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MONTE CARLO BETA DOSE CALCULATION AT CELLULAR LEVEL FOR INTERNALLY DEPOSITED RADIONUCLIDES

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ABSTRACT

Standard macroscopic methods to assess the dose in nuclear medicine are limited in the case of inhomogeneous radionuclide distributions, especially with β emitters. In a few applications, like radioimmunotherapy, the mean dose to an organ is not suitable to explain clinical observations and the knowledge of dose at the cellular level is necessary. Though, we have written a software (CLUSTER3D) which is able to build a biologically representative spheres cluster model. The corresponding mathematical description has been implemented in our EGS4-PRESTA usercode, called DOSE3D, using the combinatorial geometry package MORSE-CG in order to calculate the deposited dose in various compartments. We present here principles of this dosimetric method, and first results obtained on thyroid models. They highlight the need of cellular models to take into account actual radionuclides distributions in tissues. The flexibility of developed softwares make them useful tools to study the energy deposition at various cellular levels. That could complete standard methods in most cases.

Key Words: cellular dosimetry, combinatorial geometry, Monte Carlo, radionuclide distribution, beta emitters

1. INTRODUCTION

In nuclear medicine, the more commonly used method to assess the absorbed dose in organs from internally distributed radionuclide is MIRD [1]. Knowing the cumulated activity (determined from residence times), one can calculate absorbed fraction and mean absorbed dose in organs using age-specific and sex-specific phantoms. This method was popularized and automatized with the widely used software MIRDOSE3 [2], which has proven its utility for radiation protection of patients.

But this intrinsically macroscopic approach, which supposes an homogeneous distribution within organs, seems to be inadapted in the case of an inhomogeneous distribution of the radionuclide, like, for example, radioimmunotherapy [3–6]. In recent papers, the dose calculated with MIRDOSE3 could not be correlated with observed myelotoxicity [7]. Thus, it appears that efficient dose calculations require new methods [8], especially when using β emitters.

Different methods were developped to take into account radionuclide distribution inhomogeneity, like convolution of point kernel [9, 10], or S factor calculation in voxelized phantoms [11]. But these methods

are limited by the voxel size (millimeter level) which could not be sufficient for strongly inhomogeneous distributions. To complete this approach, we chose to investigate a method to obtain improved knowledge of dose deposition at the cellular level.

We have written a sofwtare (CLUSTER3D) which is able to randomly generate a cell cluster distribution that is biologically representative of the studied problem. The obtained geometric model was then implemented in our EGS4-PRESTA Monte Carlo usercode called DOSE3D (described by *Clairand et al* [12]), in order to perform transport simulation. In the past decade, computers perfomances have increased, and it is now possible to develop this approach, using full Monte Carlo calculation and geometric model, because of dramatically reduced calculation times. This allows us to study various parameters (like biological distribution of radionuclides) in reasonable time. Details of this method are exposed in the following report, and an example of application using a geometric model of thyroid follicle for absorbed dose calculation in epithelial cells is described, demonstrating the utility of such approach.

2. MATERIALS AND METHODS

2.1 Formalism

Most of internal dosimetry calculations are performed using the MIRD formalism, which has been extensively described [1, 13, 14]. Although its use at the organ level is not suited for dose calculation in the case of inhomogeneous distribution, the concept can be used at any level. Calculations are based on the *absorbed fraction*, ϕ, a dimensionless quantity defined as the amount of energy emitted by the source absorbed by the target:

$$\phi(target \leftarrow source) = \frac{E}{E_0} \tag{1}$$

where E_0 is the energy emitted by the source and E the energy absorbed in the target. The *specific absorbed fraction* is then defined by $[kg^{-1}]$:

$$\Phi(target \leftarrow source) = \frac{\phi(target \leftarrow source)}{m_t} \tag{2}$$

m_t being the target mass $[kg]$. The absorbed dose, D $[Gy]$, in the target is then given by:

$$D = \tilde{A}.\Delta.\frac{\phi(target \leftarrow source)}{m} = \tilde{A}.\Delta.\Phi(target \leftarrow source) \tag{3}$$

with $\tilde{A}$ the cumulated activity in $Bq.s$, Δ $[J.Bq^{-1}.s^{-1}]$ the mean energy emitted per decay.

Our Monte carlo code calculate either ϕ or Φ, as explained in paragraph 2.2. To facilitate comparisons, we present results as dose per unit of cumulated activity in $mGy.MBq^{-1}.h^{-1}$.

2.2 The DOSE3D Usercode

The usercode we have developped in our laboratory (DOSE3D) is based on the EGS4-PRESTA 3.2 distribution. This very popular Monte Carlo code was first described by Nelson *et al* [15]. Its main originality is the use of the combinatorial geometry package MORSE-CG [16], implemented as described in the user code UCSAMPCG [15]. This package allows the user to model the wide range of geometries encountered in biological tissues. Clairand *et al* [12] have used DOSE3D for a radiation protection purpose in anthropomorphic phantoms. The structure of DOSE3D is given figure 1.

