Human lymphocytes exposed to co irradiations and i decays

Chapter 1: Introduction

1. 1. Microdosimetry & Problem statement

Nuclear medicine and molecular imaging use unsealed radionuclides for diagnostic or therapeutic purposes. In targeted radiotherapy, the aim is to address tumor cells using suitable radiopharmaceuticals and achieve a high dose deposition inside the target structures. “ Macrodosimetry” generally entails estimating the dose effect in organs (or dimensions of at least some millimeters) and is outlined in detail by the Medical Internal Dose (MIRD) Committee, the U. S. Society of Nuclear Medicine and the International Commission of Radiological Protection (ICRP) [1]. Microdosimetry therefore entails estimating the dose absorbed in microscopic objects such as cells. Dose deposition in cells can originate from extracellular media, intracellular uptake in a single cell and from surrounding cells.

As an alternative to characteristic photon emissions, radionuclides decaying by electron capture or internal conversionmay undergo a process known as the Auger effect. In the Auger effect, an electron from an outer shell fills the lower electron vacancy, but the energy released in the process is transferred to another orbital electron. This electron is then emitted from the atom instead of a characteristic X-ray [2]. The emitted electron is called an Auger electron, with ranges in tissue typically at the micro- or nanometer level [3]. Their unique property of depositing significant amounts of energy in minute volumes around the decay site opens up the possibility of using them as microscopic probes to study fundamental questions regarding the interaction of radiation with cells.

^{123} I is used mainly in nuclear medicine because of its ideal γ-ray energy (159 keV) and relatively short half-life (13. 2 h). The decay of ^{123} I is, however, also associated with the production of Auger electrons. These low energy particles (< 500 eV) have a very short range (< 25 nm) in tissue and as a result induce biological damage similar to that of high linear energy transfer radiations such as 5 MeV α-particles, provided that the isotope is allowed to decay within the cell nucleus[4].

Knowledge of the absorbed dose is required for evaluation of the observed biological effects and to predict or compare the effectiveness of different radiation modalities. However, direct dose measurements in cells are impossible due to the small cellular dimensions [5].

According to the stochastic character of all of the decay processes, a large number of pathways exist by means of which a radioactive particle can decay and the excited atom can de-excite, i. e. each initial inner shell vacancy may cause a different number of Auger electrons to be emitted resulting in a more or less broad distribution of differently charged ions. Because these electron transitions and particle interactions are random processes, the Monte Carlo technique is an appropriate tool for the simulation of Auger emissions and electron spectra, as well as a feasible method to obtain correct absorbed dose values under consideration of all irradiation aspects like geometry and activity distributions [5],[6], [7]. Bingham *et al* . found that the dose delivered to the cell nucleus is underestimated by a factor of 7. 4 for ^{123} I in cells with nuclear radius of 4 μm and cell radius of 12 μm when compared to conventional electron

dosimetry, indicating the need of developing dosimetric calculations for electrons emission at a cellular level [8].

Geant4 is an open source Monte Carlo (MC) toolkit, based on object orientated programming rules using the C++ language, which provides functions for simulating the passage of particles through matter [9]. The code is freely downloadable from the Geant4 web site. Detailed descriptions of the toolkit design and the physical fundamentals may be found in the “ Geant4 User’s Guide for Application Developers” and the “ Physics Reference Manual” [10], [11]. Besides the fact that it is entirely open-source and freely available to all users, the main advantage of this toolkit is its openness to modification and extensions.

Originally Geant4 comes from high-energy physics but it also provides low-energy physics processes necessary for medical applications. Users may construct stand-alone applications or applications built upon another object-oriented framework. In either case the toolkit offers support from the initial problem definition to the production of results and graphics for publication. At the heart of Geant4 is an abundant set of physics models to handle the interactions of particles with matter across a very wide energy range. Data and expertise have been drawn from many sources around the world, and in this respect Geant4 acts as a repository which incorporates a large part of all that is known about particle interactions[12]. All aspects of the simulation process have been included in the toolkit: the geometry of the system, the materials involved, the fundamental particles of interest, the generation of primary events, the tracking of particles through materials and electromagnetic fields, the physics processes governing particle interactions,

the response of sensitive detector components, the generation of event data, the storage of events and tracks, the visualization of the detector and particle trajectories, and the capture and analysis of simulation data at different levels of detail and refinement.

1. 2. Objectives & Aims

The level of biological effects of certain radiations is not always directly proportional to the dose they impart. Since the delivered dose on a cellular level is not directly measurable using current instrumentation, scientists and physicians have developed correlations between the biological response and the exposed dose through experiment and theory of atomic physics. An alternative method of predicting the delivered dose in a cell is by using Monte Carlo simulations. These simulations however, have to describe the biological composition and geometries of the material as accurately as possible, as well as the interactions of different particles with the material and can therefore result in complex codes and extremely long computation times.

