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Doctoral Thesis

Development of an Integrated Stochastic Radiobiological Model for Electromagnetic Particle Interactions in a 4D Cellular Geometry

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Declaration of Authorship

I, Michael John James Douglass, certify that this thesis titled, 'Development of an Integrated Stochastic Radiobiological Model for Electromagnetic Particle Interactions in a 4D Cellular Geometry' and the work presented in it are my own. I confirm that:

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Peer Reviewed Publications

Published

1. Douglass M., Bezak E. and Penfold S., Development of a Randomised 3d Cell Model for Monte Carlo Microdosimetry Simulations. *Medical Physics*, 39:3502-3519, 2012.

2. Douglass M., Bezak E., Physical Modelling of Proton and Heavy Ion Radiation using Geant4, *EPJ Web of Conferences* 35, 2012.

3. Kempson I.M., Smith E., Douglass M., Thierry B., Liu T.Q., Howard D., DeJonge M. and Bezak E., Applications of Large Area XRF Mapping of Metals in Biology at the Australian Synchrotron *IAEA X-ray Fluorescence Newsletter*, 2012.

4. Douglass M., Bezak E. and Penfold S., Monte Carlo Investigation of the Increased Radiation Deposition due to Gold Nanoparticles using Kilo- and Mega-Voltage X-Rays in a 3D Randomized Cell Model", *Medical Physics*, 40, 2013.

Submitted for Publication

1. Douglass M., Bezak E. and Penfold S., An integrated radiobiological model for the prediction of the biological effects of protons and heavy ion radiation", *NASA Space Radiation*, 2014 (Submitted November 2013).

2. Douglass M., Bezak E. and Penfold S., Development and Calibration of a Simulation Toolkit for Cell Growth, Irradiation and Repair, Michael Douglass, *Medical Physics*, 2014 (Submitted March 2014).

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Conference Presentations and Awards

Local

- Douglass M., Bezak E., *Proton and Heavy Ion Radiotherapy*, ACPSEM (SA/NT) Student Paper Night, 2009, **1st Place (Physics Category)**.
- Douglass M., Bezak E. and Penfold S., *Proton and Heavy Ion Radiotherapy*, ACPSEM (SA/NT) Student Paper Night, 2010, **2nd Place (Physics Category)**.
- Douglass M., Bezak E. and Penfold S., *Heavy Ion Microdosimetry*, Postgraduate Poster Seminar - University of Adelaide, 2010, **"Prize for best first year physics research poster".**
- Douglass M., Bezak E. and Penfold S., *Development of a 3D randomised cell model*, Three minute thesis competition, 2010.
- Douglass M., Bezak E. and Penfold S., *Cellular Microdosimetry*, Three minute thesis competition, 2011.
- Douglass M., Bezak E. and Penfold S., *Development of a Randomized 3D Cell model for microscopic level radiation cell damages*, ACPSEM (SA/NT) Student Paper Night, 2011, **1st Place (Physics Category)**.
- Douglass M., Bezak E. and Penfold S., *Development, Testing and Application of a Complete Cell Growth, Irradiation, Repair and Death Model*, ACPSEM – SA/NT Student Paper Night, 2013, **1st Place**.
- Douglass M., Bezak E. and Penfold S., *Development, Testing and Application of a Complete Cell Growth, Irradiation, Repair and Death Model*, Adelaide University School of Chemistry and Physics Postgraduate Research Seminar, 2013, **Recipient of "Bob Crompton Award" for physics**.

National

- Douglass M., Bezak E. and Penfold S., *Development of Monte Carlo Input Code for Proton, Alpha and Heavy Ion Microdosimetric Track Structure Simulations*, EPSM, 2010. Melbourne, Australia

