

Geant4 Estimation Model of High Z Atom Concentration for Tumor Vessel Ablation

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Abstract—In our novel technique of tumor vessels treatment, High Z (HZ) contrast atoms are injected into the blood vessel and the tumor region is irradiated with “narrowband” fluorescence photon (FP) beam tuned to the “resonance energies”. Theoretically, this technique guarantees a dose $10^2 - 10^3$ higher than that achieved in conventional radiation therapy (RT). Meanwhile, this high dose is confined to a region of tens of micrometers. This will minimize the side effects caused by the high dose to the surrounding tissues. The FPs are generated by electrons impinging onto target made of the same material as the HZ contrast. In order to support the experiment, an estimation model has been developed based on Geant4 Monte Carlo (MC) simulation. This model takes into account physical and biological factors, which can be determined separately. In this work, the derivation of the model was described in detail, and four HZ atoms, gadolinium (Gd), platinum (Pt), gold (Au) and uranium (U) were evaluated using the model. The scaling law for the capability to yield FPs from IEs had been deduced for these HZ atoms. The results also showed that the minimum molar concentration required for apoptosis of tumor endothelial cells (ECs) for Gd, Pt, Au and U in normal experimental condition were 220.44 nmol/ml, 55.57 nmol/ml, 49.78 nmol/ml and 9.05 nmol/ml, respectively.

I. BACKGROUND AND INTRODUCTION

DESTRUCTION of tumor vessels is a promising method of inhibiting the supply of oxygen and nutrients and preventing tumor growth and progression. The R-Matrix Theory [1, 2] revealed the existence of large resonance complexes in photo-absorption by high-Z (HZ) atoms at precisely located energies, namely, the “resonance energies”. Orders of magnitude higher preferential dose absorption within the range of Auger electrons (AE) released from the HZ atoms can be gained due to fluorescent cascade following the implosion of “hollow atoms”. In our novel technique, by combining a “narrowband” photon beam tuned to the resonance energy of HZ atoms together with contrast media (CM) consisting of these HZ atoms being injected into the blood, tumor vessel endothelium can theoretically be treated by a dose $10^2 - 10^3$ higher than what is achieved by conventional radiation therapy through AE irradiation from the contrast atoms within a limited range. These AEs will significantly enhance the killing of immature tumor endothelial cells (ECs) but will not be energetic enough to damage mature myoblasts and fibroblasts beyond the range of

AE, which is typically tens of micrometers in normal vessels.

The concentration of the HZ atoms in the blood is crucial in generating the AEs from the radiation of “narrowband” fluorescence photon (FP) tuned to the HZ atom of specific kind. Sufficient amounts of AEs have to be released from the HZ atoms to ensure apoptosis of the tumor ECs. The “narrowband” FPs can be realized by employing electrons with energy barely above the K shell binding energy of the HZ atom impinging onto HZ target and filtering out the low energy part in the spectrum. The induced FP to incidence electron (IE) ratio is dependent on the choice of the HZ materials. An estimation model has been developed together with Geant4 Monte Carlo (MC) simulation to evaluate the minimum molar concentration of the HZ contrast required in the blood that ensures the apoptosis of tumor ECs. The efficiencies of generating FPs from IEs for four HZ atoms, gadolinium (Gd), platinum (Pt), gold (Au), and Uranium (U) are also compared in this work.

II. MATERIALS AND MODELING

A. The Physical Process and Factors

The physical processes involved in the estimation can be summarized as follows: 1. Electrons impinge on the HZ target and induce FPs. An electron gun of sufficient energy is used to generate the electron beam. 2. The FPs interact with the nanoparticles, chemotherapy agents or imaging contrast of the same HZ atoms in the blood and release AEs. 3. AEs emitted from the HZ contrast hit the nucleoli of tumor ECs and cause DNA double strand break and consequent apoptosis of the cells.

In this model the SI units are adapted. Based on the physical processes, the main factors involved in the modeling are list below:

1. The current of IEs is I in unit of mA. The number flux rate (FR) for IE is ψ_{IE} in number/s and the surface flux density (FD) is σ_{IE} in number/($\text{cm}^2 \cdot \text{s}$).
2. The induced FP to IE number-ratio is represented by $r_{FP/IE}$, and the surface FD of FP is σ_{FP} , which has the unit of number/($\text{cm}^2 \cdot \text{s}$).
3. The efficiency of AEs being released by FPs in HZ contrast is symbolized by the number ratio $r_{AE/FP}$.

which means out of $(1/r_{AE/FP})$ FPs impinging upon a HZ atom, there is one AE being released from the atom. The average range of AE is d_{AE} in μm .

