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I, Durude Mahee, hereby submit this original work as part of the requirements for the degree of Master of Science in Physics.

It is entitled:

Numerical simulation and graphical illustration of ionization by charged particles as a tool toward understanding biological effects of ionizing radiation.

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Numerical simulation and graphical illustration of ionization by charged particles as a tool toward understanding biological effects of ionizing radiation.

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Abstract

This thesis presents the numerical simulation and 3D representation of the “track model” [1, 2], a statistical ionization model developed to describe the ionization distribution at sub-molecular level in biological materials by energetic charged particles. The track model is based on the theory of stopping power [3] and is used to calculate the rates of clustered ionization in DNA. In the numerical simulations, ionization patterns from charged particles are shown for three different levels of linear energy transfer (LET) - Low, medium (10 times Low-LET) and high (100 times Low-LET), corresponding to 1 Gray (Gy) radiation dose for different charged particles. For the graphical visualizations, human DNA genome is represented as cubic cells and the clustered ionization is shown as cluster of holes (created by the ionization) on linear tracks. All holes occurring on the same track within a 3 nm radius is considered to form a cluster. The visualization shows how the clustered ionization depends on LET and the probability of occurrence of clusters with higher complexity (defined as the number of holes in a cluster) increases from low to higher LET radiation.

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Chapter 1 Introduction

Radiotherapy has been used for cancer treatment for long time. But the physical understanding of this treatment has not been developed enough. To fill the gap between physical and biological understanding of this aspect a physical model named track model [1, 2] has been developed by Professor Kay Kinoshita. This model can account for the resulting ionization distributions from radiation at the sub molecular scale and can calculate the rates of clustered ionization in DNA genome. Numerical simulation of this model is the very first attempt to visualize the clustered ionization in the DNA genome when the human body is exposed to radiation. This can give an idea of how the ionization density as well as the complexity of clusters in DNA genome varies depending on the LET (the amount of energy that an ionizing particle transfers to the material traversed per unit distance) of radiation. The graphics corresponding to various LET of radiation can help interpreting experimental data.

This thesis reports the creation of a Monte Carlo simulation of 1 Gy dose in 15 compact genomes for three different radiations- low-LET (minimum ionization energy transferred per unit path length) radiation, 10 × low-LET radiation, 100 × low-LET radiation. Since the number of created electron vacancies (holes) in irradiated DNA genome is proportional to dose, in this simulation we have first calculated total number of holes created in a mammalian genome for 1 Gy dose that is same for all radiations. Using the theory of stopping power [3] we can find the mean linear hole density for low-LET radiation and since mean linear hole density is proportional to LET, we can get the mean linear hole density for other two radiations. In this thesis we have represented the human genome by a cube and the side of this cube is calculated from the relation of mass

and mass density of DNA genome. When we know the total number of holes in a DNA genome for 1 Gy dose, side of the genome, by using the value of mean linear hole density for a particular LET of radiation we can get the corresponding average number of tracks in a genome. As track model says, distribution of holes in tracks and distribution of tracks in cube will follow the Poisson distribution, once we know the mean linear hole density and mean number of tracks we can easily generate the corresponding graphics by using Monte Carlo simulation.

The layout of this thesis is as follows. In chapter 2 we have described the current prevailing models, focusing on the multitarget model and linear-quadratic model. In chapter 3 we have described the theoretical background for this simulation mainly the track model. Chapter 4 is designed to present the calculation required for simulation. This calculation is done using the assumptions made in the track model. In chapter 5 we describe how we generate the graphics and in chapter 6 we present and discuss the graphics. Finally, some conclusions are drawn in chapter 7.

Chapter 2 Current Prevailing Models

When radiation can eject one/more electrons from atom/molecule, then that radiation is called ionizing radiation. In case of biological effects, the effects on Deoxyribonucleic Acid (DNA) is most relevant. Its double helical structure consists of two strands held together by hydrogen bonds between the bases. Ionizing radiation induces base damage, single strand breaks {SSBs), double strand breaks (DSBs), and DNA protein crosslinks. SSBs are easily repaired and do not have much biological consequence; on the other hand, DSBs are not easily repaired and are thought to cause serious biological consequence like cell death because DSBs lead to chromosomal aberrations that cause problems in cell division.

The relationship between the radiation dose and cells that survive is described by the cell survival curve. In this curve dose is plotted on a linear scale and surviving fraction on a logarithmic scale. At low doses for sparsely ionizing (low-linear energy transfer i.e. low-LET) radiations, the survival curve starts out straight with a finite initial slope. At higher doses, the curve bends and at very high doses it tends to straighten again. In contrast, for densely ionizing (high-LET) radiations, survival approximates to an exponential function of dose. There are multiple models to describe the shape of survival curve. Two of them are described below.

Multitarget Model: In this model, the survival curve is described in terms of D_1(initial slope resulting from single event killing), D_0(final slope resulting from multiple event killing) and n (extrapolation number, measure of the width of the shoulder) or D_q (the quasi threshold dose, another measure of shoulder width). D_1 / D_0 is the dose required to reduce the fraction of surviving cells to 37% of its previous value i.e. D_1 is the dose required to reduce the fraction of

surviving cells to 0.37 on the initial straight portion of the survival curve and D_0 is the dose required to reduce survival from 0.1/0.01 to 0.037/0.0037 or so on. Although a threshold dose is the dose below which radiation produces no effect, practically this is impossible; so, there is no true threshold dose, D_q is the closest thing. The relation between D_0 ,D_q and n is [4] -

$$\ln n = \frac{\mathrm{Dq}}{D_o} \tag{2.1}$$

Linear-Quadratic Model: According to this model, there two components to cell killing by radiation, one is proportional to dose and another one is proportional to the square of the dose. The expression for the cell survival curve is [4]-

$$S = e^{-\alpha D - \beta D^2} \tag{2.2}$$

Where, S is the fraction of cells surviving a dose D, and α and β are constants. The linear and quadratic contributions to cell killing are equal at a dose that is equal to the ratio of α to β i.e. when-

$$\alpha D = \beta D^2$$

$$\text{or, } D = \frac{\alpha}{\beta} \tag{2.3}$$

The linear-quadratic model is an adequate representation of the data and has the advantage of only two adjustable parameters, α and β. The resultant cell survival curve of the linear-quadratic formulation is continuously bending, and it does not have any final straight portion.