- Douglass M., Bezak E. and Penfold S., *Development of Monte Carlo Input Code for Proton, Alpha and Heavy Ion Microdosimetric Track Structure Simulations*, EPSM-ABEC, 2011, Darwin, Australia **"Prize for best student radiobiology presentation"**.
- Douglass M., Bezak E. and Penfold S., *Application of a Novel Cellular Microdosimetry model to investigate the impact of Gold Nanoparticles on the dose to cells*, EPSM-ABEC, 2012, Gold Coast, Australia.
- Douglass M., Bezak E. and Penfold S., *Physical Modelling of Proton and Heavy Ion Radiation Using Geant4*, Heavy Ion Accelerator Symposium, 2012, Australian National University ACT, Australia, **Prize for "Best student oral presentation**.
- Douglass M., Bezak E. and Penfold S., *Investigation of the dose enhancement effect of gold nano particles using a 3D randomized cell model*, Modelling of Tumours Meeting (MOT), 2012, Adelaide, Australia.
- Douglass M., Bezak E. and Penfold S., *Application of a Novel Cellular Microdosimetry model to investigate the impact of Gold Nanoparticles on the dose to cells*, MMND (Micro- Mini and Nanodosimetry conference), 2012, University of Wollongong, Australia.
- Douglass M., Bezak E. and Penfold S., *Development, Testing and Application of a Complete Cell Growth, Irradiation, Repair and Death Model*, 2nd Geant4 and Monte Carlo Workshop, 2013 University of Wollongong, NSW, Australia.

International

- Douglass M., Bezak E. and Penfold S., *Development of Monte Carlo Input Code for Proton, Alpha and Heavy Ion Microdosimetric Track Structure Simulations*, First Geant4 School and Users Workshop, 2010, University of Wollongong, NSW, Australia.
- Douglass M., Bezak E. and Penfold S., *Development of a Randomised 3d Cell Model for Microscopic Level Radiation Damages*, International Conference on Biological Physics, 2011, University of San Diego, CA, USA
- Douglass M., Bezak E. and Penfold S., *Investigation of the dose enhancement effect of gold nano particles using a 3D randomized cell model*, Medical Physics World Congress, 2012, Beijing, China.

- Douglass M., Bezak E. and Penfold S., *Development, Testing and Application of a Complete Cell Growth, Irradiation, Repair and Death Model*, Radiation Research Meeting 2013, New Orleans, LA, USA

"The fact that we live at the bottom of a deep gravity well, on the surface of a gas covered planet going around a nuclear fireball 90 million miles away and think this to be normal is obviously some indication of how skewed our perspective tends to be."

Douglas Adams

Abstract

An integrated radiobiological model has been developed in this thesis using the Monte Carlo toolkit "Geant4" to produce a radiobiological modelling software package. The result is a simulation capable of: (a) growing a simulated 3D cell structure (i.e. tumour or mammalian tissue) composed of individual cells (with accurate chemical composition and geometry), (b) irradiating the cells and recording the microdosimetric track structure in each cell, (c) clustering spatially correlated ionisation events into DNA double strand breaks and then (d) predicting the likelihood that any given cell will survive. The novelty of this model is its ability to predict both the microscopic and macroscopic outcome of radiobiology experiments while varying input parameters such as cell line, radiation type, tumour geometry, dose etc. Previous research in this area has been limited to simple water volumes as representations of cells and none have been combined into an integrated radiobiological model.

Model Development

Cellular Growth Model

The cellular growth model consists of two parts. The first part is a geometrical and chemical description of a single cell. The second is a cellular growth model describing the growth kinetics of a group of cells. When combined, they form a simulated macroscopic cell mass composed of individual microscopic cells.

A template was first designed within Geant4 for a single cell containing properties such as cell size, nucleus dimensions, and cytoplasm composition. Cellular dimensions and composition were obtained from previous publications.

The cellular growth model is a mathematical model which attempts to replicate the growth characteristics of either regular or cancerous cells. The code populates a volume of specified dimension and shape with cells of random dimension, rotation and position governed by the characteristics of a given cell line. A general requirement for Geant4 simulations is a non-overlapping geometry. A custom algorithm was developed in the current work to ensure that the cells in the tumour geometry did not overlap before importing into Geant4.

The time required to "grow" a tumour using this code is proportional to the number of cells in the volume. The time to produce a tumour containing approximately 10^5 cells is typically less than 1 hour. However, the time required to complete the irradiation stage of the code is strongly dependant on the number of cells in the tumour. To produce results in a reasonable amount of time, we were limited to using tumours containing less than 10^4 cells.

The position, rotation and size of each tumour were then exported to a file in a format which could be imported by our custom Geant4 simulation.