4. The probability of released AE being in the direction towards the EC is p_{AE} .
5. EC is very flat with a central nucleolus. The average area of ECs is A_{EC} in μm^2 , typically, EC has a rectangular shape, with length of l_{EC} μm , width of w_{EC} μm , and thickness t_{EC} μm .
6. A HZ atom has a diameter of D_{HZ} in μm and a two dimension projection area of A_{HZ} μm^2 .
7. The mole concentration of HZ contrast in the blood is C_{HZ} mol/ml and the overlapping factor is O , which is related to the degree of crowding of HZ atoms in blood.
8. There are n_B DNA bases (Bs) in a single EC nucleolus. Normally there are 6×10^9 Bs in a cell. And the ratio r_{BD} measures the minimum ratio of base damage that causes the DNA not repairable, thus genomes are no longer replicable, in other words, the apoptosis of the tumor cell.
9. The volume ratio of all Bs in a cell to the cell is $r_{B/C}$.

B. Flux Rate and Flux Density of Incidence Electrons

The number FR of IEs ψ_{IE} can be estimated from the current of electron and the charge of an electron, q_e , which has a value of 1.602×10^{-19} C. The relation between the current of IEs, I , in mA, and the number FR is given by, with conservation of unit,

$$\psi_{IE} = I / (1000 \times q_e), \quad (1)$$

which has the unit of number/s. If the IEs are confined to an incidence area of A_{IE} in cm^2 , the surface FD is

$$\sigma_{IE} = \psi_{IE} / A_{IE}. \quad (2)$$

C. Fluorescence Photon to Incidence Electron ratio and Flux Density

Geant4 MC Simulation is employed to estimate the fluorescence photon flux rate (FPFR) induced by electrons impinging upon the HZ target. A virtual setup of the experiments is described in Fig. 1.

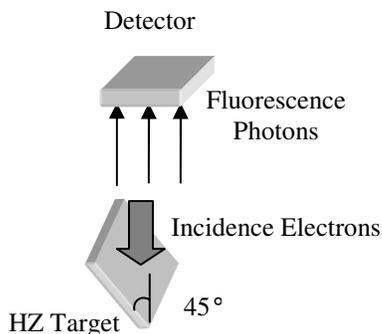


Fig. 1. Scheme of Virtual Setup in Geant4 Simulation

Electron beam of $1 \text{ cm} \times 1 \text{ cm}$ is impinging on a HZ target with an angle of 45° and the FPs are collected by a detector of $1 \text{ cm} \times 1 \text{ cm}$, which is 180° to the direction of the IEs. The FP to IE number-ratio $r_{FP/IE}$ is calculated by dividing the number of FPs collected by the detector by the number of IEs. Therefore, σ_{FP} , the surface FD of FP is

$$\sigma_{FP} = r_{FP/IE} \cdot \sigma_{IE} \quad (3)$$

D. Endothelial Cell Block

The endothelial cell block (ECB) is the elementary unit for evaluation of the HZ contrast concentration in the blood that ensures sufficient amounts of AEs being generated to kill the tumor EC. The ECB is defined as the block region in the interface at EC and blood in which the AEs released from HZ atoms are able to reach the EC on top, which requires the body diagonal of ECB, d_{ECB} , be less than or equivalent to the average range of AE, d_{AE} . This is illustrated in Fig. 2.

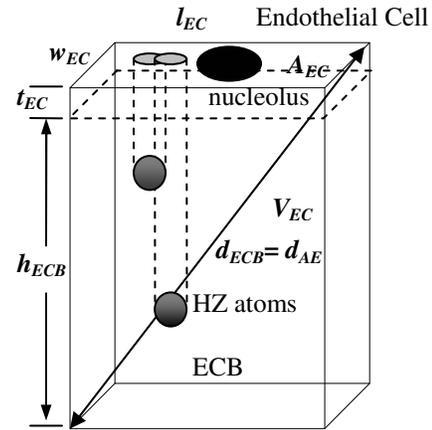


Fig. 2. Endothelial Cell Block and HZ Atoms in ECB.

