Monte Carlo evaluation of Auger electron-emitting theragnostic radionuclides

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ABSTRACT

Several radionuclides used in medical imaging emit Auger electrons (AE) which, depending on the targeting strategy, could either be exploited for therapeutic purposes or may contribute to an unintentional mean absorbed dose burden. The virtues of twelve AE emitting radionuclides are evaluated in terms of cellular \( S \)-values in concentric and eccentric cell/nucleus arrangements and by comparing their dose-point kernels (DPKs).

**Methods:** The Monte Carlo code PENELOPE was used to transport the full particulate spectrum of \(^{67}\text{Ga},^{80m}\text{Br}, ^{89}\text{Zr}, ^{90}\text{Nb}, ^{99m}\text{Te}, ^{111}\text{In}, ^{117m}\text{Sn}, ^{119}\text{Sb}, ^{123}\text{I}, ^{125}\text{I}, ^{195m}\text{Pt} \) and \(^{201}\text{Tl} \) by means of event-by-event simulations. Cellular \( S \)-values were calculated for varying cell and nucleus radii and the effects of cell eccentricity on \( S \)-values were evaluated. DPKs were determined up to 30 \( \mu \)m. Energy deposition at DNA scales are also compared to an \( \alpha \)-emitter, \(^{223}\text{Ra} \). **Results:** PENELOPE determined \( S \)-values were generally within 10\% of MIRD values when the source and target regions strongly overlap, i.e. \( S(N\leftarrow N) \) configurations, but greater differences were noted for \( S(N\leftarrow Cy) \) and \( S(N\leftarrow CS) \) configurations. Cell eccentricity has the greatest effect when the nucleus is small compared with the cell size and for cases where the radiation sources are located on the cell surface. DPKs taken together with the energy spectra of the radionuclides can account for some of the differences noted in energy deposition patterns between the radionuclides. Energy deposition of most AE-emitters at DNA scales \( \leq 2 \) nm exceeds that of a monoenergetic 5.77 MeV \( \alpha \)-particle, but not for \(^{223}\text{Ra} \). **Conclusion:** A single-cell dosimetric approach is required to evaluate the efficacy of individual radionuclides for theragnostic purposes, taking cell geometry into account with internalizing and non-internalizing targeting strategies.

**Key words:** Auger electron-emitters, Cellular dosimetry, Targeted Radiotherapy, Theragnostics, Monte Carlo (MC) simulation, \( S \)-values, Dose point kernels.
INTRODUCTION

The therapeutic rationale for molecularly targeted radiotherapy (mTRT) is the selective delivery of a radionuclide to tumor cells via a targeting moiety, thereby enhancing the therapeutic index of the agent. Several Auger electron (AE) emitting radionuclides have been proposed for mTRT of small metastases and disseminated cancer cells with some promising clinical results (1-3). These radionuclides are well suited for mTRT agents due to the extremely short range in matter (nanometers to a few micrometers) of the low-energy, intermediate linear energy transfer (LET) Auger and Coster-Kronig (CK) electrons they emit (4). These electrons account for high energy deposition in the immediate vicinity of the decay site and, owing to their short range, irradiation of normal neighboring cells is limited, thus reducing non-specific radiotoxicity. In addition, radiation emitted during the nuclear decay can be exploited for imaging purposes either with single photon emission computed tomography (SPECT in the case of γ-rays in the energy range of 70 – 360 keV or Bremsstrahlung imaging for pure β-emitters) or positron emission tomography (PET in the case of annihilation photons), thus making AE emitting radionuclides ideal as theragnostic agents (5, 6).