Cellular Irradiation

A method called parameterisation was used inside Geant4 to combine the single cell structure and the spatial properties of the cells (generated by the cellular growth model) to produce a cellular mass which can be irradiated virtually. To our knowledge, Geant4 has not been used to simulate particle interactions in such a large number of complex volumes. This achievement is the result of the efficiency of the unique parameterisation code developed in this thesis. The Geant4 particle tracking tool kit enables the cells to be irradiated with different types of radiation (such as protons, electrons, photons) and records the positions of the ionisation damage in each cell. For high LET radiation (such as heavy ions), the primary cell damage mechanism is direct ionisation damage. By recording the position and energy deposited in each ionisation event, the probability of a cell surviving or dying can be calculated.

The first two stages of the code were tested by predicting and quantifying the radiosensitisation effect of cells by gold nanoparticles. Gold nanoparticles were introduced into the cellular geometries and the frequency of ionisation effects within the cells was measured. It was determined that the radiosensitisation effect of gold nanoparticles is proportional to the concentration of gold within the cell, inversely proportional to the energy of the incident photon and strongly dependant on position within the cell. When the cells were irradiated with 80 kVp x-rays, the damage to the cells was determined to be approximately 10 times that of cells irradiated without gold nanoparticles. When a typical 6 MV linear accelerator x-ray beam was used to irradiate the cells, the damage to the cells was only 1.2 times higher that measured without gold nanoparticles. These results suggest that the primary dose enhancement effect is the result of the increase in photoelectric cross section caused by the local increase in the effective atomic number within the cell.

Ionisation Clustering

In order to predict the biological damage to the cells, the ionisation damage calculated in the previous two stages of the code needed to be clustered into DNA strand breakages. To cluster the ionisation events into double strand breaks, a hierarchical clustering algorithm was developed. Ionisation events are clustered into a DSB if the Euclidean distance from the centre of the DSB centroid ("centre of mass" of the cluster) is less than 3.4 nm (length of 10 base pairs in DNA). A DSB is defined to be "simple" if the cluster contains two ionisation events. A DSB is "complex" if it contains three or more ionisation events. In typical radiotherapy treatments, several grays of radiation dose are delivered. Microscopically, this corresponds to billions or trillions of individual ionisation events. When simulated computationally, this has obvious storage and processing issues. The effects of this problem were minimised by considering only a small volume of cells ($< 10^3$ cells). Even with such a small number of cells, the total number of ionisation events to process was in excess of 10^7. In terms of computational time, this section of the code is highly efficient but at the expense of system resources. The large system RAM requirements mean that the code can only be executed on a 64 bit processor in its current form.

DNA Repair Model

The basis for the DNA repair model in the current work is the two lesion kinetics (TLK) model. In the current work we have expanded on the TLK model and implemented it as a method of describing the repair of the ionisation damages produced in Geant4. The most notable improvement lies in implementing the model on a cell by cell basis instead of modelling the repair kinetics as an average of all cells in the volume (e.g. a tumour).

The DNA repair model was calibrated and tested using experimental data for V79 Chinese hamster cells irradiated with 0.76 and 1.9 MeV proton radiation. Once calibrated, the experimental and calculated values for cell survival were in good agreement ($< 7\%$ difference).

Cross Section Verification

The validity and accuracy of the Geant4 cross sectional data was tested by comparing simulated and experimental data.

Geant4 has been shown to be able to simulate radiation interactions of very low energy particles (to approximately ~ 1 eV (debated)). However, our investigation (and previous publications) has shown differences of up to $\pm 30\%$ (between simulated and experimental data) in the differential cross section of electrons and protons at energies below 100 eV. Our investigation also revealed a similar discrepancy with other comparable Monte Carlo packages including PARTRAC and RITRACKS. However, within the energy range we have investigated throughout this research, there is good agreement between both experimental data and data predicted by other MC packages.

Effect of Indirect Radiation Damages on Cellular Survival

To investigate the contribution from indirect damages in our previous studies, a MC software package called RITRACKS was used which is capable of simulating the production yields of free radical species due to the physical interactions of ionising radiation in water.

Utilising the clustering algorithm and DNA repair model from our previous Geant4 investigation, we attempted to quantify the cellular lethality of direct and indirect radiation damages. Our study has shown that for particles with LET ~ 1000 keV/µm (50 MeV/amu ^{56}Fe ions, the contribution to DNA damage from indirect damages is still approximately 50%.

