Simulation of Cellular Irradiation With the CENBG Microbeam Line Using GEANT4

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Abstract—Light-ion microbeams provide a unique opportunity to irradiate biological samples at the cellular level and to investigate radiobiological effects at low doses of high linear energy transfer ionizing radiation. Since 1998 a single-ion irradiation facility has been developed on the focused horizontal microbeam line of the CENBG 3.5 MV Van de Graaff accelerator. This setup delivers in air single protons and alpha particles of a few MeV onto cultured cells, with a spatial resolution of a few micrometers, allowing subcellular targeting. In this paper, we present results from the use of the GEANT4 toolkit to simulate cellular irradiation with the CENBG microbeam line, from the entrance to the microprobe up to the cellular medium. We show that a 3 MeV incident alpha particle may deliver a dose of 0.33 Gy to a typical cell nucleus.

Index Terms—Cellular irradiation, GEANT4, microbeam, microdosimetry, Monte Carlo, ray tracing.

I. INTRODUCTION

The risk to human health caused by exposure to low dose of radiation (<200 mSv) like environmental exposure (radon, medical imaging, telluric, air flights, etc.) is currently only estimated from high dose data extrapolation [1]. Monte Carlo tools could provide a novel approach by simulating the micrometer and nanometer scale effects of radiation on biological samples [2]. Our understanding of the biological effects of ionizing radiation requires a profound knowledge on interaction of ions with biological cells and tissues. For that purpose, the CENBG has developed a focused microbeam line allowing the irradiation of single cells with a micrometer targeting accuracy [3], [4]. The object oriented simulation toolkit GEANT4 [2] allows us to follow ion diffusion through the CENBG microbeam line elements (beam pipe residual gas, collimators, focusing magnetic quadrupoles, single ion transmission detector, exit window, air gap, irradiation well, etc.), which can increase the spatial and energy dispersions of the beam and degrade the targeting resolution. First estimations of GEANT4 simulation capabilities at the micrometer scale appear promising, encouraging us to study for the first time the entire experimental setup, paying particular attention to the modeling of the magnetic lenses [5]. From this simulation, we can estimate the dose deposit in a typical cell nucleus at the micrometer scale, a first step in the simulation of radiation effects at the cellular level in the framework of the Monte Carlo tool GEANT4.

II. THE MICROBEAM LINE SETUP

The microbeam line of CENBG allows single ion irradiation of individual cells with proton or alpha particles. The incident beam is strongly collimated using a 5 μm circular object collimator and a 10 μm circular diaphragm, 6 m away from the collimator, allowing to reach a low flux mode required for single ion irradiation (typically a few hundred particles on target per second). The residual air pressure of the whole beam line is kept under 5 × 10^-6 mbar. The beam is then focused using four magnetic quadrupoles in the so-called Dymnikov magnetic configuration, leading to symmetrical transverse demagnification factors $D_x = D_y = -1/10$ on target. Their gradients $G_1$ and $G_2$ have been iteratively adjusted with preliminary GEANT4 simulations in order to focus the beam on the cellular target location, 235 mm away from the physical exit of the last quadrupole. Single ions are counted using a 3.5-mm-long isotube proportional counter running at a gas pressure of 10 mbar; a 10 μm circular collimator ensures the pressure transition between the beam pipe and the counter. The beam is extracted back into the air through a 150 nm square Si$_3$N$_4$ window (1 mm$^2$) and is sent through a 100 μm ambient air gap to a 4 μm polypropylene foil, where HaCat cells have attached and grown. HaCat cells represent one of the standard epithelial cellular lines and are obtained from human adult keratinocytes. They are widely used in radiobiology. The cells are kept alive in a dedicated well containing keratinocyte growing medium, sealed by a microscope glass slide. The whole beam line geometry and associated materials have been simulated with GEANT4 (version 5.2) and are shown on Fig. 1. We have used the Low Energy Electromagnetic Package (with associated data G4LOWEM2.2) [6]. Ion processes include multiple scattering simulated with the G4MultipleScattering class, and ionization simulated with the G4hLowEnergyIonization class using the electronic stopping power table ICRU_R49He (the ”chemical effect” option was not used) [7]. To ensure reliable multiple scattering modeling and to reproduce experimental beam straggling measurements performed on the microbeam line, we have forced a maximum elementary step length in each volume equal to one-tenth of the corresponding volume thickness along the beam propagation axis $z$. The value of the secondary particle cut has been uniquely set to 100 μm. These cuts have been optimized from a comparison between GEANT4 beam straggling simulations through thin polymer foils and experimental measurements performed on the CENBG microbeam line [5].

