International Student Project 2018,
Stage-2

JINR
University
Centre

Computer Modeling of Radiation Biophysics using the Geant4

Microdosimetry, DNA damage and Cluster analysis

27 July 2018, Dubna

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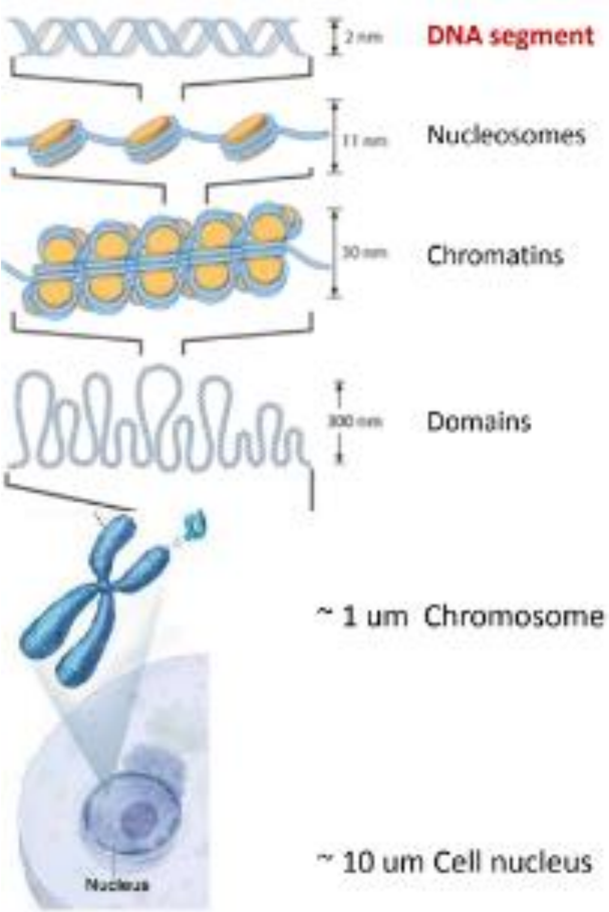
Sector of Mathematical Modeling of Radiation-Induced Effects

Outline

- Introduction
- Purpose and motivation
- Simulation Method
- Results
  - **Microdosimetry by Andrei**
    - Energy deposition of particles in different biological targets
    - Specific energy (Gy) and linear energy (keV/um)
    - Conclusion
  - **DNA damage by Vasile**
    - DNA radiation interaction
    - DNA damage calculation
    - Conclusion
  - **Cluster analysis by Ioana**
    - Probability of clustered and isolated damage
    - SSB and DSB per track per micrometer
    - Conclusion

Introduction

- Radiation biophysics is studying the effect of ionizing radiation upon biomolecules to living organisms (DNA, chromosomes, cells)
- The most sensitive target to radiation is the DNA molecule
- In order to better understand and predict damage done by charged particles like electrons, protons, alpha particles and heavy ions can be used Monte Carlo-based computer simulations



Purpose of the project and Motivation

The goal of our work was:

- To better understand the relation between radiobiology and physical quantities of ionizing radiation
- To predict the effect of different charged particles on biological targets
- To estimate the DNA damage induced by various charged particles

The estimation of initial DNA damage is very useful in the treatment of cancer and as well as for radiation protection, especially for astronauts in deep space missions.