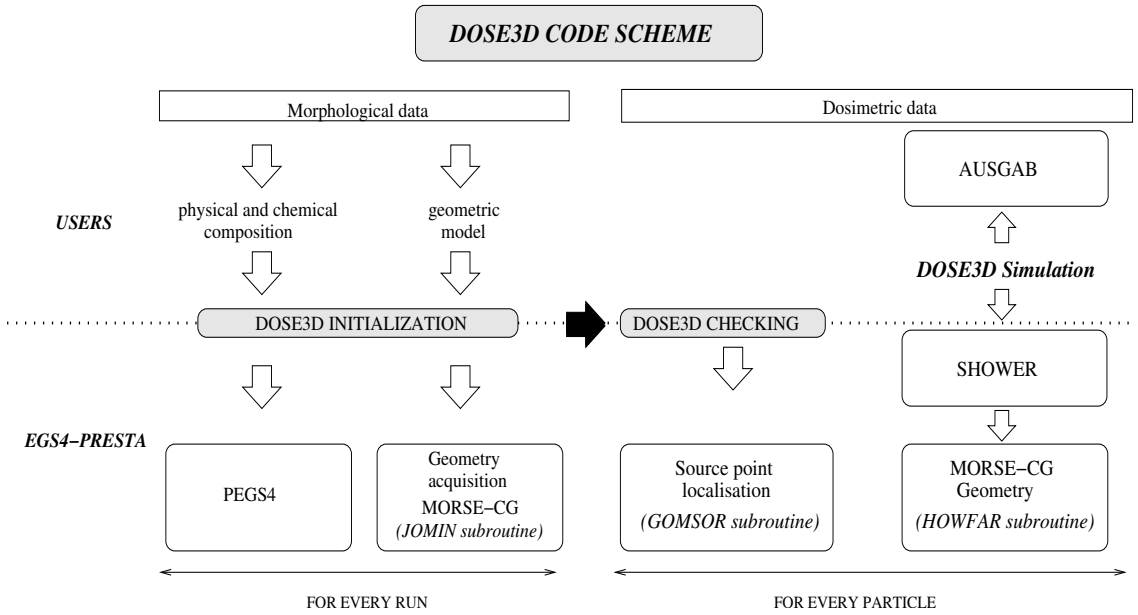

Figure 1. Flow Chart of DOSE3D

The originality of this code is that geometric parameters are contained in a separated input file; they are read at the start of the simulation by the JOMIN subroutine, and then DOSE3D only needs to localize (GOMSOR subroutine) the particle initial position. To implement a new model, the user only writes the input file, describing the geometry in two steps:

- He gives coordinates, size and shape of elementary volumes as shown figure 2.
- Then, he defines input zones made of volumes association, using logical operators +, - , and OR.

Input zones are those taken into account by MORSE-CG and EGS4 as zones of interest. The main advantage of this package is its flexibility: the user don't have to compile a new code each time a new geometry is necessary. Thus, using this formalism, one only needs to build a representative mathematical model of the biologic material involved in its problem.

Different source volumes are included in DOSE3D. One can define point sources, surface charged spheres, homogeneously charged spheres, annular distributions, or more complex source volumes using one of the defined input zone. Transport of photons and electrons, and monoenergetic sources as well as radionuclide spectra by sampling a cumulated probability density function can be simulated by DOSE3D.

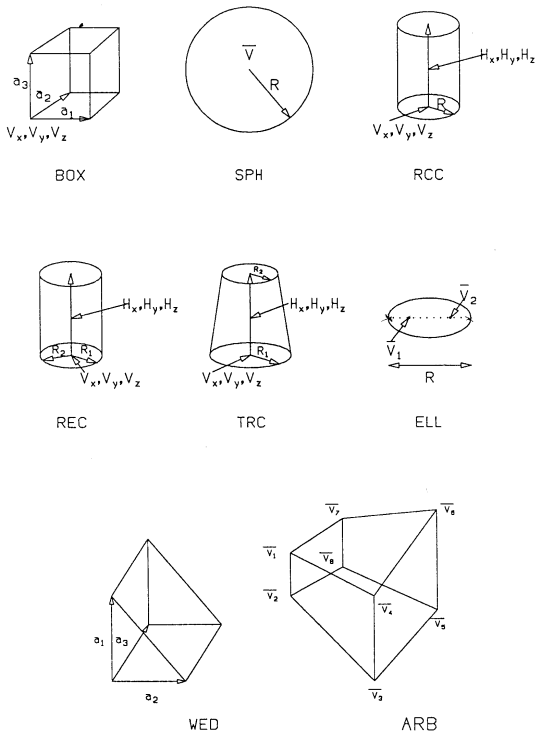

Figure 2. Geometric Volumes Available in MORSE-CG [16]