When evaluating AE emitting radionuclides as potential theragnostic agents, the following aspects should be addressed. The therapeutic efficacy of a radionuclide depends on the total number of electrons emitted per decay (including AE, CK and internal conversion electrons (IE) as well as β-particles) along with the total energy released. When the total energy released is carried by a small number of relatively high-energy long-range electrons, then targeting of the nucleus from the cytoplasm or cell surface is possible (7). Another key factor is the physical half-life ($T_{p/2}$). As the maximum theoretical specific activity of a radionuclide is inversely proportional to $T_{p/2}$, a prolonged $T_{p/2}$ may result in redistribution of the therapeutic agent before sufficient decays have occurred to cause lethal damage. It is also important to consider the ratio of penetrating (x- and γ-ray) to non-penetrating (electron or β-particle) forms of ionizing radiation (p/e) because the moderate-high energy but low LET γ-emissions from some radionuclides could irradiate and potentially kill non-targeted normal cells. It has therefore been proposed that an ideal therapeutic radionuclide should have a (p/e) ratio of 2 (8). Conversely, for imaging purposes a high proportion of γ emissions is required, which poses a trade-off between sparing healthy tissue surrounding the target region and providing adequate mean absorbed dose to the target region.

The most critical point to consider when using AE emitting radionuclides for mTRT is the very short range of Auger and CK electrons as this necessitates intra-nuclear accumulation if maximum therapeutic effect is to be achieved. Since the dimensions of the different DNA condensation states (e.g., chromatin fibers, nucleosomes and double-stranded DNA) are all within the range of typical Auger and CK electrons, nuclear incorporation leads to extreme radiotoxicity, resembling high-LET radiation with relative biological effectiveness (RBE) similar to that achieved by α-emitting radionuclides (9). Several strategies have been proposed to achieve the optimal localization of the radionuclides with respect to the sensitive targets in cells (5, 10, 11). However, recent
observations suggest that nuclear accumulation may not be required for an Auger electron emitter to produce high-LET type radiotoxicity (12). In contrast, radionuclides bound outside the cell nucleus, e.g. in the cytoplasm, on the cellular membrane or extra-cellularly, do not produce severe lethal effects, and have RBE values comparable to those observed for low-LET radiation (13).

Regardless of the targeting strategy adopted, cellular geometry could influence the mean absorbed dose to the nucleus and thus the biological effect of an AE emitting theragnostic agent. The S-value estimates provided by the MIRD Committee (14) assume spherical cell geometry, but it is conceded that cellular geometry could affect these values. This was demonstrated by Nettleton and coworkers (15) who noted differences between S-value calculations in spherical and ellipsiodal cell geometries especially towards the edge of the cell. Considering that many cells exhibit irregular geometries and eccentric cell/nucleus arrangements, dose to the nucleus may be over or underestimated when using MIRD tabulated S-values.

The aim of this study was to evaluate the properties of twelve AE emitting radionuclides that have been proposed as theragnostic agents, namely 67Ga, 80mBr, 89Zr1, 90Nb1, 99mTc, 111In, 117mSn, 119Sb1, 123I, 125I, 195mPt and 201Tl (16-18) (Supplemental Table 1), in terms of 1) S-values from MC simulations 2) the effect of cellular geometry – eccentric cell/nucleus arrangements on S-values, 3) dose-point kernels (DPKs) and 4) energy deposition on a DNA scale in comparison with an α-emitter, 223Ra.

MATERIALS AND METHODS

Monte Carlo simulations – The PENELOPE code

The S-values and DPKs were calculated with the general-purpose Monte Carlo code PENELOPE (19). PENELOPE simulates the coupled electron/photon transport in arbitrary materials from 50 eV to 1 GeV. The simulation is controlled by seven user-defined parameters: Eabs(1), Eabs(2), Eabs(3), C1, C2, Wcc and Wcr. The first three parameters fix the absorption energy for electrons, photons and positrons defining the cut-off energy below which simulation is discontinued (50 eV) and the residual energy of the particle is deposited locally. The remaining parameters control the mixed simulation algorithm for the transport of electrons and positrons. To force detailed (event-by-event) simulation the latter parameters were set to zero (20).