The GEANT4 DNA Project: http://www.ge.infn.it/geant4/dna/.

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1The GEANT4 DNA Project: http://www.ge.infn.it/geant4/dna/.
III. INCIDENT BEAM PROPERTIES

The modeling of ion beam transportation in the microbeam line requires the knowledge of several beam-optical parameters. In the absence of acceleration along the \( z \) propagation axis, the transverse motion of the beam can be represented by ellipses in the phase spaces \( (x, x') \) and \( (y, y') \) where \( x' = p_x/p_z \), \( y' = p_y/p_z \) represent, respectively, the beam angular divergences \( \theta \) and \( \phi \), and \( p_x, p_y, p_z \) stand for the three coordinates of the beam momentum. The beam is delivered to the microbeam line through a 5 \( \mu \text{m} \) diameter circular collimator with a maximum divergence of 0.5 mrad. To quantify higher order aberrations of the focusing system, we have chosen to describe the beam external envelope at the collimator \( z \) location by ellipses in the phase spaces \( (x, \theta) \) and \( (y, \phi) \), identical on both transverse axes

\[
\frac{x^2(\mu\text{m}^2)}{2.5^2} + \frac{\theta^2(\text{rad}^2)}{0.5^2} = 1 \tag{1}
\]

\[
\frac{y^2(\mu\text{m}^2)}{2.5^2} + \frac{\phi^2(\text{rad}^2)}{0.5^2} = 1. \tag{2}
\]

In a nonaccelerating field, the beam emittance \( E \) remains constant and is defined from the ellipse surface \( A \)

\[
E = \frac{A}{\pi} = 1.25 \mu\text{m} \times \text{mrad.} \tag{3}
\]

GEANT4 is able to calculate the evolution of the beam space phase along the beam propagation axis as shown on Fig. 2, allowing a precise description of the beam properties along the line.

The irradiation setup described in this paper has been optimized for high linear energy transfer (LET) 3 MeV alpha particles. The beam kinetic energy distribution is assumed to be Gaussian with a mean of 3 MeV and a full-width at half-maximum of 0.150 keV. The corresponding quadrupole focusing gradients have been calculated iteratively with GEANT4: \( G_1 = 3,406 \pm 0.001 \text{ Tm}^{-1} \) and \( G_2 = 8,505 \pm 0.001 \text{ Tm}^{-1} \). The corresponding beam profiles in both transverse planes along the beam propagation axis are shown on Fig. 3, as well as the beam spot shape near the target plane.

IV. THE FOCUSING QUADRUPOLET

A. Fringing Field Description

GEANT4 can track a charged particle in any type of magnetic field, as long as the field can be described analytically. It takes approximately 3 s on a Intel Xeon 2.7 GHz PC using the Linux RedHat 7.2 operating system and the gcc 2.95.2 compiler, to track a single charged particle with a maximum step length of 100 \( \mu \text{m} \) in the magnetic field region. In order to calculate the particle trajectories through the quadruplet system, we have chosen to describe the magnetic field profile using the Enge model [8], including the modeling of fringing fields. In the case of a perfect quadrupole, without fringing field, the magnetic field inside the quadrupole is simply given by \( B_x = yG \) and \( B_y = xG \). When including the fringing field, these expressions become