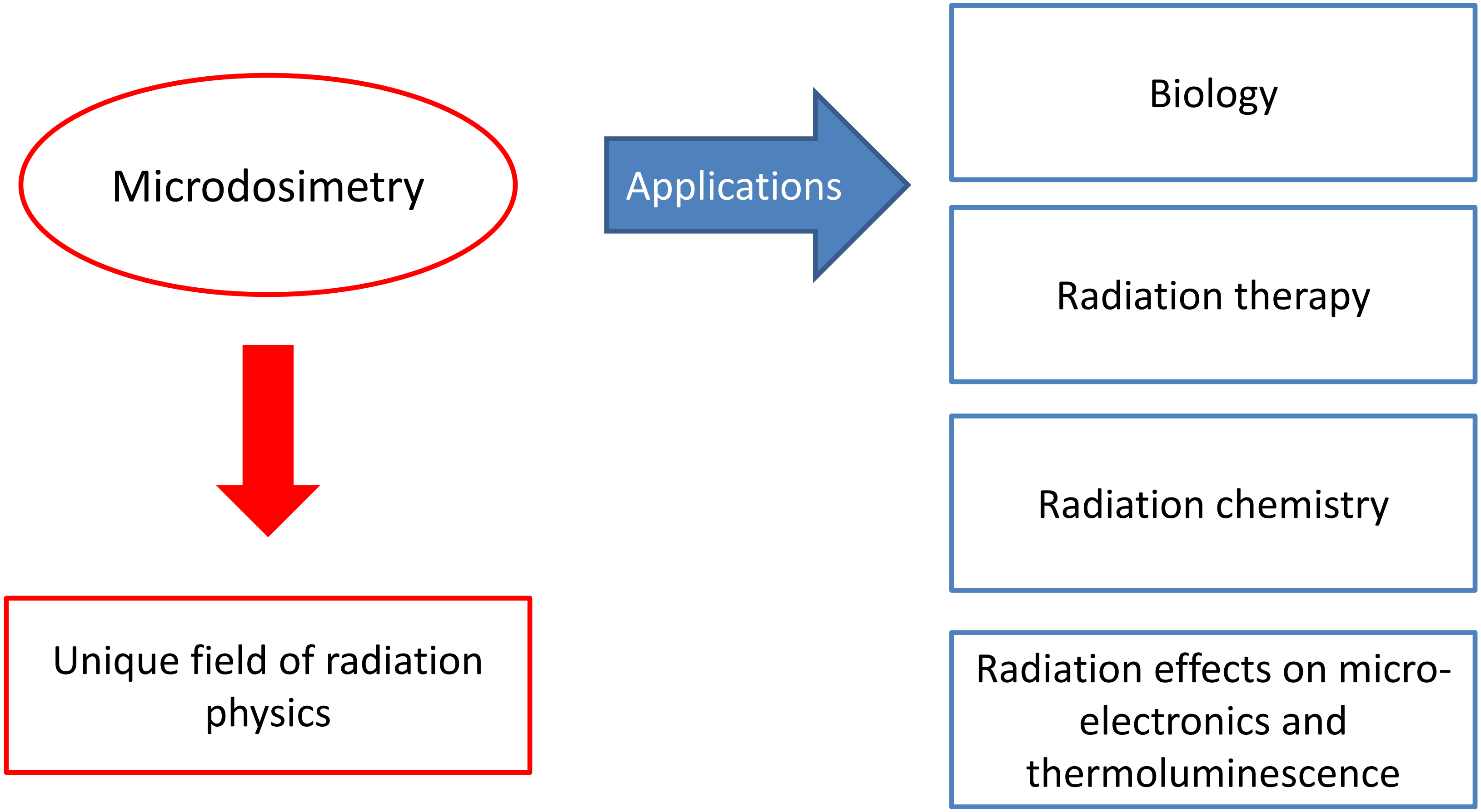
Simulation Method

- The Geant4 is a general particle-matter Monte Carlo simulation toolkit, which includes the Gent4-DNA models for microdosimetry simulations of stochastic nature of particle track structure in small targets.
- http://geant4.cern.ch/; http://geant4-dna.org/.
- Monte Carlo virtual-experiment applications of radiation biophysics developed in the Geant4 toolkit is used in this practice.
- Particle energy and physical interaction of particles with biological media:

Particle	Kinetic energy (keV)	Physical processes in liquid water
Electron	1, 2, 5, 10, 20, 100, 300, 1000	Elastic scattering, Ionisation, Electronic excitation, Dissociative electron attachment
Proton	10, 20, 100, 300, 1000, 5000	Ionisation, Electronic excitation, Charge decrease, Elastic scattering
Alpha particle	10, 20, 100, 300, 800, 1200, 5000, 10000	Ionisation, Electronic excitation, Charge decrease, Elastic scattering