The cell model consists of two homogeneous spheres of liquid water (mass density \( \rho = 1 \text{ g cm}^{-3} \)), representing the cell and its nucleus, immersed in an infinite water medium (Figure 1). Cell \((R_C)\) and nucleus \((R_N)\) radii combinations as tabulated by the Medical Internal Radiation Dose (MIRD) Committee (14) were considered, and the list of \((R_C, R_N)\) values was expanded to include larger cell geometries (up to \(R_C = 12 \mu\text{m}\) and \(R_N = 11 \mu\text{m}\)) (21). Typically \(2 \times 10^9\) primary particles were simulated in each run.

\(^1\) Not included in the MIRD monograph (21).
**S-value Calculations**

MC transport of the complete radiation spectra based on the unabridged nuclear decay data (RADTABS software Ver. 2.2) (22), was used for all radionuclides, except for $^{90}$Nb and $^{117m}$Sn, where the condensed AE+CK+IE spectrum was employed as the unabridged spectrum was not provided in tabulations. In the case of $^{89}$Zr, $^{90}$Nb and $^{99m}$Tc, the full $\beta$-spectra were included. The Auger, CK and IE electrons as well as $\beta$ particle contributions to $S$-values were determined separately. Taking the nucleus as the target, simulations were run assuming uniformly distributed activity in the nucleus ($N\leftarrow N$), in the cytoplasm ($N\leftarrow Cy$) or on the cell surface ($N\leftarrow CS$). Cellular $S$-values, that is, the mean absorbed dose to the target region (T) per unit cumulated activity in the source region (S), i.e. $S(T\leftarrow S)$, according to the MIRD formalism is

$$S(T \leftarrow S) = \frac{1}{m_T} \sum_j y_j E_j \phi_j (T \leftarrow S),$$

where $y_j$ is the number of electrons (yield) emitted per transition $j$ with energy $E_j$ and $\phi_j (T \leftarrow S)$ is the fraction of the source energy deposited in the target region $T$ (mass $m_T$) from activity in the source region $S$. $S$-values included in Supplemental Tables 2-13 were calculated from an event-by-event MC simulation implementing equation (1). The resulting $S$-values except for the nuclides $^{89}$Zr, $^{90}$Nb and $^{119}$Sb not included in the MIRD monograph, were compared with those in the MIRD tabulations (14) derived from equation (2). The $S$-value in the continuous-slowing-down, straight-trajectory approximation is given by

$$S(T \leftarrow S) = \frac{1}{m_T} \sum_j y_j E_j \int_0^{r_{CSDA}(E_j)} \psi_{T-S}(r) \frac{1}{E_j} S_{col}(E_j; r) \, dr,$$

where $\psi_{T-S}(r)$ is the geometric reduction factor (14), $S_{col}(E_j; r)$ is a semi-empirical electronic (collision) stopping power of an electron with initial energy $E_j$ after passing a distance $r$ through the medium and $r_{CSDA}$ is the range in the continuous-slowing-down approximation.

**DPKs**

For DPKs a point isotropic radiation source was placed in an infinite liquid water medium and the mean absorbed dose from the emitted electrons (AE, CK, IE and $\beta$ particles) was scored in $1\text{nm}$-thick spherical shells around the decay site. Mean absorbed doses were tallied up to a radial distance of 30 $\mu$m from the point source. This corresponded to the radius of a sphere in which 100% of all emitted energy from the AE+CK-spectra was absorbed for $^{67}$Ga, $^{80}$Br, $^{89}$Zr, $^{90}$Nb, $^{99m}$Tc, $^{111}$In, $^{117m}$Sn, $^{119}$Sb, $^{123}$I, $^{125}$I and 90% for $^{195m}$Pt and $^{201}$Tl.
To compare the dose deposition of the radionuclides to that of $^{223}$Ra (22), the ratio of the DPKs calculated for spheres representing different DNA condensation states was determined. The energy deposited by the 5.77 MeV $\alpha$ particles was approximated by multiplying the mass electronic stopping power (800 MeVcm$^2$/g) over the path length (i.e. the radius of the sphere), while energy deposition of the AE+CK+IE spectrum was determined by event-by-event simulation.