Conclusion

A comprehensive radiobiological simulation has been developed capable of predicting the complex ionisation track structure of ionising radiation (e.g. photons, protons and carbon ions) through individual cells. Subsequently, predicting the biological outcome within

individual cells by tracking the formation and repair of DNA strand breaks. The capabilities of the software have been demonstrated for use in novel radiotherapy treatment techniques.

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Abbreviations

AC	**A**lternating **C**urrent
AE	**A**uger **E**lectron
ATP	**A**denosine **Trip**hosphate
CHO	**C**hinese **H**amster **O**vary
CPU	**C**entral **P**rocessing **U**nit
CSG	**C**onstructed **S**olid **G**eometry
CT	**C**omputer **T**omography
DEF	**D**ose **E**nhancement **F**actor
DER	**D**ose **E**nhancement **R**atio
DNA	**D**eoxyribo**n**ucleic **A**cid
DSB	**D**ouble **S**trand **B**reak
EBRT	**E**xternal **B**eam **R**adio**t**herapy
GBP	**G**iga **B**ase **P**airs
GEANT	**Ge**ometry **an**d **T**racking
GNP	**G**old **N**ano **P**article
GPU	**G**raphics **P**rocessing **U**nit
IGRT	**I**ntensity **G**ated **R**adio**t**herapy
IMAT	**I**ntensity **M**odulated **A**rc **t**herapy
IMRT	**I**ntensity **M**odulated **R**adio**t**herapy
LET	**L**inear **E**nergy **T**ransfer
LPL	**L**ethal **P**otentially **L**ethal
LQ	**L**inear **Q**uadratic
MC	**M**onte **C**arlo
MCDS	**M**onte **C**arlo **D**amage **S**imulation

MRI	**M**angetic **R**essonance **I**maging
PC	**P**ersonal **C**omputer
PDF	**P**robability **D**ensity **F**unctions
PET	**P**ositron **E**mission **T**omography
RAM	**R**andom **A**ccess **M**emory
RBE	**R**elative **B**iological **E**ffectiveness
RMR	**R**epair **M**is**r**epair
RNA	**R**ibo**n**ucleic **A**cid
TLK	**T**wo **L**esion **K**inetic
XFM	**X**ray **F**luorescence **M**icroscopy

Physical Constants

Speed of Light	c	=	$2.997\ 924\ 58 \times 10^{8}$ ms^{-1}
Gravitational Constant	G	=	$6.673\ 84 \times 10^{-11}$ m^{3} kg^{-1} s^{-2}
Plank's Constant	h	=	$6.626\ 069\ 57 \times 10^{-34}$ m^{2} kg s^{-1}
Fine Structure Constant	α	=	$7.297\ 352 \times 10^{-3}$
Electron Rest Mass Energy	m_e	=	510.99 keV
Proton Rest Mass Energy	m_p	=	938.27 MeV
Neutron Rest Mass Energy	m_n	=	939.56 MeV
Alpha Particle Rest Mass Energy	m_α	=	3727.37 MeV
Charge of an Electron	e	=	1.6021×10^{-19} C
Classical Electron Radius	r_e	=	$2.817\ 940 \times 10^{-15}$ m
Bohr Radius	a_0	=	0.529177×10^{-10} m
Compton Wavelength	λ_C	=	2.426×10^{-12} m
Stefan-Boltzmann Constant	σ	=	$5.670\ 373 \times 10^{-8}$ W m^{-2} K^{-4}
Boltzmann Constant	k	=	$1.380\ 658 \times 10^{-23}$ J K^{-1}
Rydberg Constant	$\mathfrak{R}$	=	$10\ 973\ 731.568 \times 10^{-1}$ m^{-1}
Avogadro's constant	N_A	=	6.0221×10^{23} mol^{-1}
Permittivity of Free Space	ϵ_0	=	8.8541×10^{-12} F m^{-1}
Permeability of Free Space	μ_0	=	$12.566\ 370 \times 10^{-7}$ N A^{-2}
Gas Constant	R	=	8.3144 J K^{-1} mol^{-1}

Symbols

D	Absorbed radiation dose	Gy
P	Power	Watts
S	Survival fraction	(dimensionless)
E	Particle energy	MeV
σ	Interaction cross section	cm^{-1}
Z	Atomic number	(dimensionless)
T	Kinetic energy	MeV
B	Binding energy	eV