Calculation of microdosimetry

by Andrei Mohut



Microdosimetry

Applications

Biology

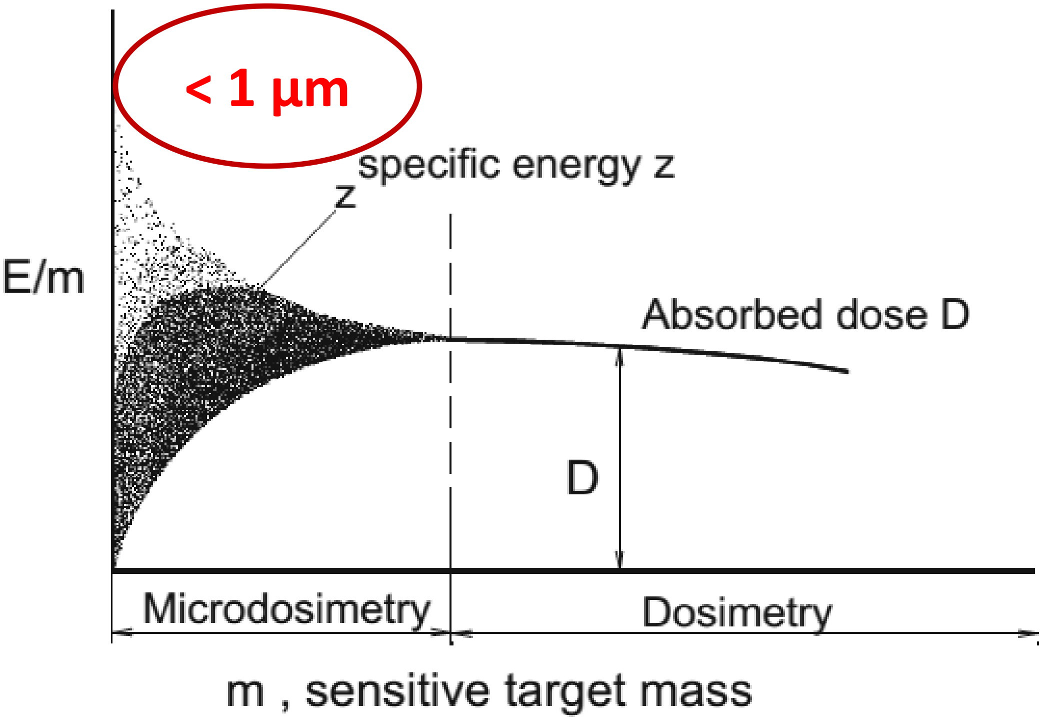
Radiation therapy

Radiation chemistry

Radiation effects on micro-electronics and thermoluminescence

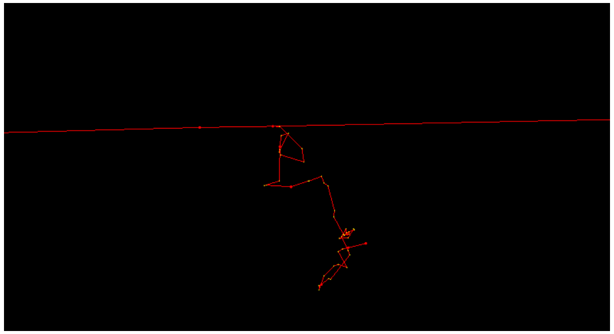
Unique field of radiation physics

Calculation of microdosimetry

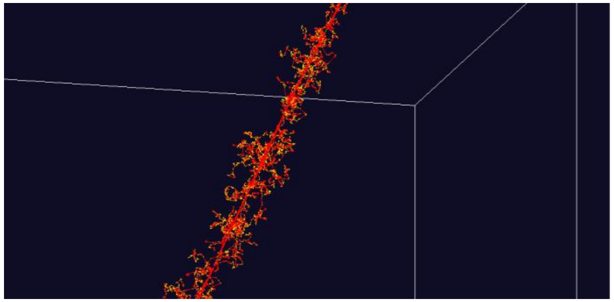


Aim: Having small targets (3.4 nm to 1 µm) → calculation of radiation quality

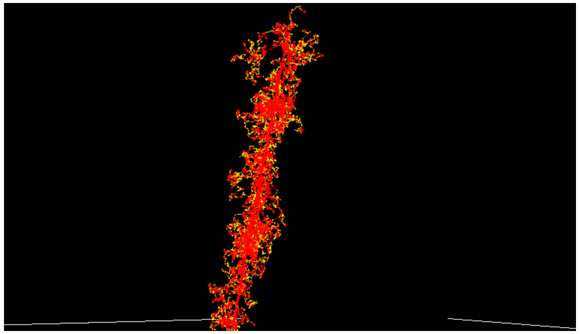
Track structure of different particles



Electron, 10 keV