Chapter 3 Track Model

Understanding the physical root of biological effects from ionizing radiation is very important to improve the effectiveness of radiation therapy for cancer treatment. There is a well-defined theory of ionizing radiation with matter but the relationship between physical dose and its biological effects has not been developed enough. Biological effects occur primarily in the form of damage to DNA molecules. This molecule is structured as a double helix where two helices (strands) are joined like a ladder and the rungs are formed with millions to billions nucleotide base pairs. Here each strand carries identical information. Damage in only one strand does not cause permanent damage to the DNA genome. As the other strand retains the full genetic information, they can repair fully. So, for permanent damage to the genome, there has to be damage in both strands of the DNA and it has to occur in very close proximity (about ten base pairs ≈ 3nm [1]). This type of damage may be induced when at least two independent ionization events occur within 3nm distance. Here arises the need of a physical model which would be able to account for such clustering. Currently, there is no such model.

To explain the basis for biological effects from ionizing radiation, a physical model has been developed by Professor Kay Kinoshita. In this model, she calculates the resulting ionization clustering rate from radiation at the sub molecular (nanometer) scale which is required for complex ionization to cause unrepairable damage in DNA genome. Damage to DNA can be direct or indirect. Ionization in DNA molecule results in direct damage whereas the indirect damage results due to the ionization in the local environment. This model accounts for only the direct ionization.

Ionizing radiation results in electron vacancies, known as 'holes', by freeing electrons in biological material. This initiates the chemical activity responsible for impairment and biological effects. It is assumed that damages in the form of single- strand DNA breaks occur at a rate proportional to hole density. However, for double strand breaks, a cluster of holes with at least two localized within a few nm is required [1]. The model described above assumes that the resultant holes for a given radiation are randomly distributed on 1D trajectories (tracks) embedded randomly in a 3D volume and the model is named the track model. My project is numerical simulation and graphical representation of this track model. So, here the track model will be discussed in detail to provide the theoretical basis of my computation.

Track model is based on the theory of stopping power and this theory is well validated for the particles travelling with speed, $v \geq 0.01c$, where, c is the speed of light. Charged particles lose energy while traveling through matter by causing ionization of electrons in the matter. The relationship between numbers of freed electrons and energy lost by the projectile is proportional to the effective ionization potential (I_{eff}) i.e. the logarithmic mean (Bragg rule) of binding energies of all electrons in the target [3]. Application of the Bragg rule on the component atoms of a compound target material shows good approximation at the percent level. The mean ionization potential over the combination of atoms contained in a DNA molecule is approximated as 64.9 eV (63.9 eV) for C-G (A-T) base pairs or 64.4 eV for all four bases together [2].

For calculational purposes some simplified assumptions are made in this model; charged particles take a straight path and ionize in the DNA genome such that electron vacancies, i.e. holes, are created in the genome with a uniform 1-D probability distribution which is proportional to stopping power/LET. We define two or more holes created within 3nm distance as a cluster and

the cluster size (n_h) is defined as the number of holes in a cluster. The unit for biological radiation experiments is considered to be the entire DNA genome of a cell; in the case of mammalian cell it is approximately 3 billion base pairs.

The number of holes {N} created in a DNA target is proportional to the mass (M) of target and the dose (D) and is inversely proportional to the effective ionization potential (I_{eff}). i.e.

$$N = n_1 DM \tag{3.1}$$

Where, D is the size of dose in Gray and M is the mass of target in Mbp. n_1 is the number of holes created for one Gy dose to 1 Mbp of DNA.

The holes produced by a dose are distributed on tracks with hole density, λ. This λ is proportional to stopping power/ LET. A slow charged particle's stopping power is roughly proportional to the inverse square of its speed and reaches a minimum ionizing value when $\frac{v}{c} \approx 0.95$. As $v \to c$ it rises slowly with energy.

If N is the number of holes created in a DNA target for a given dose (D), assuming holes will be distributed on tracks with hole density λ, the length of associated tracks,

$$T = \frac{N}{\lambda} = \frac{n_1 DM}{\lambda} \tag{3.2}$$

And the mean linear dimension of a genome,

$$R_o = [V]^{\frac{1}{3}} = \left[\frac{M}{\rho}\right]^{\frac{1}{3}} \tag{3.3}$$

The mean number of tracks per DNA unit per dose,

$$\bar{n}_t = \frac{T}{R_o} = \frac{N}{\lambda R_o} \tag{3.4}$$

The value of $\bar{n}_t$ is inversely proportional to LET. For high LET, it is less than 1 per Gy, so the distribution of clusters among DNA units must account for the statistical fluctuations in the number of tracks through them [2].

The mean number of tracks per unit genome is $\bar{n}_t$D. The probability distribution in number of tracks is given by the Poisson probability,

$$P(i;\ \bar{n}_t D) = \frac{(\bar{n}_t D)^i e^{-\bar{n}_t D}}{i!} \tag{3.5}$$

Where, i is the number of tracks.

If the track is divided in small segments of length r_o, each segment will have a mean number of holes,

$$\bar{n}_h = \lambda r_o \tag{3.6}$$

Here, r_o is the the relevant length scale for complex lethal damage which is approximately 3nm [1].

A segment containing j holes is called a cluster of complexity j, and the probability of a random segment to have complexity j is given by the Poisson distribution.

$$P(j;\ \bar{n}_h) = \frac{(\bar{n}_h)^j e^{-\bar{n}_h}}{j!} \tag{3.7}$$

The number of segments encompassed by the track length,

$$N_{seg} = \frac{T}{r_o} \tag{3.8}$$

When Poisson Probability is multiplied by N_{seg} that will give the mean number of clusters with complexity j, i.e.

$$\bar{N}_{clus}\,(j) = N_{seg} P(j;\, \bar{n}_h) \tag{3.9}$$

The value of $\bar{n}_h$ is proportional to LET. That's why clustering rate will be affected by it.

Chapter 4 Calculations

This project is about Numerical simulation and graphical representation of radiation dose in cells via the track model. As biological effect is considered as damage in DNA molecule, visualization of how this damage occurs due to ionizing radiation is important for understanding dependence on LET. As it is already stated that damage in a single strand in DNA genome is repairable, for cell death damage in both strands are required and track model is able to consider how the likelihood of double strand break depends on complexity of cluster, it is important to visualize and analyze the clustering behavior in irradiated DNA genome.