2.3 Cluster Generation Program

Geometric modelisation have a great incidence on results, since high gradients of dose deposition occur with β emitters. At cellular level, the way that volumes are associated can lead to large discrepancies with biologic reality. Our program (CLUSTER3D) is able to build a cluster of spheres of various sizes **randomly** distributed in a 3 dimension matrix. It automatically writes the DOSE3D input file in the MORSE-CG syntax. The flow chart of this program is given figure 3. Its main originality is that CLUSTER3D build a cluster with spheres of various size which was not the case for other published softwares [17].
The size distribution previously obtained from biologic data (sorted from the bigger to the smaller) is read by CLUSTER3D. It places the first sphere (i.e the bigger) at the center of a matrix filled with 0 values, and then fill each point inside the sphere with 1, meaning that these points are disabled. Then, the software randomly samples a sphere placed in the matrix (source sphere) and a point at its surface, and puts the next sphere tangentially at the sampled position. At each step, CLUSTER3D makes a test to see if all points are filled with 0, unless it samples a new point and then a new source sphere if it is still not possible to place the sphere. If the size of the matrix is too small, or if random numbers sequence lead to impossible arrangements, then CLUSTER3D reinitializes the system and retries. To force spheres to be as close as possible, user introduces constraints, placing a new sphere only next a sphere which has even one, two, or more tangents. The more the user asks CLUSTER3D to be restrictive with sphere placement (number of tangents), the longer it takes to construct the model. To build various arrangements for given distribution and constraint, one only has to change the random number sequence, (*i.e.* seeds of the generator). CLUSTER3D is using the RANMAR random number generator (Marsaglia) implemented in EGS4-PRESTA [15]. This gives us a relevant geometric model, which includes the presence of