Proton, 100 keV

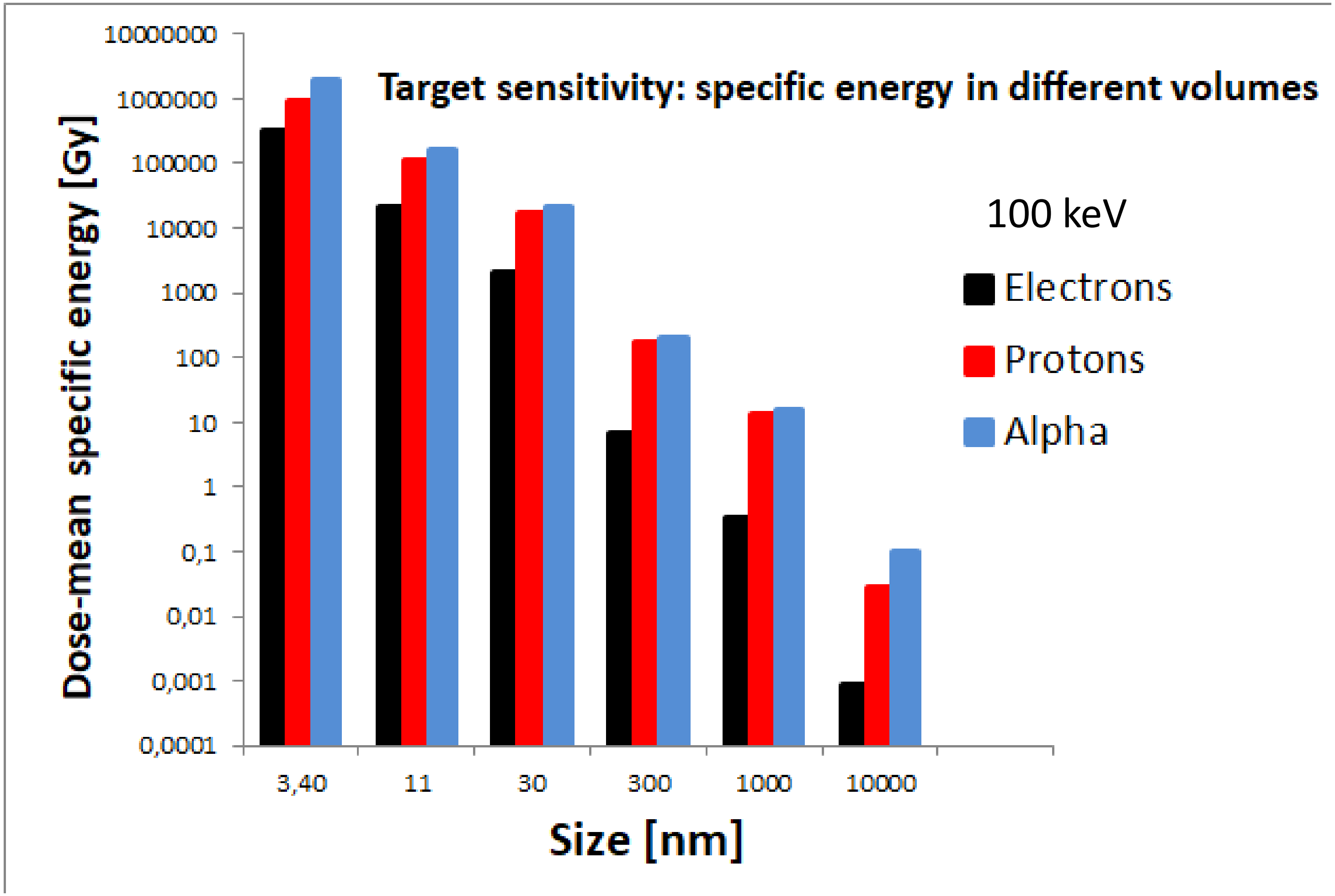


Alpha, 1000 keV

Specific energy of particles

- $z = \frac{E}{m} and\ m = \rho V$
- $\overline{z_d} = \int z d(z) dz = \frac{\int z^2 f(z) dz}{\int z f(z) dz}$
- $\overline{z_d} = \frac{\sum_{j=1}^{N} \left(\frac{\sum_{i=1}^{M} {z_i}^2 \omega_{tp,ij}}{\sum_{i=1}^{M} \omega_{tp,ij}} \right) \frac{\omega_{av,i}}{\sum_{j=1}^{N} \omega_{av,j}}}{\sum_{j=1}^{N} \left(\frac{\sum_{i=1}^{M} z_i \omega_{tp,ij}}{\sum_{i=1}^{M} \omega_{tp,ij}} \right) \frac{\omega_{av,i}}{\sum_{j=1}^{N} \omega_{av,j}}}$