In our study, the aim was to determine (through experiments and using Monte Carlo simulations) the relative biological effectiveness[1](RBE) of isolated and stimulated human lymphocytes exposed to ^{60} Co irradiations and ^{123} I decays.

The first phase of experiments was the exposure of 3 different types of cellsto a ^{60} Co-teletherapy unit. The proposed cell lines were: human lymphocytes, rat brain endothelial cells(bEND5, a cell with high radiosensitivity) andChinese hamster ovarian cells (CHO-K1, a cell with low

radiosensitivity). The cells were exposed to graded doses of ^{60}Co γ-radiation, after which they were cultured and the micronuclei formations in binucleated cells were used to analyze the effects of γ-radiation on the cell types.

The second phase of experiments was the exposure of a known number of isolated and stimulatedhuman lymphocytes to certain activities of ^{123}I for a discrete amount of time. The thymidine analogue 5-[^{123}I]-iodo-2-deoxyuridine (^{123}IUdR) was prepared and used to incorporate ^{123}I into theDNA of human lymphocytes. This was done such that the radionuclide could be transported across the cell and nuclear membrane to permit the deposition of Auger and Coster-Kronigelectrons in close proximity to cellular DNA. After exposure, the samples werecultured to express residual radiation damage. The cellular damage was quantified by numerating the micronuclei (MNi) frequency in binucleated (BN) cells. The experiments were done at iThemba LABS under the supervision and guidance of Prof. Slabbert and Philip Beukes.

The experimental work followed the same approach as that of Slabbert, et al[13]. In the study they focused on the targeting and accumulation of ^{123}I in human lymphocytes and CHO-K1 (a Chinese hamster ovary cell line). They found that the combined effect of intracellular and extracellular disintegrations of ^{123}I is about 3. 7 times more potent to lymphocytes compared to when the disintegration of the radionuclide is restricted to only the extracellular medium, among other results. It was concluded that this

enhancement is due to the short range Auger electrons emitted by the isotope.

Next, we wished to recreate the above experiments through Monte Carlo simulations and thereby determine as accurately as possible the absorbed energy and dose due to the irradiations, specifically the energy and dose deposited by Auger electrons produced during the decay of ^{123} I. We will make use of a Monte Carlo based simulation code Geant4. The code must be mastered and used to simulate the scenarios mentioned above.

We attempted to simulate the above ^{60} Co exposures. This simulation was an investigation into the irradiation of a macroscopic volume by a radioactive source. The geometry was set up to replicate the experimental setup with regards to the source location and type, collimation, build-up and backscatter, the Petri dish and cellular media. The individual cells were not used as detectors, only the effective volume in the Petri dish. The energy and the dose deposited by the ^{60} Co source (γ-rays, primary and secondary electrons) was then quantified by the Monte Carlo simulation.

Our main endeavor was to simulate the energy deposition from the decay of ^{123} I within a cell using Geant4. Basically, a geometry representing a biologicalcell (with the same density, etc. as the proposed lymphocytes) was created as a detector to measure the dose, energy and particles traversing it due to a radionuclide prone to emit Auger electrons, i. e. ^{123} I. A similar simulation was performed by Bousis, et al (2012), using their in-house Monte Carlo code [14]. More advanced simulations are the calculation of DNA

strand breaks due to direct and indirect effects of Auger electrons as was demonstrated by Raisali, et al (2013), which werehowever not attempted in this investigation [15], [16], [17].

Furthermore, an empirical formula relating the activity(and consequently the absorbed dose) to the biological response was determined. The curveswere compared to other dose-response curves from literature, thereby indicating if the simulations are a viable option for predicting accurate dose depositions. We could then calculate the RBE values from our dose-response curves and compare them to values available in literature.

Finally, we aimed to determine the accuracy and feasibility of Geant4 as a simulation toolkit for medical and radiobiological purposes. To this end we considered the practicality, effort and time spent using Geant4, as well as by the comparison of RBE values and dose-response curves.

Geant4 is an advanced, extensive and comprehensive simulation toolkit. Its advantage over similar packages with regards to availability, artistic and geometric freedom, physics models and materials libraries and openness to modification are undeniable. It is a very powerful simulation toolkit and can be used in a large number of areas of expertise as is shown by the examples supplied alongside the toolkit.

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[1]RBE values indicate the effectiveness of two radiation qualities to produce a certain biological response.