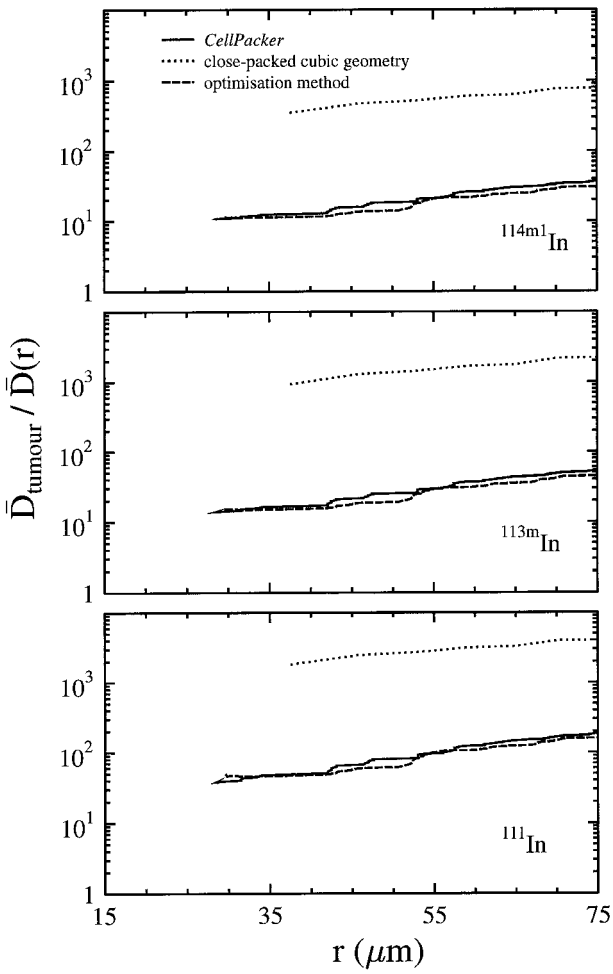

Fig. 6. The dose ratio [i.e. the ratio of the mean absorbed dose in tumour cells (normalized to unity) to the mean absorbed dose of the healthy cells inside radius r, $\overline{D}_{tumour}/\overline{D}(r)$] for different cluster models (tumour radius 15 μm) and isotopes, ^{111}In, ^{113m}In and ^{114m1}In.

the radiation to the healthy cells is most effectively absorbed. These phenomena can be seen in the tumour to healthy tissue dose ratio in Fig. 5. The calculated tumour to healthy tissue dose ratio depends on the absorbed dose to the healthy cells, which in the case of the optimization cluster method is the highest and therefore the tumour to healthy tissue dose ratio is the lowest. The differences in the calculated doses show that the choice of the cell-cluster model is a crucial part in calculating cellular level doses.

Clearly, the best feature in the close-packed cell-cluster model is the easy way it can be constructed. Using a 400 MHz/128 MB personal computer it takes about a minute to construct a file containing the cell coordinates. The CellPacker-algorithm and our new optimization algorithm have much more computing procedures and constructing clusters is thus rather time-consuming. Even when the computing is well optimized building a cluster of 2000 cells takes about a day.

The clinical usefulness of the present optimization model is reduced by the fixed spherical cell shape and the long processing time. In the future more powerful computers can be waited for and better computing capabilities will make it possible to simulate cells of more complex forms. This study can be seen as groundwork for the way to clinically more useful models with more complex forms. Along with the straight applicability to tissues of cells close to spherical form, the experiences in constructing different models of simple forms and the results of this study can also be utilized in the search for the packing methods for other than spherical forms. The future steps in applying cell-cluster models and the developments in radiobiology will eventually show the practical relevance of this study and the current 'first generation' cell-cluster models. In this study we have chosen to simulate the most optimal case concerning the distribution of the activity in the tumour and healthy tissues, i.e. activity homogeneously distributed only in the tumour. In the future the study is expandable to cover also the clinically more relevant cases, e.g. activity also in the healthy tissue and on the surface of the tumour.

In conclusion, according to our dose calculations with three indium isotopes, differences in the geometrical composition of the cell-cluster models have a great effect on the calculated absorbed doses. Our two cell-cluster models, the CellPacker model and the new optimization model may be used in calculations considering either rigid or diffuse tumours, respectively, depending on the characteristics of the tissue in question. Our models are more flexible than the traditional close-packed cubic geometry model because of the possibility to construct the cluster of cells of variable sizes. This study has also built foundation for the future development of the cluster models of more complex cell forms.

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