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Track structure model of microscopic energy deposition by protons and heavy ions in segments of neuronal cell dendrites represented by cylinders or spheres

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ABSTRACT

Changes to cognition, including memory, following radiation exposure are a concern for cosmic ray exposures to astronauts and in Hadron therapy with proton and heavy ion beams. The purpose of the present work is to develop computational methods to evaluate microscopic energy deposition (ED) in volumes representative of neuron cell structures, including segments of dendrites and spines, using a stochastic track structure model. A challenge for biophysical models of neuronal damage is the large sizes ($>$ 100 μm) and variability in volumes of possible dendritic segments and pre-synaptic elements (spines and filopodia). We consider cylindrical and spherical microscopic volumes of varying geometric parameters and aspect ratios from 0.5 to 5 irradiated by protons, and ^{3}He and ^{12}C particles at energies corresponding to a distance of 1 cm to the Bragg peak, which represent particles of interest in Hadron therapy as well as space radiation exposure. We investigate the optimal axis length of dendritic segments to evaluate microscopic ED and hit probabilities along the dendritic branches at a given macroscopic dose. Because of large computation times to analyze ED in volumes of varying sizes, we developed an analytical method to find the mean primary dose in spheres that can guide numerical methods to find the primary dose distribution for cylinders. Considering cylindrical segments of varying aspect ratio at constant volume, we assess the chord length distribution, mean number of hits and ED profiles by primary particles and secondary electrons (δ-rays). For biophysical modeling applications, segments on dendritic branches are proposed to have equal diameters and axes lengths along the varying diameter of a dendritic branch.

1. Introduction

Radiation induced impairment of cognition, including changes to memory, involves damage to neuronal cells in the hippocampus and pre-frontal cortex (Greene-Schloesser et al., 2012; Cacao and Cucinotta 2016a, 2016b; Chakraborti et al., 2012; Parihar et al., 2015a). Cognitive changes after irradiation with protons and heavy ions are of concern in cancer treatment with particle beams and space radiation exposures to astronauts (Cucinotta et al., 2014). The dendrite and synaptic elements of neurons are the locations of chemical and electrical processes central to neuronal cell communication and have been reported to be modified by low doses of protons, heavy ions, and X-rays (Shirai et al., 2013; Raber et al., 2016).

In this paper we discuss methods to predict ED in microscopic volumes of spherical and cylindrical geometries with the goal of developing models of radiation damage to dendrites and spines of neuron cells. At this time very little is known about the mechanisms leading to changes in dendritic morphology or spine density in neuron cells and how radiation quality dependent effects are manifested (Parihar et al 2014, 2015a, 2015b). Possible mechanisms are direct energy deposition, initial and persistent production of reactive oxygen species (ROS), microglial activation and neuro-inflammation. From published experimental studies with X-rays, protons, and heavy ions, there are clear dependences on radiation quality and dose to the changes observed (Parihar and Limoli, 2013, Parihar et al., 2015a; 2015b), which suggests track structure plays an important role in changes to dendritic morphology.

An important computational challenge is the large spatial extent of the dendritic arbors of neuronal cells, which are typically 100′s of microns and dependent on neuronal cell type. Furthermore, possible geometric parameters describing dendrites and spines will be of varying diameter and length. The track structure of high energy particles consists of a core of high ED events close to the particle track ($<$ 10′s of nm) and a penumbra of secondary electrons denoted as δ-

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rays produced through ionization that may extend for 1000′s of microns or more from a primary particles path dependent on the particle velocity and kinematic constraints. Therefore computational approaches must ultimately be developed for microscopic volumes of variable sizes with significant heterogeneity in microscopic ED for different radiation types and primary particle fluence or absorbed dose.

In our previous work we considered details of neuron cell geometries, which have tree like cellular architecture (Ascoli 2006; Cucinotta et al., 2014; Alp et al., 2015) using a stochastic model of radiation track structure (RITRACKS) which has been show to have good agreement with experiments for ionization and excitation cross sections for particles and electrons, LET, and nano-dosimetry measurements (Plante and Cucinotta, 2008; 2009; 2010). Dendritic branches of neurons like cylindrical pipes extend from the cell's soma and branch out with initial diameter at the range of 2 to 3 µm and thin out at distal ends reaching the light resolution limit to approximately 0.4 µm in microscopy studies (Meijering 2010). Geometrical reconstruction of neuron branches can be made using right circular cylindrical segments of varying length and diameter, with a 3D structure constructed by rotation of azimuthal angle of consecutive segments (Ascoli et al., 2007; Ascoli 2015). Continuously varying diameters of dendrites segments sets a biological constraint on geometry and axes lengths of cylinders, which are determined by reconstruction processes in experimental studies, including sectioning of samples and image processing (Kubota et al., 2009; Peng et al., 2011).