To proceed with calculation, the unit of biological damage is generally taken as the whole genome of a cell, which for the mammalian genome is comprised of 3 billion base pairs (= 3000 Mbp). Average base pair mass is 650 Daltons (or amu), which gives the mass of 1 Mbp, 1.08×10^{-15} g. The mass density (ρ) of DNA genome is assumed to be 1.4 g/cm^3. In this illustration, human genome will be represented by a cube of side L; hence the length of each track is also L. Since we know the mass density and mass of genome, L can be easily calculated as-

$$\rho = \frac{M}{V} = \frac{M}{L^3}$$

$$L = \left[\frac{M}{\rho}\right]^{\frac{1}{3}} = \left[\frac{3000 \times 1.08 \times 10^{-15}\ g}{1.4\ g/cm^3}\right]^{\frac{1}{3}} = 1.32\ \mu m$$

When the biological body is irradiated, energy loss (stopping power) by fast charged particles occurs through ionization or excitation of electron in the irradiated body. The mean number of ionizations per track length (λ) is the deposited energy per track length (LET) divided by the

mean/effective ionization potential (I_{eff}). We know, 64.4eV is the effective ionization potential (I_{eff}) and for low- LET particle, the linear hole density,

$$\lambda = \frac{1}{I_{eff}} \left|\frac{dE}{dX}\right|_{min,DNA} \approx 4.04 \frac{holes}{\mu m}$$

Where, $\left|\frac{dE}{dX}\right|_{min,DNA} = 1.86\ MeV g^{-1} cm^2$ (0.260keV μm^{-1}). Here, the minimum ionizing value in water is taken as reference point and the adjustment made in I_{eff} and charge to mass ratio has given this corresponding LET in DNA [2].

Now since we know the linear hole density and clustering distance, r_o (3nm), we can easily get the mean number of holes for each segment for low- LET radiation-

$$\bar{n}_{h-LL} = \lambda r_o = 4.04\ \mu m^{-1} \times 0.003\ \mu m = 1.21 \times 10^{-2}$$

And average no of holes for each track

$$n_{h-LL} = \lambda L = 4.04\ \mu m^{-1} \times 1.32\ \mu m = 5.33/track$$

As we know already, the number of holes created on a genome is proportional to radiation dose and mass of genome, using equation (3.1), we can get number of holes created for 1 Gy (10^{-4} erg/g) dose to 1 Mbp of DNA i.e.

$$n_1 = \frac{10^4 \frac{erg}{gm}\ (Gy) \times 1.08 \times 10^{-15}\ g\ (Mbp)}{64.4\ eV \times 1.602 \times 10^{-12}\ erg/eV} = 1.05 \times 10^{-1}\ \text{holes/Mbp}$$

Where, 1 eV = 1.602×10^{-12} erg. And for 1 Gy dose, total number of holes created in a mammalian DNA genome is

$$N = 1.05 \times 10^{-1} \times 3000 = 315$$

Hence the corresponding average no. of tracks per unit genome, $\bar{n}_t = \frac{315}{4.04 \times 1.32} = 59.1$

Now as we know the average number of tracks per unit genome and average number of holes for each 3nm segment of a track for low- LET radiation, we can proceed to the simulation to generate the corresponding graphics.

Linear hole density is proportional to LET. So, the corresponding rate of linear hole density for medium LET (10 times low-LET) and high- LET (100 times low-LET) radiations are 40.4 holes/μm and 404 holes/μm respectively. And following the above calculations, we can find the related average number of tracks for each genome and the average number of holes per segment of a track which are summarized in following table.

Table 4.1 Hole rate and track rate for a 3 Gbp DNA unit with 1 Gy dose for three different LET.

	$\lambda(\mu m^{-1})$	$n_h(track^{-1})$	$\bar{n}_h$	$\bar{n}_t$
low- LET	4.04	5.33	1.21×10^{-2}	59.1
10 × low-LET	40.4	53.3	1.21×10^{-1}	5.91
100 × low-LET	404	533	1.21	0 .591

Once we have all the required rates for all three radiations we can simulate the conditions to generate corresponding graphics for each type of radiation.

Chapter 5 Simulation of the Track Model

For visual illustration of the track model, each genome is represented as a solid cube of DNA matter. An array of such cubes is embedded in a three-dimensional coordinate system representing multiple genomes within a tissue and each cubic cell is identified through the coordinate of the bottom-left vertex (***O***) as shown in Figure 1. We term the 3D coordinate of $\boldsymbol{O} \equiv (O_x, O_y, O_z)$ the cell position. A track within the genome is represented as a straight -line segment parallel to the z-axis of the coordinate system. Each track is identified through the 3D coordinate, $\boldsymbol{C} \equiv (C_x, C_y, C_z)$, of its intersection point with the bottom XY plane of the cubic cell. We term the parameter ***C*** as track position. The length of each track is equal to the side of the cube, ***L.*** A cluster on the track is represented as a solid circle with radius proportional to the complexity of the cluster (number of holes present in a cluster).

For the computer simulation, a two-dimensional array of genomes (laid on the XZ plane) are assumed. The cell position of the first cubic cell of the array is assigned at the origin of the coordinate system, that means $\boldsymbol{O}_{0,0} = \{0,0,0\}$. Then utilizing the parameter ***L***, we generate a list of cell positions as

$$\{\boldsymbol{O}_{i,j}\} = \{(i-1) \times \boldsymbol{L}, \quad 0, \quad (j-1) \times \boldsymbol{L}\}, i = 1 \dots \dots N; j = 1 \dots \dots M$$

where, *N* and *M* are the number of genomes along the *x* and *z* axis respectively.

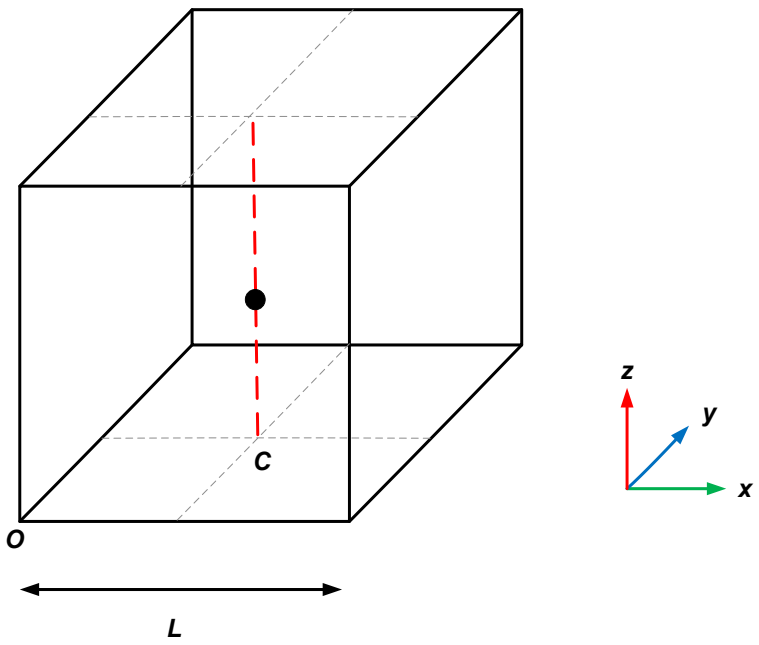

Figure 5.1 Representation of a genome as a cubic cell with tracks represented as straight-line segments and cluster of holes represented as sphere in a coordinate system.