Therefore, the ECB is constructed such that the height of ECB, h_{ECB} , is

$$h_{ECB} = (d_{AE}^2 - l_{EC}^2 - w_{EC}^2)^{1/2} - t_{EC}, \quad (4)$$

for $d_{AE}^2 \geq l_{EC}^2 + w_{EC}^2$, and

$$h_{ECB} = d_{AE} / \sqrt{2}, \quad (5)$$

for $d_{AE}^2 < l_{EC}^2 + w_{EC}^2$.

The surface area of EC in μm^2 is

$$A_{EC} = l_{EC} \cdot w_{EC}, \quad (6)$$

whereas the volume of an ECB in μm^3 is

$$V_{ECB} = A_{EC} \cdot h_{ECB}, \quad (7)$$

and the area of the nucleolus of an EC in μm^2 is given by

$$A_{NEC} = r_{N/C} \cdot A_{EC}. \quad (8)$$

E. Overlapping Factor

Diameter of HZ atom is D_{HZ} in μm . So maximally there are $1/(\pi D_{HZ}^2/4)$ atoms closely placed per μm^2 without overlapping. If the number of atoms in an ECB is n_{HZ} , there

will be n_{HZ}/A_{EC} atoms under every μm^2 surface in the ECB. The overlapping factor (OF) is defined as

$$O = (n_{HZ}/A_{EC}) \cdot (\pi D_{HZ}^2/4), \text{ for } O > 1, \\ O = 1, \text{ for } O \leq 1. \quad (9)$$

The significance of OF is that if there are more than $1/(\pi D_{HZ}^2/4)$ of atoms under $1 \mu\text{m}^2$ surface in ECB, some of the atoms must be overlapped in the projection to the surface and the total projection area on the surface is just A_{EC} .

F. Number of Fluorescence Photons Impinging on HZ Atoms in Endothelial Cell Block

The projection area of a HZ atom on the surface of ECB is A_{HZ} in μm^2 . There are n_{HZ} atoms in an ECB. With the surface FD of FP being σ_{FP} , the number of FP impinging onto the HZ atoms is given by

$$n_{FP} = n_{HZ} \cdot A_{HZ} \cdot \sigma_{FP} \cdot t, \quad (10)$$

where t is the radiation time in s.

G. Number of Auger Electrons Needed in Endothelial Cell Block to Kill Tumor Cell

The minimum number of base damage caused by Auger electrons in order to get the tumor EC killed is

$$n_{BD} = r_{BD} \cdot n_B. \quad (11)$$

Consider the volume ratio of all Bs to EC is $r_{B/C}$, and after the creation of the AE, the possibility of the AE hitting the cell (surface of ECB) is p_{AE} , the number of AEs needed is

$$n_{AE} = n_{BD} / (p_{AE} \cdot r_{B/C}). \quad (12)$$

H. Molar Concentration of HZ

Number of HZ atom in an ECB n_{HZ} is evaluated by

$$n_{AE} = r_{AE/FP} \cdot n_{FP}, \quad (13)$$

together with (10), yielding

$$n_{HZ} = n_{AE} / (r_{AE/FP} \cdot A_{HZ} \cdot \sigma_{FP} \cdot t),$$

which can be further expanded to, with (11) and (12),

$$n_{HZ} = \frac{r_{BD}}{p_{AE} \cdot r_{B/C} \cdot r_{AE/FP}} \cdot \frac{n_B}{A_{HZ} \cdot \sigma_{FP} \cdot t}. \quad (14)$$

Notice that σ_{FP} could be modified with (1)-(3) as

$$\sigma_{FP} = (r_{FP/IE} \cdot I) / (1000 \cdot q_E \cdot A_{IE}). \quad (15)$$

With $A_{HZ} = \pi \cdot D_{HZ}^2 / 4$, (14)-(15), and conservation of units, Number of HZ atom becomes

$$n_{HZ} = \frac{4 \times 10^{11}}{\pi} \cdot \frac{r_{BD}}{p_{AE} \cdot r_{B/C} \cdot r_{AE/FP} \cdot r_{FP/IE}} \cdot \frac{n_B \cdot q_E \cdot A_{IE}}{D_{HZ}^2 \cdot I \cdot t}. \quad (16)$$