\[
B_x = y \left[ G - \frac{1}{12} (3x^2 + y^2) \frac{d^2G}{dz^2} \right] + \text{higher orders} \tag{4}
\]

\[
B_y = x \left[ G - \frac{1}{12} (3y^2 + x^2) \frac{d^2G}{dz^2} \right] + \text{higher orders} \tag{5}
\]

\[
B_z = xy \left[ \frac{dG}{dz} - \frac{1}{12} (x^2 + y^2) \frac{d^3G}{dz^3} \right] + \text{higher orders} \tag{6}
\]
where $G \equiv G(z) = G_0 K(z)$. $G_0$ is the gradient value in the case of a perfect quadrupole. $K(z)$ can be estimated using the experimental profile of the field measured through the lens axis, at a given nonzero radius. Enge uses the following formula:

$$K(z) = \frac{1 + e^{F_0}}{1 + e^{P_0(z)}}$$  \hspace{1cm} (7)

where

$$s = \frac{(z - z_1)}{a_0} \text{ if } z > z_1$$  \hspace{1cm} (8)

$$s = -\frac{(z + z_1)}{a_0} \text{ if } z < -z_1$$  \hspace{1cm} (9)

$P_n(z) = c_0 + c_1 s + c_2 s^2$.  \hspace{1cm} (10)

$z_1$ is the quadrupole positive lower limit of the fringing field region and $a_0$ is the bore radius of the element $a_0 = 10$ mm.

Then

$$\frac{dK}{dz} = -(1 + e^{F_0}) \frac{dP}{dz} \frac{1}{(1 + e^{P(z)})^2} e^{P(z)}$$  \hspace{1cm} (11)

$$\frac{d^2K}{dz^2} = -(1 + e^{F_0}) e^{P(z)} \times \left[ \frac{d^2P}{dz^2} \frac{1}{(1 + e^{P(z)})^2} + 2 \frac{d^2P}{dz^2} \frac{1}{1 + e^{P(z)}} \frac{1}{1 + e^{F_0}} \frac{dK}{dz} \right]$$  \hspace{1cm} (12)

$$\frac{d^3K}{dz^3} = -(1 + e^{F_0}) e^{P(z)} \times \left[ -\frac{1}{(1 + e^{F_0})^3} \left( \frac{d^3P}{dz^3} + 3 \frac{d^2P}{dz^2} \frac{d^2P}{dz^2} \frac{d^2P}{dz} + \frac{dP}{dz} \frac{d^2P}{dz^2} \right) + \frac{1}{1 + e^{F_0}} \frac{dK}{dz} \frac{d^2P}{dz^2} \frac{d^2P}{dz^2} \right]$$  \hspace{1cm} (13)
For a given quadrupole, the uniform field region extends from \( z = -z_1 \) to \( z = z_1 \). The fringing field region extends from \( -z_2 \) to \( -z_1 \) and from \( z_1 \) to \( z_2 \). Beyond \( z_2 \) (or \( -z_2 \)), the field is zero. The \( c_i \) coefficients and the value of \( z_1 \) must be adjusted in order to fit to the experimental profile of the field, which has not been measured yet in our system. However, we have chosen typical values [9]: \( c_0 = -5, c_1 = 2.5, c_2 = -0.1, z_1 = 6 \) cm, and \( z_2 = 13 \) cm, leading to an effective length \( L_e \) of 16.5 cm (the quadrupole geometrical length is 15 cm and it is distant from the next one by 4 cm), where \( L_e \) is defined by

\[
B_0 L_e = \int_{z=-z_1}^{z=-z_2} B_r(z)dz.
\]

\( B_0 \) is the value of the field at \( z = 0 \) and \( r = 3\sqrt{2} \) mm is chosen to have a nonzero value of \( B_r \). The whole field profile within the quadruplet is shown in Fig. 4.