Next for each cell, we generate a list of n_t track position coordinates $\{\boldsymbol{C}_{k,l}\}$ where the number N_t is sampled from a Poisson distribution of event rate $\bar{n}_t$ tracks per unit volume of the cube. For $(i,j)^{\text{th}}$ cube in the array, $\boldsymbol{C}_{k,l}$ is generated by drawing a two-dimensional vector from the uniform distribution over the square region $[(i-1)\boldsymbol{L},\ i\ \boldsymbol{L}]\ \mathbf{X}\ [0,\ \boldsymbol{L}]$ to form the *x* and *y* coordinates of $\boldsymbol{C}_{k,l}$. The z coordinate of $\boldsymbol{C}_{k,l}$ will be $(j-1)\times L$. Once the lists $\{\boldsymbol{C}_{k,l}\}$ of all the cubic cells are generated, they are merged into one list $\{\boldsymbol{C}\}$.

The following code snippet in Mathematica shows the generation of tracks for a given cubic cell:

```
(* CellPos: three-element list for cell position
CellLength: size of the cubic cell
*)
Nt = RandomVariate[PoissonDistribution[Rt]];  (* Sample number of tracks from Poisson distribution *)
(* position and dimension of a cubic cell *)
xmin = CellPos[[1]]; xmax = xmin + CellLength;
ymin = CellPos[[2]]; ymax = ymin + CellLength;
(* generate Nt tracks by uniformly sampling within the cell*)
TrackPos = RandomVariate[UniformDistribution[{{xmin, xmax}, {ymin, ymax}}], Nt]; (* 2D position*)
TrackPos = Partition[Append[Riffle[Flatten[TrackPos], CellPos[[3]], 3], CellPos[[3]]], 3, 3]; (* 3D position*)
```

Now to generate a hole on any track in the combined list $\{\boldsymbol{C}\}$, we only need the position of the hole on the linear manifold, which is obtained by generating the *z* coordinate of the hole position. The *z* coordinates can be drawn randomly from a uniform distribution over the one-dimensional region $[(j-1)\boldsymbol{L}, j\ L]$. The number of holes, n_h to appear on a track is sampled from another Poisson distribution with event rate $\bar{n}_h$ holes per unit length of a track. Once all the 3D coordinates of all the tracks are generated they can be combined into a list $\{\boldsymbol{B}\}$.

Now a cluster finding algorithm is needed for the 3D coordinate points in $\{\boldsymbol{B}\}$. A clustering algorithm requires calculating the distance between every possible pair of holes in the list $\{\boldsymbol{B}\}$. Once all the distance pairs are calculated, any set of points within a radius r_o is assigned to one cluster. Afterwards the centroids (by taking the mean of coordinates of holes within the cluster) of all the clusters are calculated and stored in a list. The number of holes in each cluster is also recorded in another list.

The clustering approach described above has its drawback. For a set of *N* holes (and each having a 3D coordinate) this method requires calculation of $N(N-1)/2$ distances. For clusters of complexity 2 calculating each distance requires three subtractions, two additions and three multiplication operations. For simulation of low-LET radiation, performing these many operations do not pose a problem. However, for medium to high-LET radiation simulation, the number *N* will be very large, and the number of calculations increases by the power of the complexity.

To circumvent this issue, we made the following modifications:

We generate the cell positions and track positions as before. Now instead of generating holes for the entire length of a track we divide the track into N_{seg} segments of length r_o each, that means, $N_{seg} \approx \frac{\boldsymbol{L}}{r_o}$. With this modified scheme we do not need to perform clustering explicitly, rather any

>1 number of holes formed within any segment of length r_o is already forms a cluster. If no holes appear in a segment, it doesn't form a cluster. However, this time we need to generate holes with an event rate $\bar{n}_h \times r_o$ holes per segment. The z coordinate of the holes for the p^{th} segment on a track is randomly drawn from a uniform distribution over the region $[(j-1)\boldsymbol{L}, (j-1)\boldsymbol{L} + \boldsymbol{pr_o}]$. The centroids of the clusters are now found by calculating the mean of the *z* coordinates of the holes. The *x* and *y* coordinates are readily available from the coordinates of track position. We put all the cluster centroids into a list called $\{\boldsymbol{H}\}$ and corresponding cluster complexities into another list $\{\boldsymbol{N}\}$.

The clustering algorithm is described in the following code snippet:

```
NumTracks = Length[TrackPos];
RadClus = 0.003; (* radius of cluster*)
NumClusPerTrack = Floor[CellLength/RadClus]; (* maximum possible clusters per track*)
ClusterCentroids = List[]; (* initialize an array to hold the coordinates of the centroids *)
ClusterSize = List[]; (* Another list to hold the cluster *-*size *)
dist = UniformDistribution[{0, RadClus}];
(* do for each track *)
Do[
   Nh = RandomVariate[PoissonDistribution[Rh * RadClus]];  (* randomly sample number of holes *)
   If [Nh > 1, (* grow the arrays whenever more than one holes found within a cluster*)
     AppendTo[ClusterSize, Nh];
     AppendTo[ClusterCentroids, Flatten[{TrackPos[[i]], (j - 1) * RadClus  + CellPos[[3]] + Mean[RandomVariate[dist, Nh]]}]];
   ,{i, NumTracks}, {j, NumClusPerTrack}
];
```

The code for generating tracks and holes for an array of genomes is given below:

```
(* Rt = tracks per cell *)
(* Rh = holes per unit length of track *)
(* xgrid x zgrid = size of the cubic cell grid*)

(* placeholder for all the holes in the cell-array *)
centroids = List[];
sizes = List[];
tracks = List[];

Do[
        cp = {CellLength * (i - 1), 0, CellLength * (j-1)};
        data = clustering[Rt,Rh, cp, CellLength];
        centr = data[[1]]; siz = data[[2]]; trk = data[[3]];
        centroids = Join[centroids, centr];
        sizes = Join[sizes, siz];
        tracks = Join[tracks, trk];
        ,{i, xgrid}, {j, zgrid}
]
```