RESULTS

MC Calculated $S$-values

Cellular $S$-values calculated from MC simulations are provided in Supplemental Tables 2 to 13. The statistical uncertainty of the $S$-values was less than 1.3% with 95% probability (type A uncertainty). The contribution of photons is much smaller than that of electrons (less than 2% of total $S$-values) and was disregarded in the present $S$-value tabulations; this was also done to facilitate comparison with MIRD $S$-values, where the contribution from photon radiations was not included (Supplemental Figure 1). For each radionuclide, the contributions to $S$-values of the AE+CK electrons as well as, where appropriate, the $\beta$-spectra (BET) is provided. In the case of $^{99m}$Tc, the contribution of the $\beta$-spectra to the cellular $S$-values is negligible (on average less than 0.003% to $S(N\leftarrow N)$, as expected from the $\beta$ yield, and less than 0.03% to $S(N\leftarrow Cy)$ and $S(N\leftarrow CS)$, respectively) and therefore the contribution of $S$(BET) to the total is omitted. $S$-values were verified using the simulated DPKs, with differences $\leq 2\%$ (data not shown).

In summary, the $S$-values calculated from PENELOPE MC simulations are in excellent agreement with the MIRD data when the source and target regions strongly overlap, i.e. for $N\leftarrow N$ configurations. The differences between PENELOPE and MIRD for $S(N\leftarrow N)$-values are generally smaller than 10%, with MIRD consistently smaller than PENELOPE $S(N\leftarrow N)$-values. The differences tend to decrease with increasing $R_N$, however discrepancies increase when the source is far from the target region, for the $N\leftarrow Cy$ (up to 30%) and $N\leftarrow CS$ (up to 60%) cases, respectively. These can be ascribed to the respective calculation approaches i.e. the MIRD method propagates electrons in straight trajectories, not taking energy straggling into account. PENELOPE as a rule overestimates the dose contributions for all three source-target configurations, except for $^{67}$Ga, $^{99m}$Tc and $^{201}$Tl, where PENELOPE underestimates the $N\leftarrow Cy$ and $N\leftarrow CS$ contributions compared with MIRD $S$-values.

Effect of Cellular Geometry on $S$-values

The effect of cellular geometry on the $S$-values, taking into account only contributions from the AE+CK+IE spectrum is summarized in Supplemental Tables 2-13. The self-dose to the nucleus is obviously not influenced by the position of the nucleus relative to the cell (concentric vs. eccentric nucleus arrangements) or the shape of the cell. However, the position of the nucleus, especially for eccentric arrangements can contribute significantly
to crossfire of neighboring cells, and this would specifically be seen for radionuclides with longer range AE and IE. Generally, the contribution to \( S(N\leftarrow Cy) \) is less for eccentric compared to concentric cell arrangements, with the greatest differences (up to 30%) noted in smaller \( (R_C, R_N) \) configurations. These differences become less pronounced (< 10%) when \( (R_C, R_N) \) increase. For eccentric vs. concentric nuclear arrangements where the activity is uniformly distributed on the cell surface, the greatest contribution to the mean absorbed dose delivered to the nucleus is again seen for small \( R_N \) relative to \( R_C \) (see Supplemental Figure 2, \( R_C = 5 \) µm and \( R_N = 2 \) µm). It follows that \( S(N\leftarrow CS) \) contributions in eccentric nucleus configurations increases as the size of the nucleus decreases and thus the distance of the nucleus from the cell surface decreases in relation to the range of the particles. This is particularly apparent for \(^{89}\text{Zr}\) (Supplemental Figure 4), where up to a 60 fold increase in nuclear dose is observed for \( R_C = 10 \) µm and \( R_N = 5 \) µm. However, this effect decreases when including the contribution from the \( \beta \)-spectra (Figure 2A).