Assuming the HZ atoms are distributed in blood homogeneously, the molar concentration c_{HZ} in mol/ml is given by

$$c_{HZ} = n_{HZ} \cdot 10^{12} / (N_A \cdot V_{ECB}),$$

where N_A is Avogadro Constant, which equals to 6.02×10^{23} atoms/mol, and the factor of 10^{12} comes from the conversion from μm^3 to ml. With (6), (7), and (16), c_{HZ} can be written as

$$c_{Gd} = \frac{4 \times 10^{23} \cdot r_{BD}}{\pi \cdot p_{AE} \cdot r_{B/C} \cdot r_{AE/FP} \cdot r_{FP/IE}} \cdot \frac{n_B \cdot q_E \cdot A_{IE}}{N_A \cdot D_{HZ}^2 \cdot l_{EC} \cdot w_{EC} \cdot h_{ECB} \cdot I \cdot t} \quad (17)$$

where h_{ECB} is given by (4) or (5).

III. SIMULATION RESULTS AND DISCUSSION

A. Number Ratio of Fluorescence Photon to Incidence Electron for Gd, Pt and Au.

Geant4 MC Simulations had been done for Gd, Pt, Au and U with virtual setup illustrated in Fig 1. For these HZ target, electron sources with energy 1.5 times of the K shell binding energy were used. 100M electrons from source area of $1\text{cm} \times 1\text{cm}$ were launched towards the HZ target which had a 45° angle with IEs. The FPs with 180° from the IEs originated from the electrons jumping from other shell to K shell were collected by a detector 1 cm away from the target, with area of $1\text{cm} \times 1\text{cm}$. In the simulation A_{IE} was 1cm^2 . Fluorescence spectrum from K shell ionization of Au is given in Fig 3. In the graph, y axis represents the energy ratio of FPs at certain energy level over IEs at 121keV. For instance, the spike at 69.05keV represents that the ratio of energy carried by 69.05keV K shell FPs over the total incidence energy of IEs is 15.1×10^{-6} .

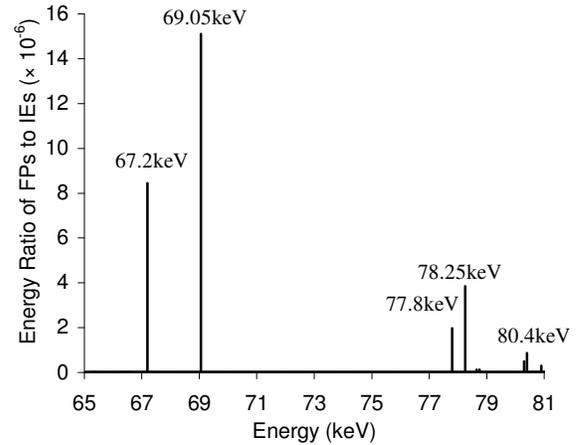


Fig. 3. Fluorescence Spectrum from K Shell ionization of Au

Incidence energy of the IEs, the average FP energies, and FP to IE number ratios for these HZ atoms are shown in Table 1.

TABLE 1
Fluorescence Photon to Incidence Electron Number Ratio $r_{FP/IE}$

HZ atoms	IE Energy (keV)	Average FP Energy (keV)	Number Ratio of FP/IE (10^{-5})
Gd	75.4	44.10	3.08
Pt	117.6	68.69	5.109
Au	121	70.66	5.377
U	173.4	101.14	7.092

If the number ratio is plotted against atomic number of these HZ atoms, the result indicates that output efficiency ratio to yield FPs from IEs is linearly proportional to the atomic number. The plot of FP to IE number ratio vs. atomic number and the linear equation that fits the data are shown in Fig. 4.