Once all the required data structures (the lists $\{\boldsymbol{C}\}$, $\{\boldsymbol{B}\}, etc.$) are constructed, we can generate the graphical visualization by invoking standard graphics libraries available in software packages like MATLAB or MATHEMATICA:

```
ScatterPoints = List[];  (* create a list of point object for each cluster centroid *)
Do[
        AppendTo[ScatterPoints, Graphics3D[{PointSize[0.004 * (sizes[[i]]-.4)],Red, Point[centroids[[i]]]}, Boxed ->
False]]
        ,{i, Length[sizes]}
]


lines = List[];   (* another list of graphics (line) object for tracks *)
Do[
        pt1 = {tracks[[i, 1]], tracks[[i, 2]], tracks[[i, 3]]};
        pt2 = {tracks[[i, 1]], tracks[[i, 2]], tracks[[i, 3]] + CellLength};
        AppendTo[lines, Graphics3D[{Thickness[.0003], Black, Line[{pt1, pt2}]}, Boxed -> False]]
        ,{i, Length[tracks]}
]

cubes = List[]; (create a list of cube object)
Do[
        cp = {CellLength * (i - 1), 0, CellLength * (j-1)};
        AppendTo[cubes, Graphics3D[{EdgeForm[{Thin, Blue}], FaceForm[], Cuboid[cp, cp + CellLength]}, Boxed -> False,
Axes -> True, AxesLabel -> {x,y,z}]]
        ,{i, xgrid}, {j, zgrid}
]

Show[{cubes, lines,ScatterPoints}, ViewPoint -> {0, -Infinity, 0}]
```

Chapter 6 Results and discussions

Simulation of the track model [4] is performed for three different LET; Low-LET, 10 × low-LET and 100 × low-LET associated with hole rates 5.33/track, 53.3/track and 533/track for 1Gy dose in 15 compact genomes. The genome is assumed to be a compact cube and the path/track length is 1.32µm. The numbers of Tracks corresponding to these LETs are 59.1/genome, 5.91/ genome and 0.591/genome respectively. Graphics from these simulations are presented below-

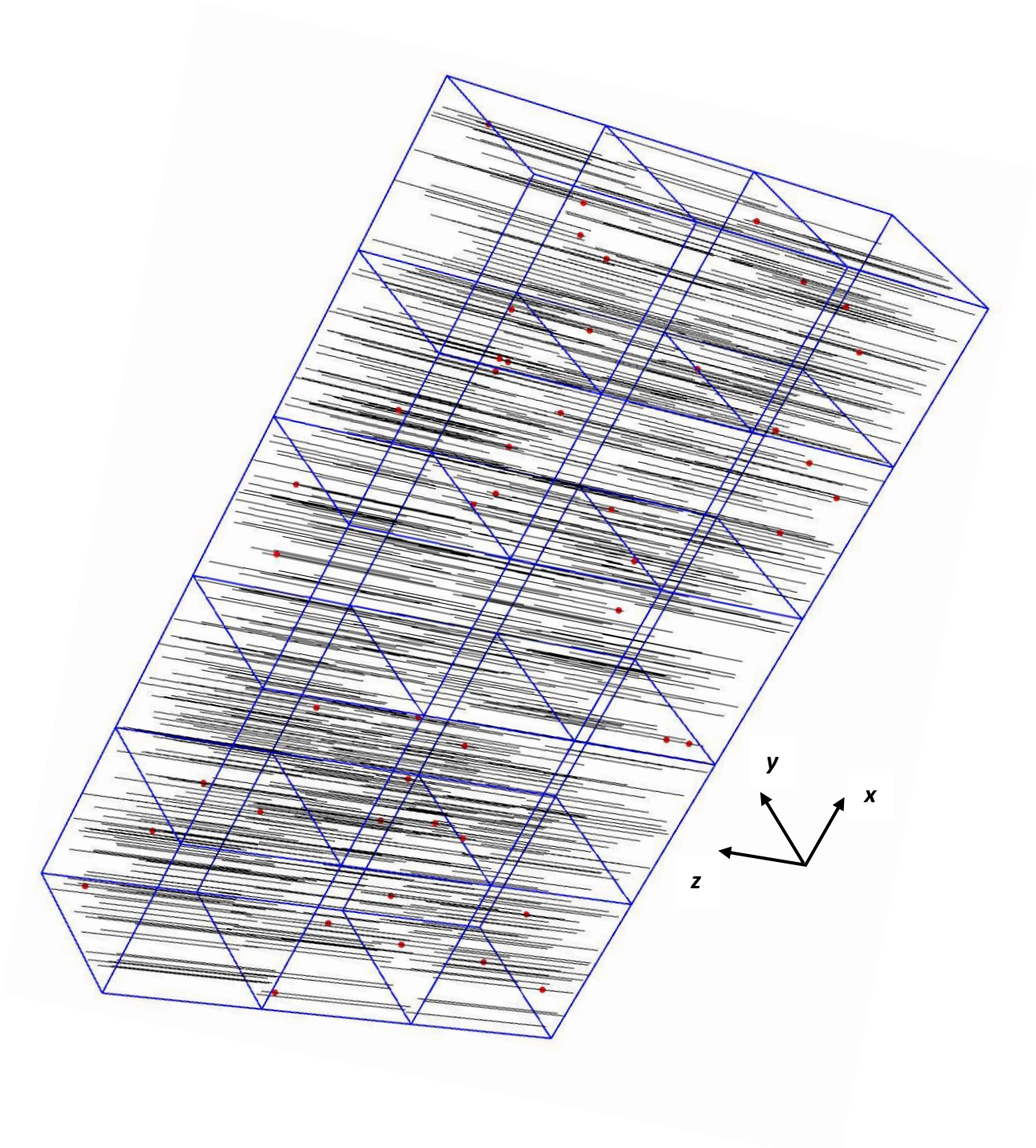

Figure 6.1a Monte Carlo simulation of 1 Gy dose in 15 compact genomes for low-LET radiation: 3D view. Tracks are shown in black, clusters are indicated with red dots with size of dots proportionate to the cluster complexity.