To assess the effect of the nucleus position (in relation to the cell surface) on \( S(N\leftarrow Cy) \) and \( S(N\leftarrow CS) \), the eccentricity is evaluated for a cell with dimensions \( R_C = 10 \) µm and \( R_N = 5 \) µm (Figure 2). Eccentricity is expressed as the ratio of \( S \)-values for eccentric compared with concentric cell-nucleus arrangements. The cell nucleus position is shifted by 0.5 µm increments from the center until it is contiguous with the cell surface. In the case of \(^{89}\text{Zr}\) and \(^{90}\text{Nb}\), the contribution of the \( \beta \)-spectra is included. Nucleus eccentricity had the least effect on \(^{80}\text{Br}, ^{117}\text{Sn}, ^{123}\text{I}\) and \(^{125}\text{I}\), with the contribution from cytoplasmic mean absorbed dose \( S(N\leftarrow Cy) \), decreasing by less than 25% and cell surface mean absorbed dose \( S(N\leftarrow CS) \), increasing by less than 30%. For \(^{89}\text{Zr}\) the \( \beta \)-spectra contributes approximately 25% to the overall mean absorbed dose for \( S(N\leftarrow Cy) \) configurations, while this contribution decreases from approximately 95 to 30% for \( S(N\leftarrow CS) \) configurations as the nucleus shifts towards the cell surface. Conversely, the \(^{90}\text{Nb} \) \( \beta \)-spectra contribution to \( S(N\leftarrow Cy) \) and \( S(N\leftarrow CS) \) configurations varied by approximately 30% and 30 - 45%, respectively. The effect of eccentricity on dose calculations is discussed in the supplemental material (Supplemental Figure 3).

**Contribution of AE to S-values**

Self-dose to the nucleus for the majority of radionuclides studied is almost exclusively due to AE, with IE (and where appropriate \( \beta \) particles) responsible for the remaining mean absorbed doses (Supplemental Tables 2-13). Cytoplasmic distributed AE contribute less as \( R_C \) increases in comparison to \( R_N \). The contribution of AE to \( S(N\leftarrow CS) \) can approximately be divided into three categories: 1) the contribution increases when the distance between \( R_C \) and \( R_N \) decreases (\(^{67}\text{Ga}, ^{80}\text{Br}, ^{99m}\text{Tc}, ^{195}\text{Pt} \) and \(^{201}\text{Tl}\); 2) the contribution increases when the distance between \( R_C \) and \( R_N \) increases (\(^{89}\text{Zr}, ^{90}\text{Nb} \) and \(^{119}\text{Sb}\)) and 3) the contribution of surface bound AE to the nucleus is influenced by the end of range of some electrons in the spectra (\(^{111}\text{In}, ^{117}\text{Sn}, ^{123}\text{I} \) and \(^{125}\text{I}\)). In the latter
category, $^{111}$In, $^{123}$I and $^{125}$I are largely unaffected by $R_c$ and $R_N$ combinations, which makes these radionuclides more attractive for targeting strategies not relying on the internalization of the construct.

**DPKs**

DPKs for the radionuclides studied are presented in Figure 3. The DPKs calculated for $^{89}$Zr and $^{90}$Nb include the contributions of their $\beta$-spectra (Supplemental Figure 4). For all radionuclides considered, the energy deposition in the first 1 nm shell ranged from a minimum of 0.14 keV ($^{67}$Ga) to a maximum value of 1.21 keV ($^{195m}$Pt) with corresponding DPKs of 5.23 MGy and 46.4 MGy, respectively. If a DNA targeting strategy is adopted, the radionuclides that will result in the highest DPK over a radial distance of 11 nm, chosen to represent chromatin structure (i.e. DNA double helix wrapped around histones) are in decreasing order of efficacy; $^{195m}$Pt, $^{201}$Tl, $^{125}$I, $^{119}$Sb, $^{111}$In, $^{123}$I, $^{117m}$Sn, $^{80m}$Br, $^{90}$Nb, $^{89}$Zr, $^{99m}$Tc, and $^{67}$Ga. DPKs decrease dramatically by 8-9 orders of magnitude over the 30 µm distance considered, falling to mean absorbed doses of a few mGy.  