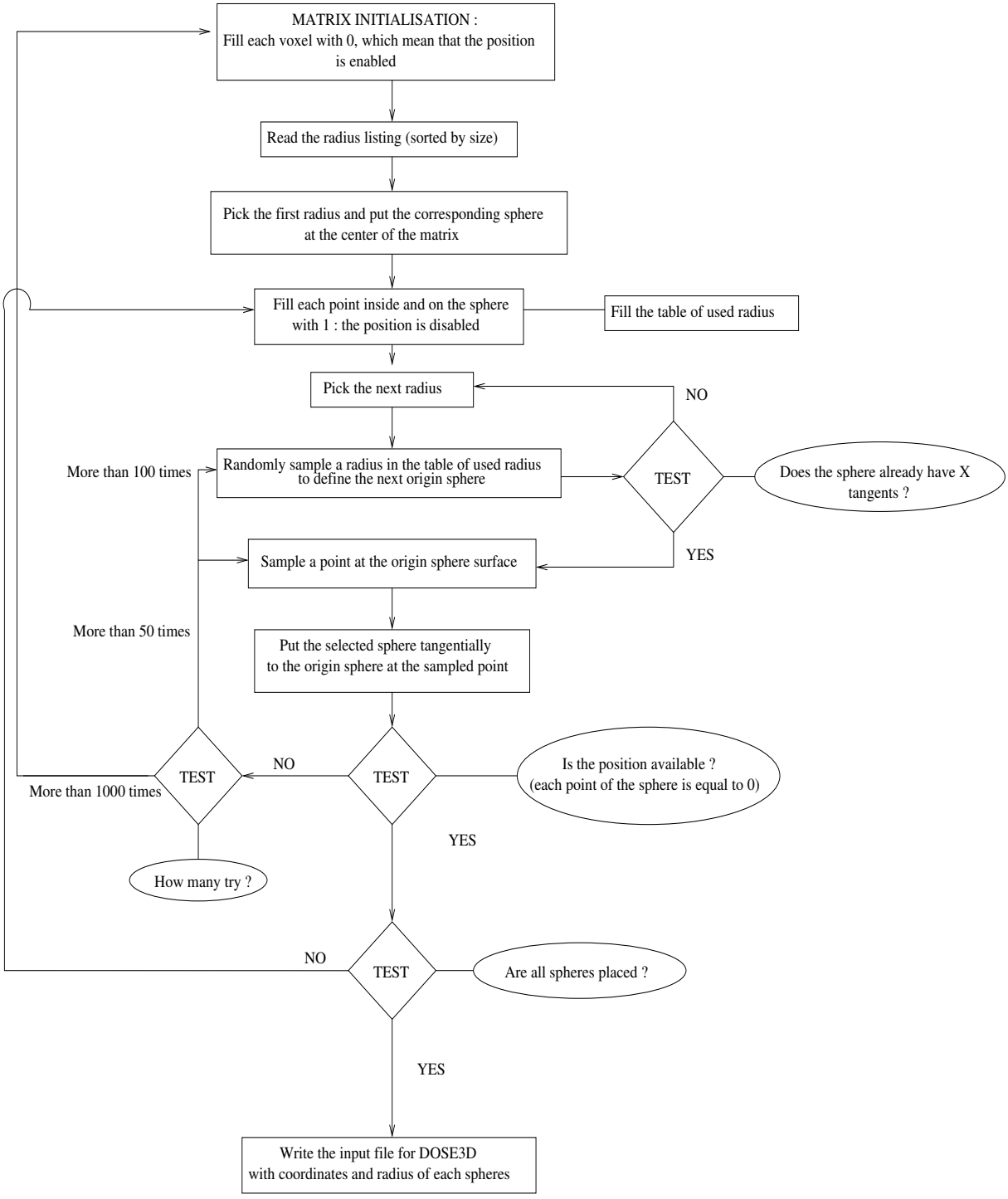

Figure 3. Flow Chart of CLUSTER3D

extra-cellular tissues.

2.4 Calculation Parameters

Monte Carlo transport algorithm must be used with care regarding physical approximations (especially for charged particles simulation, where many interactions occurs). Using a class II algorithm such as EGS4-PRESTA, one has to know multiple scaterring theory limits [18], and Continuous Slowing Down Approximation concept to use appropriate transport parameters. Thus, the choice of cross sections and cutoff energies can have a great incidence on results. In EGS4-PRESTA these parameters are PRESTA routines LCA, PLC and BCA (Lateral Correlation Algorithm, Path Length Correction, and Boundary Crossing Algorithm), ESTEPE, and cutoff energies Ecut and Pcut. The PRESTA algorithm [19] is used to fit the Moliere multiple scattering theory involved in EGS4. The principal limit of this theory is the small angle approximation which imposes a minimum number of collisions in one condensed history step. PRESTA's PLC determines each condensed history step length according to Moliere's approximation and energy of the charged particle. If ESTEPE, the maximum energy loss per step, is set to 1, then EGS4 let PLC optimizes the electron step length. Each particle trajectory is then corrected through LCA (Lateral Correction Algorithm) and BCA (Boudary Crossing Algorithm) which respectively takes into account the deviation of the particle during a step, and the presence of boundaries. For beta simulation in DOSE3D, we systematically use default parameters options, switching on PRESTA algorithm with ESTEPE = 1 (because of the great number of boundaries in that kind of simulation). The user also needs to set cutoff energies (Ecut for charged particles and Pcut for photons) below which the particle energy is deposited locally. Assuming that macroscopic codes such as EGS4-PRESTA are known to be accurate down to 10 keV kinetic energy (in water) for charged particles (due notably to the minimal number of collisions which must occur during a condensed history step) and 1 keV for photons, we set Ecut = 10 keV and Pcut = 1 keV to be consistent with EGS4 physics.

2.5 Application on a Thyroid Model

Epidemiological studies following the Chernobyl accident (April 26, 1986) have shown an increased rate of childhood thyroid carcinoma [20–22] in Belarus and Ukraine. The aim of the present study is to investigate the influence of thyroid morphological characteristics on the deposited dose in follicles epithelial cells. A morphometric study on 31 thyroid samples, obtained from prophylactic thyroidectomies made on children at the Institut Gustave-Roussy between 1983 and 2001, distinguished two statistically significant morphological groups, correlated with ages of subjects. In the following, **group 1** will refer to the < 13 years morphological group, and **group 2** to the ≥ 13 years group. These groups are defined by their follicle sizes distribution, shown figure 4. We have supposed ^{131}I to be distributed homogeneously in each follicle lumina, considering the thyroid follicle as a sphere (this is a good approximation because the study focus on healthy thyroid). We have inserted these distributions in CLUSTER3D to obtain a cluster made of 30 spheres, and to take into account epithelial cells orientation at the follicle surface as shown figure 5, follicles were separated in three families :

- Diameter less than 100 μm, with an epithelial cell thickness of 15 μm.
- Diameter between 100 μm and 200 μm, with an epithelial cell thickness of 10 μm.
- Diameter greater than 200 μm, with an epithelial cell thickness of 5 μm.