### B. Intrinsic Aberrations

For the chosen gradient configuration, preliminary GEANT4 simulation allows the extraction of intrinsic aberration coefficients up to any order from the dependence of the beam transverse position on target as a function of:

1) the initial angles \( \theta \) and \( \phi \), for the spherical aberrations (see Fig. 5)

\[
\langle x|\theta \rangle = 1.6 \mu m/\text{mrad} \quad \text{(astigmatism, first order)}
\]

\[
\langle y|\phi \rangle = 2.8 \mu m/\text{mrad} \quad \text{(astigmatism, first order)}
\]

\[
\langle x|\phi^3 \rangle = -8.7 \mu m/\text{mrad}^3 \quad \text{(spherical, third order)}
\]

\[
\langle y|\phi^3 \rangle = -25.5 \mu m/\text{mrad}^3 \quad \text{(spherical, third order)}
\]

\[
\langle x|\phi^3 \rangle = -39.3 \mu m/\text{mrad}^3 \quad \text{(spherical, third order)}
\]

\[
\langle y|\phi^3 \rangle = -38.7 \mu m/\text{mrad}^3 \quad \text{(spherical, third order)}
\]

2) the initial beam transverse position and \( \delta = \Delta p/p \) for the second order chromatic aberrations

\[
\langle x|\delta \rangle = -0.02 \mu m/\text{mrad}\%
\]

\[
\langle y|\delta \rangle = -0.02 \mu m/\text{mrad}\%
\]

\[
\langle x|\phi \delta \rangle = -103.7 \mu m/\text{mrad}\%
\]

\[
\langle y|\phi \delta \rangle = -153.2 \mu m/\text{mrad}\%.
\]

From these coefficients, it is possible to illustrate the contribution of the high order aberrations to the beam spot shape on target, as shown in Fig. 6, allowing the design of specific collimator geometries to remove the image distortions. A precise determination of these coefficients could also help in the iterative optimization of the quadruplet field gradients.

### C. Tracking Precision

The study of the transverse displacement in the image plane as a function of shooting angles over a wide range of angles (\( 10^{-1} \) mrad down to \( 10^{-10} \) mrad) shows a smooth polynomial variation in both planes (see Fig. 7) and gives us confidence in the GEANT4 tracking capabilities at this scale.

### V. CELLULAR IRRADIATION

#### A. Beam Energy and Spatial Distributions on Target

The beam energy and spatial distributions obtained with 20,000 incident alphas are shown in Fig. 8 for a pipe residual air pressure of \( 5 \times 10^{-6} \) mbar. A Gaussian fit to the energy distribution gives us the following estimate: \( \langle T \rangle \pm \sigma_T = 2.37 \pm 0.01 \) MeV. The alpha beam has consequently lost a total of 633 ± 13 keV before reaching the target cell. Most of the energy loss occurs in the polypropylene foil (~18.4%) and in the Si3N4 window (~1.7%). The loss in the gas detector and
m diameter circular area. Assume entrance collimator. The diode diameter area; then the probability at the Bragg peak just before leaving the pipe residual air is replaced by vacuum, the energy loss does account for less than 1%. When the beam pipe residual air is replaced by vacuum, the energy loss does not change significantly.

B. Targeting Probability

From these distributions, we can estimate the probability of targeting an alpha particle in a given area at the target location, typically a 10 μm diameter circular area. Assume \( N_d \) is the number of alphas detected by the isobutane counter and \( N_a \) is the number of particles among them which spread at the target location inside the 10 μm diameter area; then the probability \( p_a \) is simply defined as [10]

\[
p_a \pm \sigma_{p_a} = \frac{N_a}{N_d} \pm \sqrt{\frac{p_a(1-p_a)}{N_d}}. \tag{15}
\]