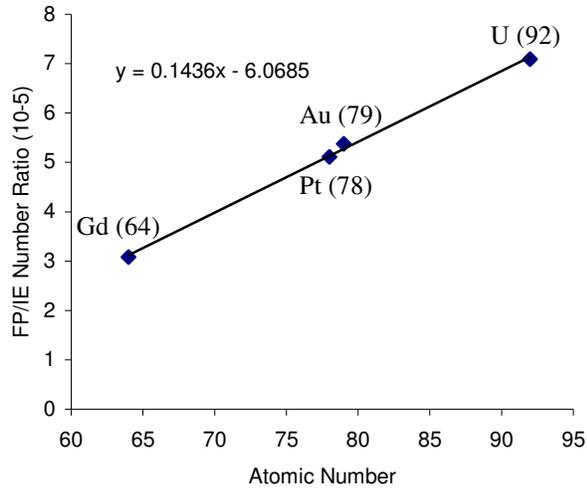


Fig. 4. FP/IE Number Ratio vs. Atomic Number for Gd, Pt, Au and U

B. Evaluation of the Factors

In (17), as mentioned before, $n_{BP}=6\times 10^9$, $q_E=1.602\times 10^{-19}C$, $A_{IE}=1cm^2$, $N_A=6.02\times 10^{23}$, D_{HZ} is 1.96×10^{-4} for the covalent radius of Gd and U atoms, whereas 1.36×10^{-4} for the covalent radius of Au and Pt atoms. In the estimation $I=10mA$ and the radiation time t is set to 60 s.

Length of EC is between 25 to 50 μm , whereas width is between 5 to 10 μm and thickness is up to 5 μm [3]. In the estimation, the lower limits of length and width, and higher limit of thickness are adapted to ensure the estimated concentration is sufficient for EC of larger dimensions. Therefore, $l_{EC}=25\mu m$, $w_{EC}=5\mu m$ and $t_{EC}=5\mu m$ are used in the estimation. So the volume of EC is $625\mu m^3$.

For Gd, Pt, Au and U atoms, the minimum energies of FPs from high shell to K shell are 42.31 keV, 65.12 keV, 66.99 keV, and 94.66 keV, respectively, which give AE ranges in water to be 30 μm , 64 μm , 67 μm , and 122 μm from Geant4 database, respectively. Thus for Gd, Pt and Au atoms, h_{ECBS} are 10.81 μm , 53.70 μm , 56.96 μm , and 114.31 μm , respectively.

The volume ratio of all Bs to EC r_{BPC} is calculated in this way. The fact that the average molar mass of Bs is 330g, together with the average number of Bs in a cell being 6×10^9 , gives the mass of all Bs in a cell

$$m_{BP/Cell} = (6\times 10^9) / (6.02\times 10^{23}) \times 330 = 3.28\times 10^{-12} g.$$

With the density of DNA close to 1.7 g/cm³ and the density of cell close to 1.0 g/cm³, and volume of EC being 625 μm^3 , volume ratio of bases in a cell to cell for EC r_{BC} is estimated to

be 0.0031.

Generally the AEs are traveling homogeneously in space after being released by FPs from the HZ atoms, then p_{AE} is approximately 1/6.

Statistically on average there are one or more lethal events happening in 63% of cells with more than 1000 base damages per cell. Consider there are 6×10^9 Bs in a cell, $r_{BPD} > 2.65\times 10^{-7}$ incurs apoptosis of tumor EC.

Assumptions have been made for $r_{AE/FP}$ that for every two FP impinging on a HZ atom, there is one AE released from the atom. Thus $r_{AE/FP} = 0.5$.

C. Minimum Molar and Mass Concentration Required for Apoptosis of Tumor EC

Putting all the factors together in (17), the molar and mass concentrations for Gd, Pt, Au and U are estimated in Table 2.

TABLE 2
Minimum Molar Concentration of HZ Atoms Required for Apoptosis of Tumor Endothelial Cell

HZ Atoms	Molar Concentration (nmol/ml)	Mass Concentration ($\mu g/ml$)
Gd	220.44	34.66
Pt	55.57	10.84
Au	49.78	9.80
U	9.05	2.56

IV. CONCLUSION AND FUTURE WORK

This model can be generalized to any HZ atoms to evaluate the efficiency of a HZ atom to kill tumor ECs through the AEs released from nanoparticle or contrast atoms, as well as the concentration of these atoms needed in the blood. The physical and biological factors involved in the process are evaluated separately. Future improvements can be made for the estimation parameters. For instance, Factors p_{AE} , and $r_{AE/FP}$ can also be evaluated by Geant4 MC Simulation. r_{BPD} can be further determined by biological techniques. The scaling law generated between Gd, Pt, Au and U provides a powerful tool for guiding experimental designs involving fluorescent X-ray production, choice of nanoparticles, chemotherapy agents or imaging contrast media, and vascular disruptive radiation.

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