**Relative Dose of AE Compared with $\alpha$-Particles**

A comparison of the energy deposition from $\alpha$- ($^{223}$Ra) and AE-emitters (AE+CK+IE+$\beta$) in spheres of diameters representing different DNA condensation states is shown in Figure 4. The energy deposition in a sphere of diameter 2 nm, representing the DNA double helix, exceeds that of a monoenergetic 5.77 MeV $\alpha$-particle for all the radionuclides apart from $^{99m}$Tc, and $^{67}$Ga (Figure 4A). When comparing the AE-emitters with the complete particulate spectrum of $^{223}$Ra (5.77 MeV $\alpha$+AE+CK+IE+daughters), the effect is vastly reduced, with only $^{195m}$Pt depositing a comparable amount of energy (Figure 4B). In general, the relative dose of the AE-emitting radionuclides diminishes dramatically as diameters representing DNA condensation states increases.

**DISCUSSION**

To evaluate the virtues of AE emitting radionuclides that have previously been suggested for therapeutic or imaging purposes, a single-cell dosimetric approach was undertaken by considering all energy deposition events and related probabilities. Firstly, cellular $S$-values were determined by MC transport of all particulate radiation following the MIRD formalism and secondly DPKs were calculated for all the radionuclides considered in 1 nm radial bins up to 30 µm. In this regard it is crucial to use an MC code that provides an event-by-event simulation, as a loss of spatial resolution during particle transport from condensed simulation algorithms (i.e. grouping elastic, inelastic and radiative events), and underestimation of secondary electrons, have a large effect on energy deposition (23). PENELOPE can carry out event-by-event coupled photon-electron transport simulations, thus providing a more accurate estimation of the energy deposition than other general-purpose MC codes (24, 25).

PENELOPE cellular $S$-values for overlapping source and target areas are in good agreement with MIRD and those previously published (26), with differences < 10 and 5%, respectively. However, larger discrepancies are
seen when the source and target volumes are further apart. The greatest difference (up to 60%) between PENELOPE and MIRD S-values was for the case where activity was assumed to be distributed on the cell surface in accordance with previous observations by Uusijärvi et al (25). These differences can be ascribed to MIRD S-values being based on approximate DPKs calculated from the collision stopping power (i.e. assuming straight electron trajectories and neglecting energy straggling). Differences could also be attributed to the different energy spectra used. Whereas the unabridged radiation spectra from the MIRD monograph (22) was adopted in the MC simulations, MIRD S-values were generated from the energy spectra provided by Eckerman and co-workers (27). A limitation of the PENELOPE code when transporting AE, is the set cut-off energy of 50 eV. Many of the radionuclides evaluated here have an abundance of low-energy AE, less than 50 eV, which are thus not transported. This could potentially lead to an overestimation of energy deposited within the first few nm shells of the DPKs calculated.

It was recently demonstrated that a small variation in mean absorbed dose could have a significant impact on tumor control probability (28). It is therefore crucial that the selection of a radionuclide-delivery vehicle addresses not only the distribution (particularly internalization) of the radionuclide but also the geometry of the targeted cells. As is shown, eccentric cell-nucleus arrangements can lead to increased S-values for some of the radionuclides studied here. The greatest effect of nucleus eccentricity was noted for S(N←CS) configurations. For example, the dose to the nucleus from cell surface source arrangements for $^{201}$Tl increased by more than 200%. As is the case with the other radionuclides ($^{67}$Ga, $^{89}$Zr, $^{90}$Nb, $^{99m}$Tc, $^{111}$In, $^{119}$Sb and $^{195m}$Pt), this huge increase in S(N←CS) is due to an abundance of very low energy electrons in their spectra. This property could be advantageous for cell types with eccentric nucleus arrangements where targeting is achieved via surface-bound receptors, but it could also have a deleterious effect on surrounding normal cells in close contact with the targeted cell. Another point of consideration with eccentric cell-nucleus arrangement is the cell size, for smaller cells and nuclei the effect of eccentricity is rather marked, with up to a 2 fold difference in dose.