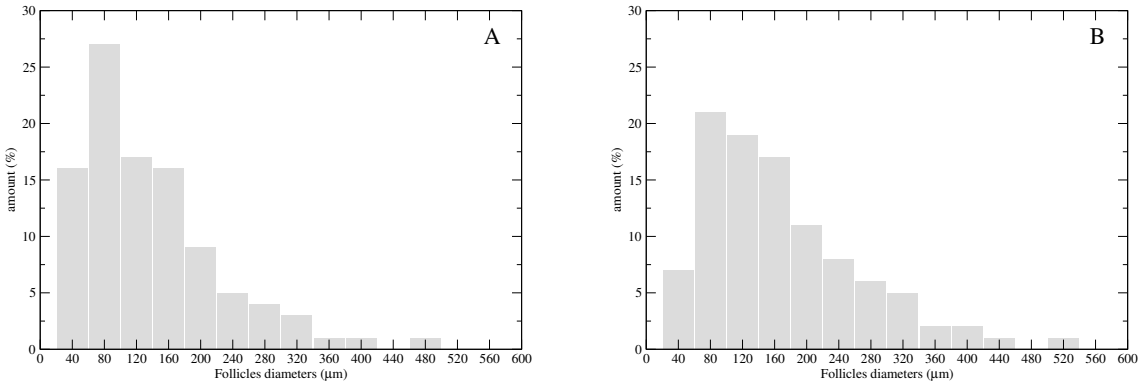

Figure 4. Follicles Size Distribution from (A) Group 1 ($<$ 13 years), and (B) Group 2 ($\geq$ 13 years)

For the simulation, these cells were represented by a shell of the corresponding thickness at the follicle surface.

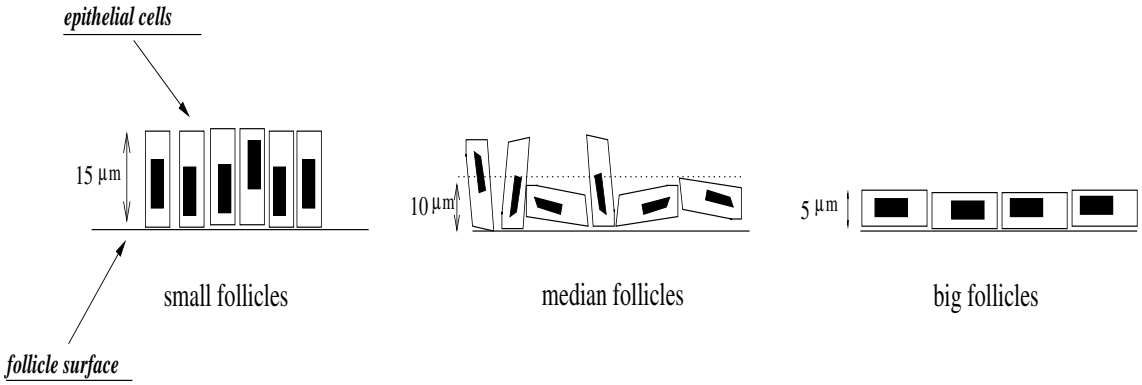

Figure 5. Epithelial Cells Orientation at Follicle Surface

The homogeneous distribution of ^{131}I is an hypothesis, since we know that it could be very inhomogeneous [21].

2.6 Hardware and Software Environment

Simulations are performed on a personal PC workstation equiped with an AMD-ATHLON MP1800+ dual processor, one Gigabytes of DDRAM, and SCSI hard disk, running under the Linux RedHat 7.2 Operating System. To visualize the cluster model constructed by CLUSTER3D, we use a commercially available 3D conception program called Rhinoceros, running under Windows NT 4.0 service pack 6.

3. RESULTS

3.1 Geometry

3.1.1 Cluster Model

Constructed thyroid follicles clusters for the two size distributions are presented figure 6. Small follicles

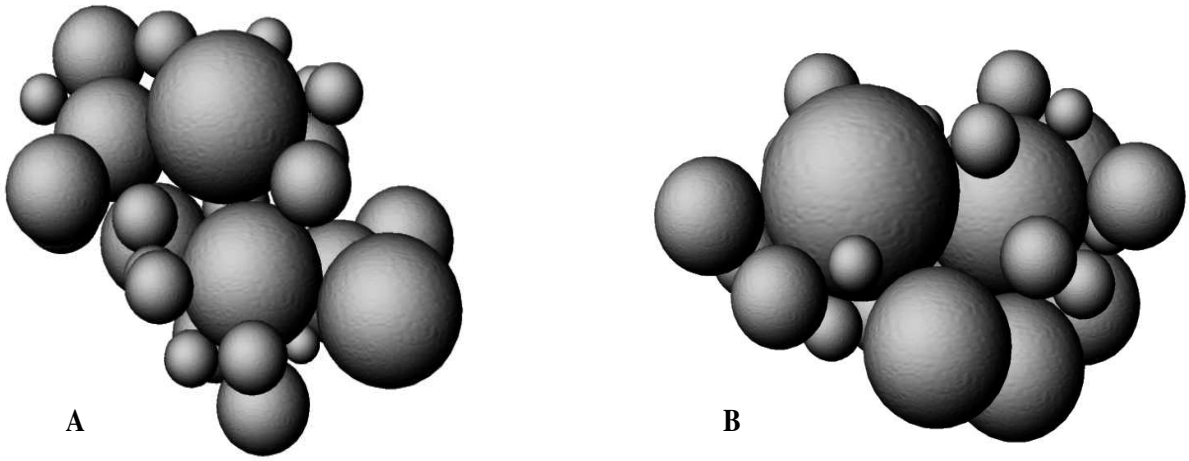

Figure 6. Examples of Thyroid Geometric Models for (A) Group 1 (< 13 years), and (B) Group 2 (≥ 13 years), Constructed by CLUSTER3D

are randomly distributed around bigger, which reflect the biologic reality. This model is completely defined through 4 variables, which are x, y, z and r (coordinates and radius of each sphere). These models were introduced in DOSE3D.