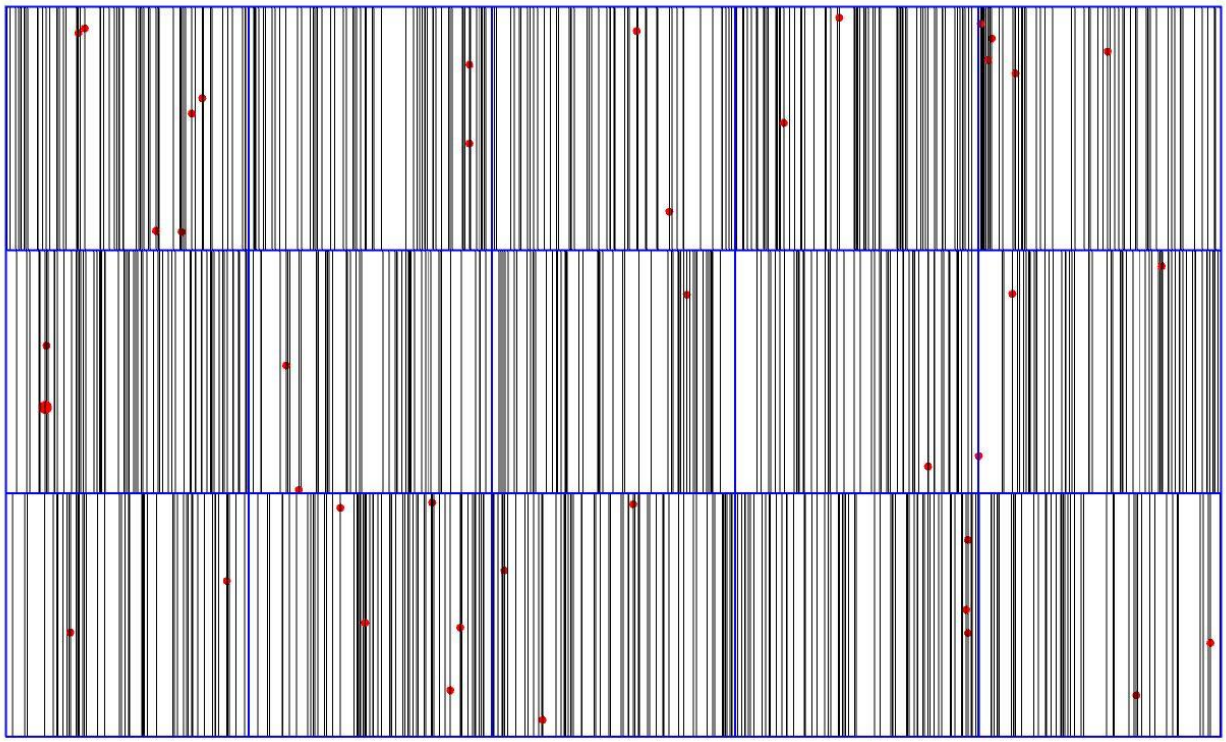

Figure 6.1b ZX projection of the simulation in Figure 6.1a.

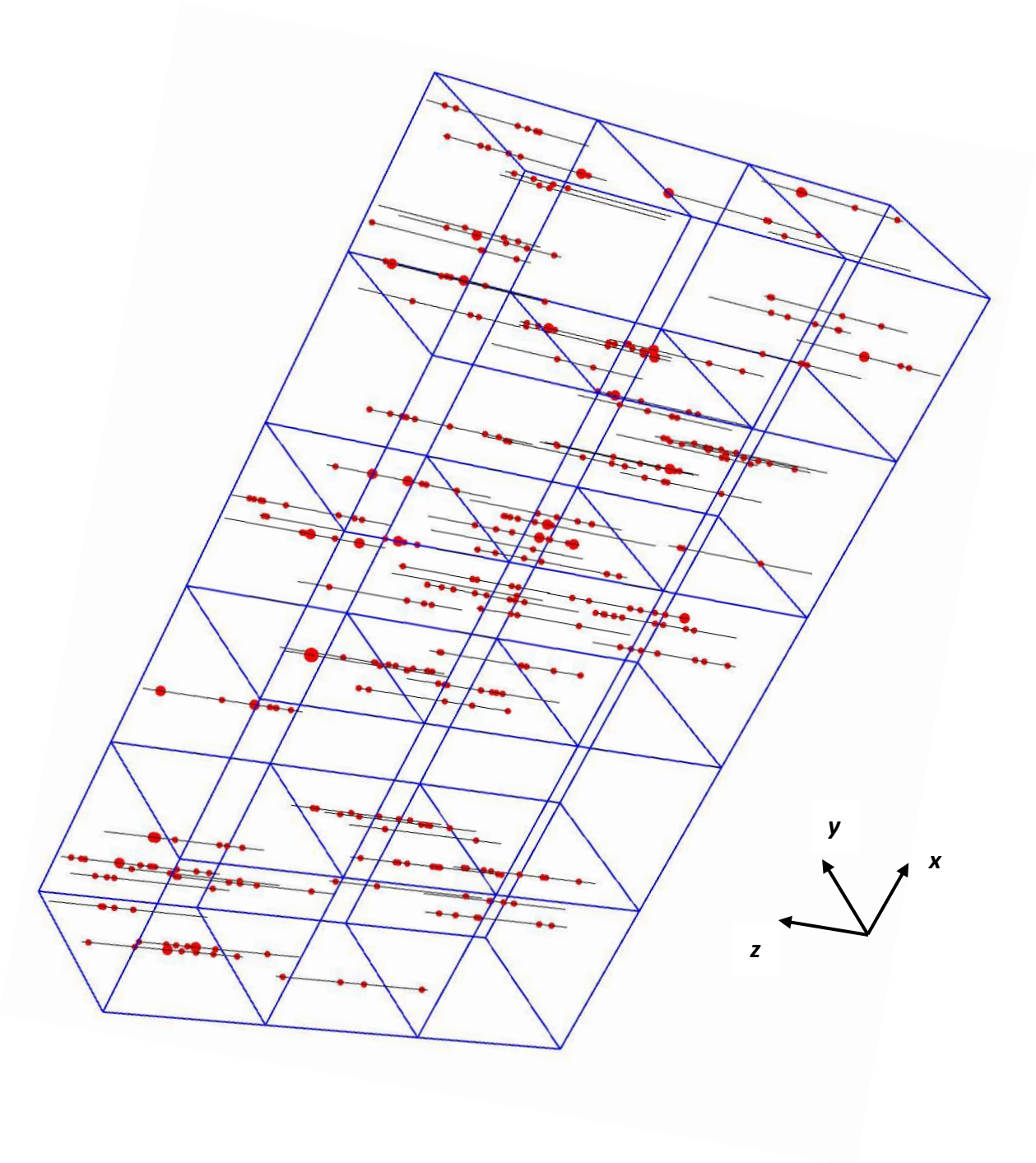

Figure 6.2a Monte Carlo simulation of 1 Gy dose in 15 compact genomes for medium-LET radiation: 3D view. Tracks are shown in black, clusters are indicated with red dots with size of dots proportionate to the cluster complexity.