An aim of this paper is to investigate optimal axis length of dendritic segments to evaluate microscopic ED and hit probabilities along the dendritic branches at a given macroscopic dose. The diameter of a dendritic section is a structural constraint on a dendritic branch and can vary from $>$ 5 µm close to the soma to $<$ 0.5 µm at the further tips of dendrite branches. We consider four cylindrical segments with different aspect ratios (ARs) that are chosen to represent dendritic sections close to soma (thicker diameter with different axes lengths), distal end (thinner diameter, long axis length) and very small protrusions on dendrites (both small diameter and axis length). The presentation of dosimetric parameters of the same volume spheres highlights the effects of ARs in cylinders (Kellerer 1981). An analytical method is also developed to find the mean primary particle microscopic dose in spheres for a given macroscopic dose. The fast analytical method can complement lengthy numerical studies of dose distributions for a given volume. Contributions of the primary core region and δ-rays in the penumbra to the ratio of hits and ED to micro-volumes (V_{micro}) are investigated by stochastic Monte–Carlo sampling. The probability (or mean number) of hit(s) by primary beam and δ-rays, chord length distribution of primary beam, distance between δ-ray hits to micro-volumes (impact parameter), and the variance of ED for given geometrical structure are described. This information for the same volume structures can be used to interpret the effects of radiation quality or linear energy transfer (LET) for a given absorbed dose or particle fluence (Kellerer and Chmelevsky 1975; El Naqa et al 2012, Palmans et al. 2015). The methods developed herein are applicable to a wide variety of particle types. For Hadron therapy applications we focus on the particle beams; proton, ^{3}He and ^{12}C with kinetic energies of 32, 38, and 59 MeV/n, respectively corresponding to a range of 1 cm from the Bragg peak, which are also important components of space radiation exposures.

2. Materials and methods

2.1. Stochastic track structure with RITRACKS Monte–Carlo simulation tool

The ED events from particle tracks are simulated with RITRACKS (Plante and Cucinotta 2008, 2009), a Monte–Carlo based computer model that calculates the positions of ED events due to ionization and excitation as a particle traverses a medium assumed to be water. The stochastic simulation environment for a given charged particle with an initial energy, propagation direction (e.g. along the *z*-axis) and entrance point, e.g. (0,0,0) creates ED events at varying positions for the initial particle and the created secondary electrons denoted as δ-rays, which are correlated with the particles path. Energy deposition events are lumped within a predetermined voxel size of 20 nm^{3}. The total ED in a voxel and its coordinates are an output value from the simulation. For a predetermined track length, voxel ED values and their coordinates are calculated, which includes contributions from the primary particle track and δ-rays. This stochastic process is repeated a large number of times using Monte–Carlo techniques with the same initial conditions to create a library of histories for a particle's ED events.

2.2. Target volume and particle beam simulation geometry

Our simulation platform is designed as the cylindrical or spherical target micro-volume, V_{micro} is fixed for randomly distributed particle beams. We consider four equivalent micro-volumes represented by right circular cylinders or spheres with of density. The cylinders and spheres that are labeled as $\mathrm{Cyl_i}$, $\mathrm{Sph_i}$, i = 1,2,3,4 have the same volume for given indices. The cylinder height (H), diameter ($\mathrm{d_{Cyl}}$), the corresponding ARs defined as H/d_{Cyl} and the sphere diameter ($\mathrm{d_{Sph}}$) are listed in Table 1. The circular base of each cylinder in Cartesian coordinates is located on the *x-y* plane centered at (0,0,0) and the mass center of the cylinder and the same volume sphere are at (0,0,H/2) along the *z*-axis.

2.3. Particle beam arrangement

Particle beams of length L_{Beam} $(0,\ L_{Beam})$ on the *z*-axis are constructed from randomly selected 20 µm track histories to comprise a longer track length as described previously (Alp et al., 2015). An entrance point for a beam on *x-y* plane with radius R_{Beam} is randomly chosen. First, the beam is translated by $(-L_{Backward}+H/2)$ on *z*-axis, then randomly rotated with respect to (0,0,H/2) point. The L_{Beam} and R_{Beam} range for (^{1}H, ^{3}He, ^{12}C) are chosen as (120, 160, 200) µm and (40, 60, 70) µm, respectively. The $L_{Backward}$ is taken as 0.23 × L_{Beam} upon analyzing Figure S.1 given in the Supplementary information file.

2.4. Scoring algorithm

The scoring algorithm for each random particle beam and V_{micro} calculates the chord length (L_{Ch}) of a beam crossing, total number of voxels, and total ED per beam. We also consider the so-called LET approximation where a stochastic beam ($Beam_{Stch}$) is reduced to a line ($Beam_{Line}$) and calculate the chord length; the length section bounded by V_{micro}, and if there is a line crossing the volume it is recorded as ‘primary beam hit’. The $Beam_{Stch}$ that constitutes voxel coordinates and deposited energy of each voxel is run on a coincidence algorithm to find if any voxels are bounded by the V_{micro}. The total number of voxels and total voxel energy per beam are recorded as primary beam properties if there is a L_{Ch} value otherwise it is categorized as ‘δ-ray hit’. This rule assigns some tangent $Beam_{Stch}$ lines to V_{micro} as δ-ray hits. If there is a primary beam and multiple δ-ray crossings all voxel number and total energy values are recorded as primary beam properties as the presence of the L_{Ch} has higher priority in the algorithm. Likewise, multiple δ-ray

Table 1
Geometric factors of the micro-volumes.

Geometric Descriptor	$\mathrm{V_{micro,1}}$	$\mathrm{V_{micro,2}}$	$\mathrm{V_{micro,3}}$	$\mathrm{V_{micro,4}}$
$\mathrm{V_{micro}}$ (µm^{3})	0.085	1.131	2.011	5.655
Sphere: $\mathrm{d_{Sph}}$ (µm)	0.545	1.293	1.566	2.210
Cylinder: (H, $\mathrm{d_{Cyl}}$) µm, $\mathrm{H/d_{Cyl}}$	(0.3, 0.6), 0.5	(1, 1.2), 0.833	(4, 0.8), 5	(5, 1.2), 4.167