3.1.2 Calculation Time

Time necessary to build a 30 volumes model depends on spheres sizes and matrix size : initialize a $500 \times 500 \times 500$ matrix takes approximately one minute, which could quickly increase the calculation time if the system needs to re-initialize it very often (figure 3). Finally, constraint strength could lead to impossible 3D distribution, so that user has to stop the program execution and retry with less restrictive options. Typical running time for building thyroid clusters as shown figure 6 is 10 minutes.

3.2 Monte Carlo Simulation

3.2.1 Absorbed Doses in Epithelial Cells

Variation coefficients of absorbed doses, due to geometry, were always less than 2 % and in most cases less than 1 %, so they are not represented on figures, in order to make them more easily readable. Using previous models we have calculated the absorbed dose in epithelial cells. Figure 7 presents the influence of compactness constraints in CLUSTER3D on the absorbed dose in epithelial cells, for the Group 2 size distribution. Note that this compactness degree is only qualitative since we have not implemented any

quantitative estimate yet. It highlights that dose distribution can be very large over a small structure, and

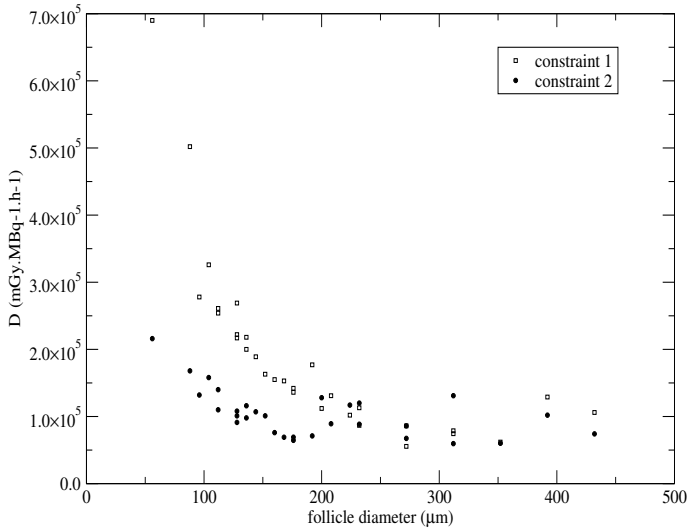

Figure 7. Dose to Epithelial Cells for Group 2 ($\geq$ 13 years), Two Different Compactness Constraints

that compactness degree (*i.e.* constraints in CLUSTER3D) could have a great influence especially for epithelial cells at small follicles surfaces. It shows the need to use a biologically representative model since it could have a great incidence on the mean absorbed dose as well as on individual follicle dose. Using same constraints (compactness degree) for the two size distribution models (figure 6), calculated absorbed doses are shown in figure 8. Curves tendancies are the same for the two distributions, and we can see that absorbed dose seems to be higher for the younger group; but these discrepancies are not significant, since figure 7 have shown the influence of geometric constraints on such calculations. It shows that accurate dose calculations needs to take into account biologic constraints and especially radionuclide distribution.

3.2.2 Calculation Time

Authors have reported that using the combinatorial geometry package MORSE CG multiply calculation time by approximately four in the case of a simple geometry [15]. Despite this fact, in our case, which includes a lot of volumes and boundaries, and where we simulate β particles, (which interacts very often with matter), simulations ranged from thirty minutes to one hour, depending on particle's energy. Simulating the five β spectrums of ^{131}I (1,000,000 histories for each spectrum), and running them at the same time (which is allowed by the Linux Operating System), results were obtained in approximately three hours (depending on how many processes were running at the same time).