The spatial dose gradients in the respective DPK spectra are the result of the end of ranges of major low-energy electron groups. The sharp drop in dose after the first few nm illustrates the highly localized energy deposition caused by the AE, with local mean absorbed doses over this range in excess of 10 MGy. Radial dose distributions diverge by less than 25% compared to that previously reported for $^{111}$In and $^{125}$I (29, 30), and could be ascribed to the different radiation spectra used.

Although β-emitters are clinically widely used because of their long range, the recent success of the α-emitting radionuclide $^{223}$Ra (31) has focused attention on the use of shorter range radionuclides for mTRT. From the viewpoint of their cell-killing potential, the advantage of AE-emitting radionuclides is their extremely short range and localized dose deposition. Intranuclear delivery of AE-emitting constructs results in RBE similar to that of α-emitters, but with a reduced crossfire effect compared with α-emitters, making them more suitable for single-cell irradiation (9). The DPKs of $^{223}$Ra and the AE-emitters show that with respect to the energy deposited
in spheres of DNA dimensions, only the higher mass number AE-emitters deposit comparable amounts of energy. While, comparison with a monoenergetic 5.77 MeV alpha particle notes the major advantage of AE-emitters at distances $< 11$ nm, which is in agreement with data presented by Charlton (32).

**CONCLUSION**

Many AE-emitters are suitable for theragnostic applications, enabling simultaneous detection (PET and SPECT imaging) and treatment. New strategies are being developed for delivery of AE-emitting radionuclides to the cell nucleus, e.g. carbon nano-tubes (33), gold nano-particles (34), antibody based (35) and cell penetrating peptides (36). The data presented here suggest that single cell characteristics should be taken into account when designing these molecularly targeted agents. The challenge will be to match the delivery strategy with the physical properties of a particular radionuclide.
REFERENCES


FIGURE 1. Spherical geometric models generated with PENEOLOPE (19): (A) concentric and (B) eccentric cells ($R_C = 10 \, \mu m$, $R_N = 5 \, \mu m$). Inserts display the cell/nucleus arrangement of MDA-MB-468 (A) and H2N (B) breast cancer cells, the cytoplasm and nucleus have respectively been stained with a green and blue fluorescent dye.
FIGURE 2. Effect of eccentricity on S-values: (A and B) Ratio of eccentric and concentric S-values for a single cell ($R_C = 10 \mu m$, $R_N = 5 \mu m$) as a function of nucleus distance from the center of the cell. Solid and open symbols denote S-value ratios for N←Cy and N←CS, respectively.
FIGURE 3. DPKs (Gy) calculated in 1 nm shells up to 30 µm from isotropic point sources of (A) $^{67}$Ga, $^{80}$Br and $^{90}$Nb; (B) $^{89}$Zr, $^{99}$mTc and $^{111}$In; (C) $^{117}$mSn, $^{119}$Sb, and $^{123}$I; and (D) $^{125}$I, $^{195}$mPt and $^{201}$Tl. DPKs show the energy deposition for the complete particulate spectra (AE, CK, IE and $\beta$).
FIGURE 4. Relative dose, comparing energy deposition of A) a monoenergetic 5.77 MeV α-particle and B) $^{223}$Ra ($\alpha$+AE+CK+IE+daughters) with the AE-emitting radionuclides. Relative dose is given as the ratio of energy deposited in spheres with diameters representing different DNA condensation states (i.e. DNA double helix (2 nm), DNA wrapped around histones –chromatin (11 nm), chromatin fibre of packed nucleosomes (30 nm), chromosome section in extended form (300 nm), condensed section of chromosome (700 nm), entire mitotic chromosome (1400 nm)).
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