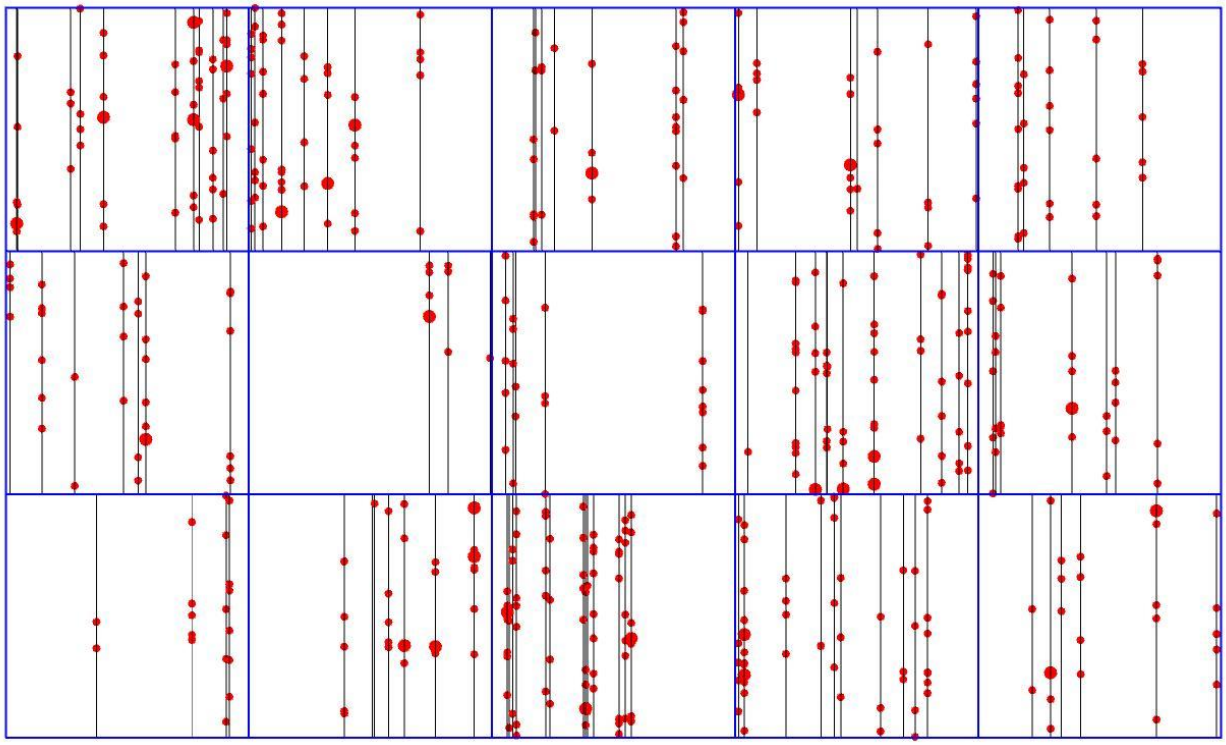

Figure 6.2b ZX projection of the simulation in Figure 6.2a.

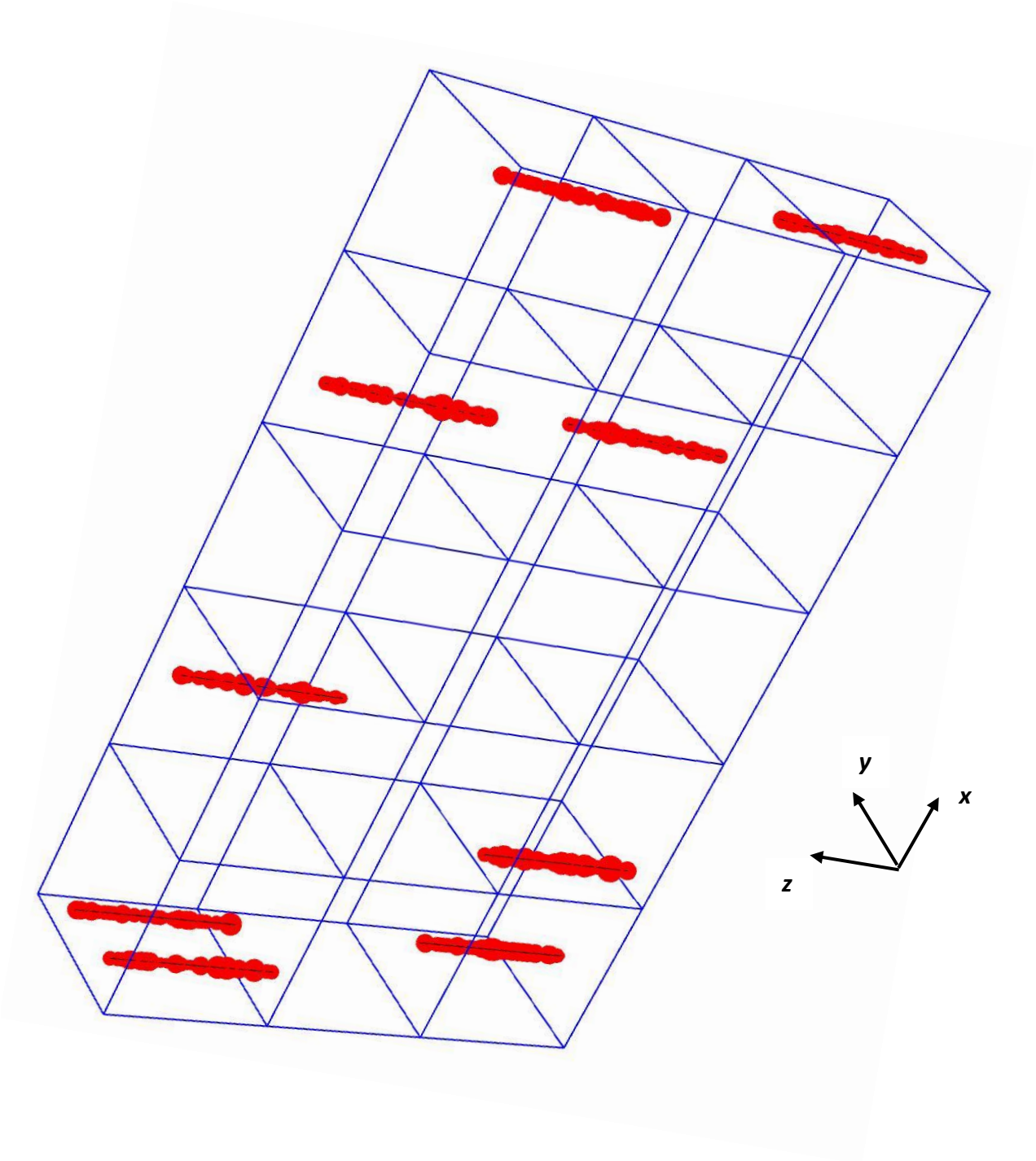

Figure 6.3a Monte Carlo simulation of 1 Gy dose in 15 compact genomes for high-LET radiation: 3D view. Tracks are shown in black, clusters are indicated with red dots with size of dots proportionate to the cluster complexity.