4. CONCLUSIONS

Recent papers have shown that usual dosimetric methods are not adapted to preview the biologic effect in internal radionuclide therapy, since macroscopic models couldn't afford true radionuclides distributions [3–6]. Although a lot of methods were proposed past ten years to take into account this inhomogeneity, like convolution models using dose point kernel [9, 10] or voxellised phantoms [11] these methods could only assess the dose at the voxel level which limits the spatial resolution. In this paper, we

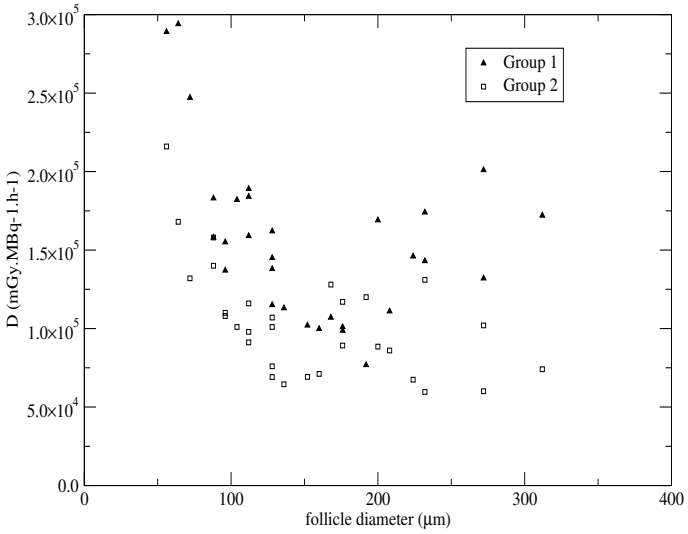

Figure 8. Dose to Epithelial Cells for Group 1 (< 13 years) and Group 2 (≥ 13 years), Using Geometric Models Constructed with Same Constraints

proposed a method in order to calculate the absorbed dose in cluster made of spheres of various sizes, and to simulate as close as possible biologic material, using full Monte Carlo simulation. This method was used to calculate the absorbed dose in epithelial cells of thyroid's follicles. There are many conclusions about these calculations:

- There is a broad dose distribution at the cellular level.
- Dose distribution is very geometry-sensitive, because the compactness degree seems to have a great influence on results.
- Although discrepancies were observed between the two morphological groups, they are not significant enough to explain epidemiological observations following the Chernobyl accident.

These conclusions show the need to build more representative models and to integrate distribution and kinetics of radionuclides. It will be the next step of this study on thyroid, using for example data derived from secondary ion mass spectrometry (SIMS) [21, 23], or autoradiography [24, 25]. Using biological distribution of radionuclides could lead to very high dose gradient in the case, for example, of radioimmunotherapy. This could be another field of application of our technique. This very general method can be used for simulation of any cell cluster size, because of the great flexibility of our code. Despite the use of combinatorial geometry, calculations times are dramatically reduced using up-to-date processors and systems; CLUSTER3D and DOSE3D are able to proceed calculations in two hours, depending on how many histories are simulated. Our calculation appraoch must be considered as a theoretical approach, which could only be considered as the first fundamental step of a more clinical study, giving users useful data to explain the macroscopic effect of any radionuclide distribution within any cell-cluster model. Future work will include the implementation of biological constraints in simulations (such as activity concentration) and the development of an operator-independant estimate of cluster's geometric compactness.

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REFERENCES

[1] E. E. Watson R. Loevinger, T.F. Budinger *MIRD PRIMER for absorbed dose calculation* Society of Nuclear Medicine, New York (1988).

[2] M. Stabin "MIRDOSE : personnal computer software for internal dose assessment in nuclear medicine" *Journal of Nuclear Medicine* **37**, pp. 538–546 (1996).

[3] A.I. Kassis "The MIRD approach : remembering the limitations" *Journal of Nuclear Medicine* **33**, pp. 781–782 (1992).

[4] D.R. Fisher "Radiation dosimetry for radioimmunotherapy, an oververwiew of current capabilities and limitations" *Cancer Supplement* **73(3)**, pp. 905–911 (1994).

[5] A.K. Erdi, Y.E. Erdi, E.D. Yorke, and B.W. Wessels "Treatment planning for radio-immunotherapy" *Physics in Medicine and Biology* **41**, pp. 2009–2026 (1996).

[6] H.M. Thiriens, M.A. Monsieur, B. Brans, I. Christiaens, and R.A. Dierckxx "Dosimetry from organ to cellular dimensions" *Comp. Med. Imaging and Graphics* **25**, pp. 187–193 (2001).

[7] G.A. Wiseman, C.A. White, T.E. Witzig, L.I. Gordon, C.E. Emmanouilides, A. Raubitschek, N. Janakiraman J. Gutheil, R.J. Schilder, S. Spies, D.H.S. Silverman, and A.J. Grillo-López "Radioimmunotherapy of relapsed Non Hodgkin's lymphoma with zevalin, a ^{90}Y-labeled anti-CD20 monoclonal antibody" *Clinical Cancer Research* **5 (suppl.)**, pp. 3281s–3286s (1999).

[8] K. Scheidhauer, I. Wolf, H-J. Baumgartl, C. von Schilling, B. Schmidt, G. Reidel, C. Peschel, and M. Schwaiger "Biodistribution and kinetics of ^{131}I-labelled anti-CD20 MAB IDEC-C2B8 (rituximab) in relapsed Non Hodgkin's lymphoma" *European Journal of Nuclear Medicine* **29 (10)**, pp. 1276–1282 (2002).