In the case of a pure vacuum beam pipe, the probability reaches \( p_a \pm \sigma_{p_a} = (90.4 \pm 0.1)\% \) and decreases down to \( p_a \pm \sigma_{p_a} = (70.5 \pm 0.8)\% \) when the pressure is raised to \( 5 \times 10^{-6} \) mbar. Experimentally, \( p_a \) can be estimated by replacing the irradiation well by a PIN diode with a 10 μm entrance collimator. The diode counts the alpha particles spread on the collimator aperture. We have measured \( p_a \approx 80 \sim 90\% \) at \( 5 \times 10^{-6} \) mbar, which is in reasonable agreement with our simulation.

C. Dose Calculation

We have estimated the dose deposited by the alpha beam in a typical HaCat cell. The dose \( D_a \) deposited in the cell nucleus by a single alpha particle is classically calculated from the macroscopic definition of dose as the ratio of the total energy lost within the nucleus to the mass of the nucleus [11]. The same procedure is applied to calculate the dose deposit in the cytoplasm. The nucleus and cytoplasm have been modeled from confocal microscopy images as tubes of elliptical cross section, fixed on the polypropylene foil along their revolution axis. For the cytoplasm, the half-axes are 4.35 and 7.3 μm long and the tube length is 15 μm. For the nucleus, the half-axes are 3.5 and 6.25 μm long and the tube length is 9.5 μm. Both are made of water. The frequency distribution of the doses for alpha particles that have hit the cell is shown in Fig. 9. The dose distribution in the cytoplasm shows two populations: the low dose part corresponding to alpha particles that have crossed both the cytoplasm and the nucleus, and the higher dose part, corresponding to alphas that have hit the cytoplasm near the edge, without reaching the nucleus. The projectile average LET is \( \sim 150 \) keV/μm when it reaches the cell cytoplasm. It goes up to \( \sim 250 \) keV/μm at the Bragg peak just before leaving the cell. The projectile is finally stopped in the keratinocyte growing medium. The most probable dose deposit in the nucleus is estimated to be

\[ D_a \approx 0.33 \text{ Gy}. \]

From this estimation, it appears that a 3 MeV alpha beam may deliver doses to cellular nuclei up to a few tenths of a gray, in agreement with previous calculations [11].

VI. CONCLUSION

This paper shows GEANT4’s capabilities and flexibility in the simulation of cellular irradiation experimental setups at the micrometer scale. The CENBG irradiation microbeam line will soon provide experimental data at this scale that will contribute to validate our simulations. In the near future (2005), a new generation Singletron accelerator will be installed at CENBG. A nanobeam line will be developed for cellular irradiation, pro...
Fig. 8. (a) shows in black the alpha beam kinetic energy distribution in the target plane, adjusted to a Gaussian distribution $\left( T' = 2.37 \pm 0.01 \text{ MeV} \right)$, and the transparent background shows alphas that have been scattered by the diaphragm edges before reaching the target plane. These two populations reach the cultured cells. (b) shows the corresponding spatial distributions in the target plane. The central peak shows the position distribution of the alpha particles whose energy distribution has been adjusted with the Gaussian distribution. The low statistics background shows the position of the alphas that have been scattered by the diaphragm. The beam is spread inside a square of side slightly over 1 mm, limited by the 1 mm$^2$ surface of the Si$_3$N$_4$ window. (c) shows the beam spatial distribution when the residual low pressure air inside the beam pipe has been replaced by vacuum. No diaphragm scattering has been observed in this case.

Fig. 9. Frequency distribution of the doses delivered to the HaCat cell cytoplasm or nucleus by a single projectile. The thin-line distribution shows the dose distribution in the cytoplasm. The low dose part corresponds to particles crossing both the cytoplasm and the nucleus. The higher dose part is deposited by alpha particles that hit the cytoplasm only, without reaching the nucleus. The thick-line distribution shows the dose distribution in the nucleus, with a most probable value of $\sim 0.33$ Gy.

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