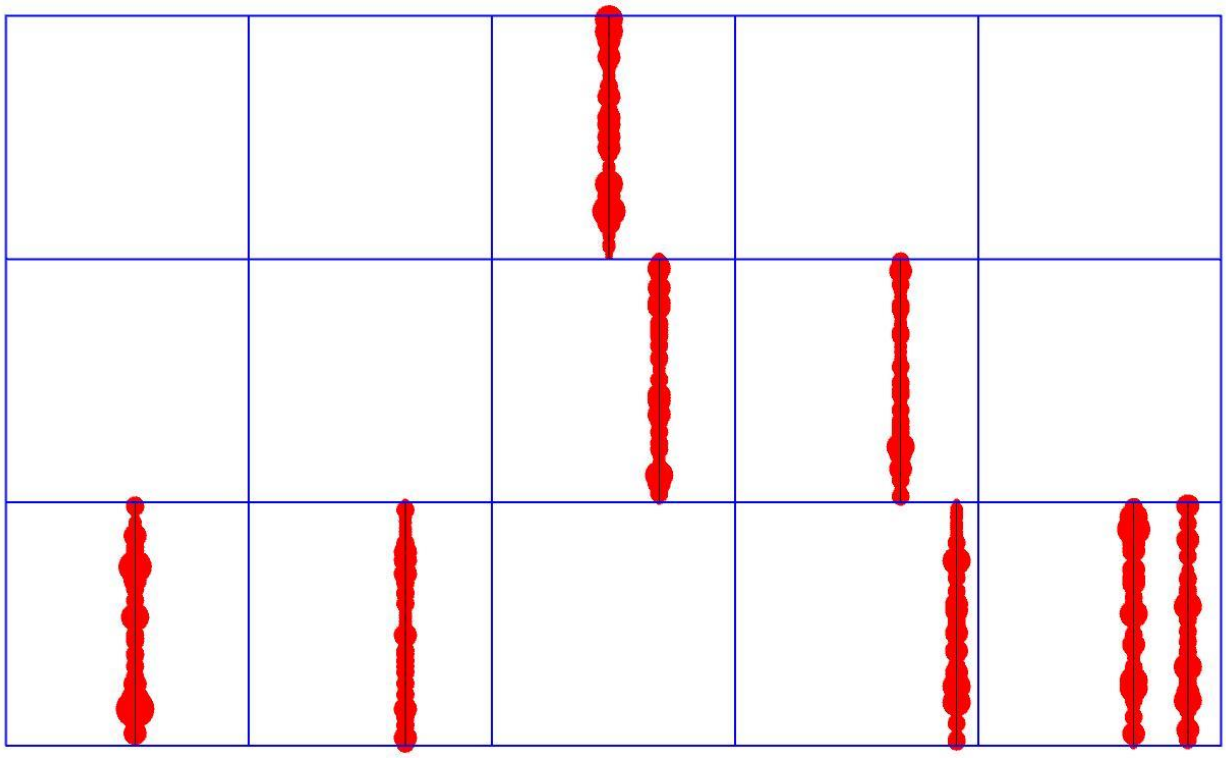

Figure 6.3b ZX projection of the simulation in Figure 6.3a.

If we analyze the graphics, we can see in each 3 graphics (corresponding to three LET) tracks are randomly generated in the cubes, in the similar fashion clusters are randomly generated in tracks. Track model is a statistical model and randomness in numbers and positions of tracks and clusters are showing their statistical behavior which is very useful to appreciate statistical fluctuation.

Again, if we analyze the graphics very closely, there are very few number of clusters compared to tracks are generated in the cubes for low-LET radiation which can be visualized as randomly distributed in 3D space. But if we look at the distribution of clusters for medium LET radiation, most of the tracks have several numbers of clusters and their position can be identified on tracks i.e. they don't seem random in 3D space. In the same manner, there are many clusters in each

track for high LET radiation and they can easily be identified by their track position. From here, it can be inferred that ionization of DNA genome along the direction of LET is more explicit in case of medium and high LET radiation.

From track model, we know that linear hole density in irradiated genome increases from low to higher LET radiation and the probability of appearance of clusters with higher complexity increases from low to higher LET radiation and the above visualization is showing the similar tendency, we can see from them, complexity of clusters and their frequency increases from low to higher-LET radiation.

The track model has the potential to address some unanswered questions such as the origins of single event killing, multiple event killing in multitarget model (MM) [4] and lethal events and sublethal events in linear quadratic model (LQM) [4]. These models do not explain what the event is. Track model clarifies the idea of events by expressing them in terms of clusters; for example, this model may hypothesize that single event killing or lethal events may be associated with complex clusters of three or four holes whereas simple clusters of two holes may be associated with multiple event killing.

But the model reveals that in case of low LET radiation nearly all damage occurs by simple clusters like clusters of two holes; complex clusters or cluster of three or more holes are responsible for very small percentage of damage. In this scenario, Consistency of track model with widely accepted LQM can be explained via these visualizations only if clusters are taken as basis for lethal/sublethal events in case of low-LET radiation and it can be predicted for low-LET radiation nearly all events should be sublethal events. On the other hand, from the above graphics we can see there are large number of complex clusters i.e. cluster of three or more holes are created in

case of high-LET radiation. So in this case if we take clusters as basis for lethal or sublethal events, nearly all events should be lethal events and there should be higher kill rate; however, the study of cell survival data [5] indicates that in this case kill rate appears to be lower than for low-LET. This can be partially (some aspects are still under study) explained by looking at above graphics, we can see how the number of tracks are decreasing from low to higher LET radiation.

Finally, it can be said this project is a very first visual representation of biological effects from radiation. This representation can give a quick and explicit idea about what is happening in the DNA genome when it is irradiated and how this biological effect varies depending on radiation type without looking at any equation or data.

Chapter 7 Conclusions

We have presented a numerical simulation with graphical representation of ionization by charged particles. This simulation has been performed for ionization in DNA genome resulted from three different radiations characterized by low-LET, 10 times low- LET and 100 times low- LET. The results of this simulation illustrate the results of track model i.e. complexity of clusters depends on LET and the frequency of occurrence of clusters with higher complexity increases from low to higher LET radiation whereas the number of tracks is decreasing following the same order. These visualizations can help interpret the experimental data by sometimes taking the complexity of clusters as basis, sometimes basis may be the tracks, sometimes it may bring up new parameter into attention. Here, human DNA genome is represented by solid cube of DNA matter. In future, this simulation will be performed taking the real shape of human DNA genome into consideration.

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