[9] H.B. Giap, D.J. Macey, J.E. Bayouth, and A.L. Boyer "Validation of a dose point kernel convolution technique for internal dosimetry" *Physics in Medicine and Biology* **40**, pp. 365–381 (1995).

[10] A.K. Erdi, E.D. Yorke, M.H. Loew, Y.E. Erdi, M. Sarfaraz, and B.W. Wessels "Use of the fast Hartley transform for three-dimensional dose calculation in radionuclide therapy" *Medical Physics* **25(11)**, pp. 2226–2233 (1998).

[11] W.E. Bolch, L.G. Bouchet, J.S. Robertson, B.W. Wessels, J.A. Siegel, R.W. Howell, A.K. Erdi, B.Aydogan, S. Costes, and E.E. Watson "MIRD pamphlet no. 17 : the dosimetry of nonuniform activity distributions - radionuclide S values at the voxel level" *Journal of Nuclear Medicine* **40**, pp. 11s–36s (1999).

[12] I. Clairand, M. Ricard, J. Gouriou, M. Di Paola, and B. Aubert "DOSE3D : EGS4 Monte Carlo code based software for internal radionuclide dosimetry" *Journal of Nuclear Medicine* **40(9)**, pp. 1517–1523 (1999).

[13] R. Loevinger and M. Berman "A schema for absorbed dose calculations for biologically distributed radionuclides" *Journal of Nuclear Medicine* **supplement 1** (1968) MIRD Pamphlet numero 1.

[14] M.J. Berger "Distribution of absorbed dose around a point beta source of electrons and beta particles in water and other media" *Journal of Nuclear Medicine* **12(supl.5)** (1971).

[15] R.F. Nelson, H. Hirayama, and D.W.O. Rogers "The EGS4 code system" Slac 265 Stanford linear Accelerator (1985).

[16] W.R. Nelson and T.M. Jenkins *Monte Carlo transport of electrons and photons* chapter Geometry Methods and Packages, pp. 385–405 Plenum Press, New York (1988).

[17] J.S. Lampinen, J.P. Valimaki, A.A Kuronen, J. Stepanek, and S.E. Savolainen "Cluster models in cellular level electron dose calculation" *Acta Oncologica* **38(3)**, pp. 367–372 (1999).

[18] P. Andreo, J. Medin, and A.F Bielajew "Constraint of the mutltiple scaterring theory of moliere in monte carlo simulation of the transport of charged particles" *Medical Physics* **20(5)**, pp. 1315–1325 (1993).

[19] A.F. Bielajew and D.W.O. Rogers "PRESTA : the parameter reduced electron step algorithm for electron Monte Carlo transport" *Nuclear Instrumentation and Methods in Physics Research* **B18**, pp. 165–181 (1987).

[20] F. Pacini, T. Vorontsova, E. Demidchick, E. Molinaro, L. Agate, C. Romel, E. Shavrova, E.D. Cherstvoy, Y. Ivashkevitch, E. Kunchinskaya, M. Schlumberger, G. Ronga, M. Filesi, and A. Pinchera "Post-Chernobyl thyroid carcinoma in belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France" *Journal of Clinical Endocrinology and Metabolism* **82(11)**, pp. 3563–3569 (1997).

[21] E. Hindié, A. Petiet, K. Bourahla, N. Colas-Linhart, G. Slodzian, R. Dennebouy, and P. Galle "Microscopic distribution of iodine radioisotopes in the thyroid of the iodine deficient new-born rat: insight concerning the chernobyl accident" *Cellular and Molecular Biology* **47(3)**, pp. 403–410 (2001).

[22] E. Hindié, L. Leenhardt, F. Vitaux, N. Colas-Linhart, P. Grosclaude, P. Galleand A. Aurengo, and B. Bok "Non-medical exposure to radioiodine and thyroid cancer" *European Journal of Nuclear Medicine* **29 (suppl 2)**, pp. S497–S512 (2002).

[23] P. Fragu, C. Briançon, S. Halpern, and E. Larras-Regards "Changes in iodine mapping in rat thyroid during the course of iodine deficiency : imaging and relative quantitation by analytical ion microscope" *Biology of the Cell* **62**, pp. 145–155 (1988).

[24] J.L. Humm, R.M. Macklis, K. Bump, L.M. Cobb, and L.M. Chin "Internal dosimetry using data derived from autoradiographs" *Journal of Nuclear Medicine* **34**, pp. 1811–1817 (1993).

[25] J.L. Humm, R.M. Macklis, Y. Yang, K. Bump, and L.M. Chin "Image analysis for the study of radionuclide distribution in tissue sections" *Journal of Nuclear Medicine* **35**, pp. 1217–1225 (1994).