Specific energy vs. Size of the target



Lineal energy vs. Size for different particles

- $y = \frac{E}{\bar{l}} \longrightarrow$ mean-chord length

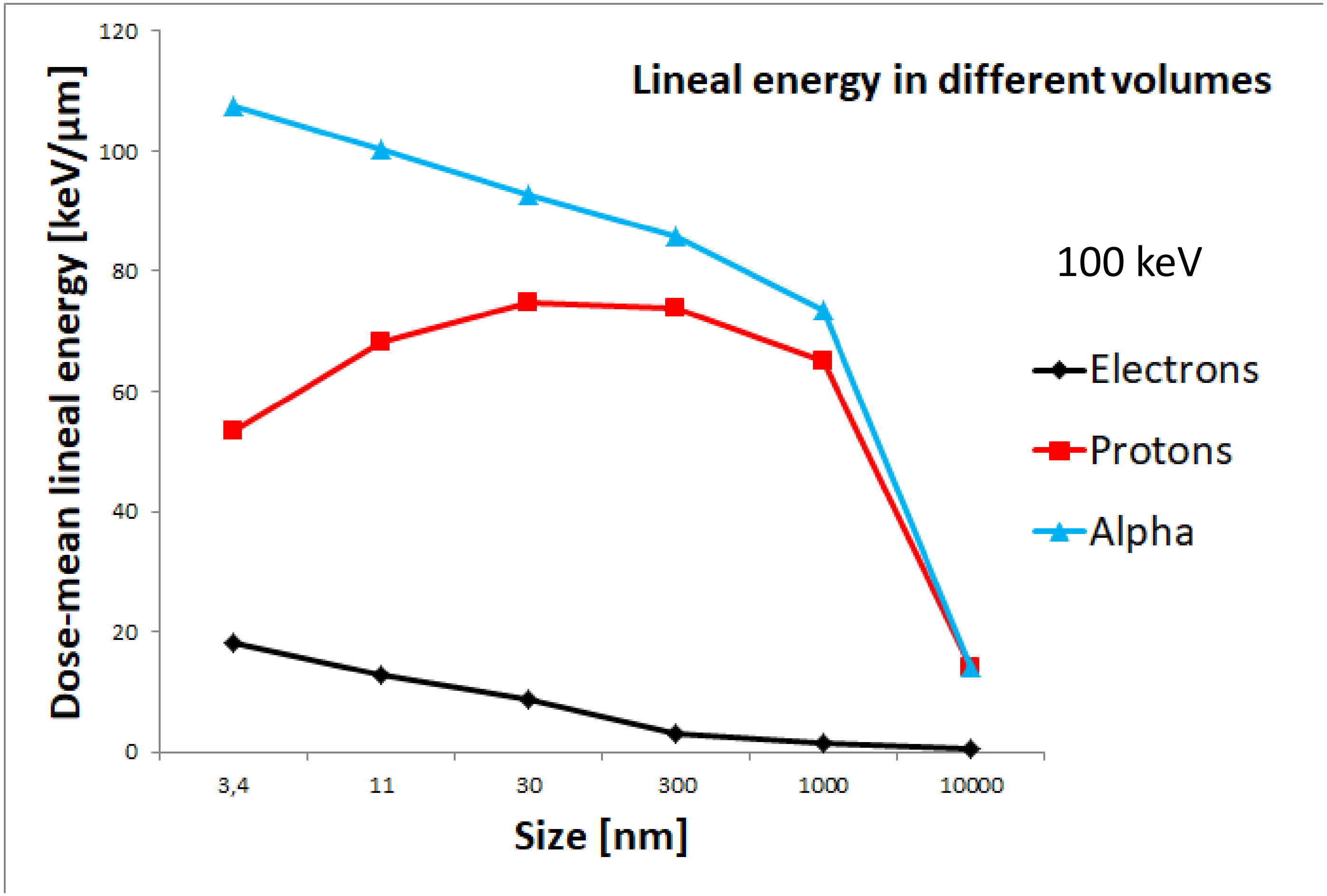
$\bar{l} = \frac{4}{3} r \text{ for spheres}$

$\bar{l} = \frac{2rh}{r+h} \text{ for cylinders}$

- $\overline{y_d} = \int y d(y) dy = \frac{\int y^2 f(y) dy}{\int y f(y) dy}$

- $\overline{y_d} = \frac{\sum_{j=1}^{N} \left(\frac{\sum_{i=1}^{M} {y_i}^2 \omega_{tp,ij}}{\sum_{i=1}^{M} \omega_{tp,ij}} \right) \frac{\omega_{av,i}}{\sum_{j=1}^{N} \omega_{av,j}}}{\sum_{j=1}^{N} \left(\frac{\sum_{i=1}^{M} y_i \omega_{tp,ij}}{\sum_{i=1}^{M} \omega_{tp,ij}} \right) \frac{\omega_{av,i}}{\sum_{j=1}^{N} \omega_{av,j}}}$

Lineal energy vs. Size of the target

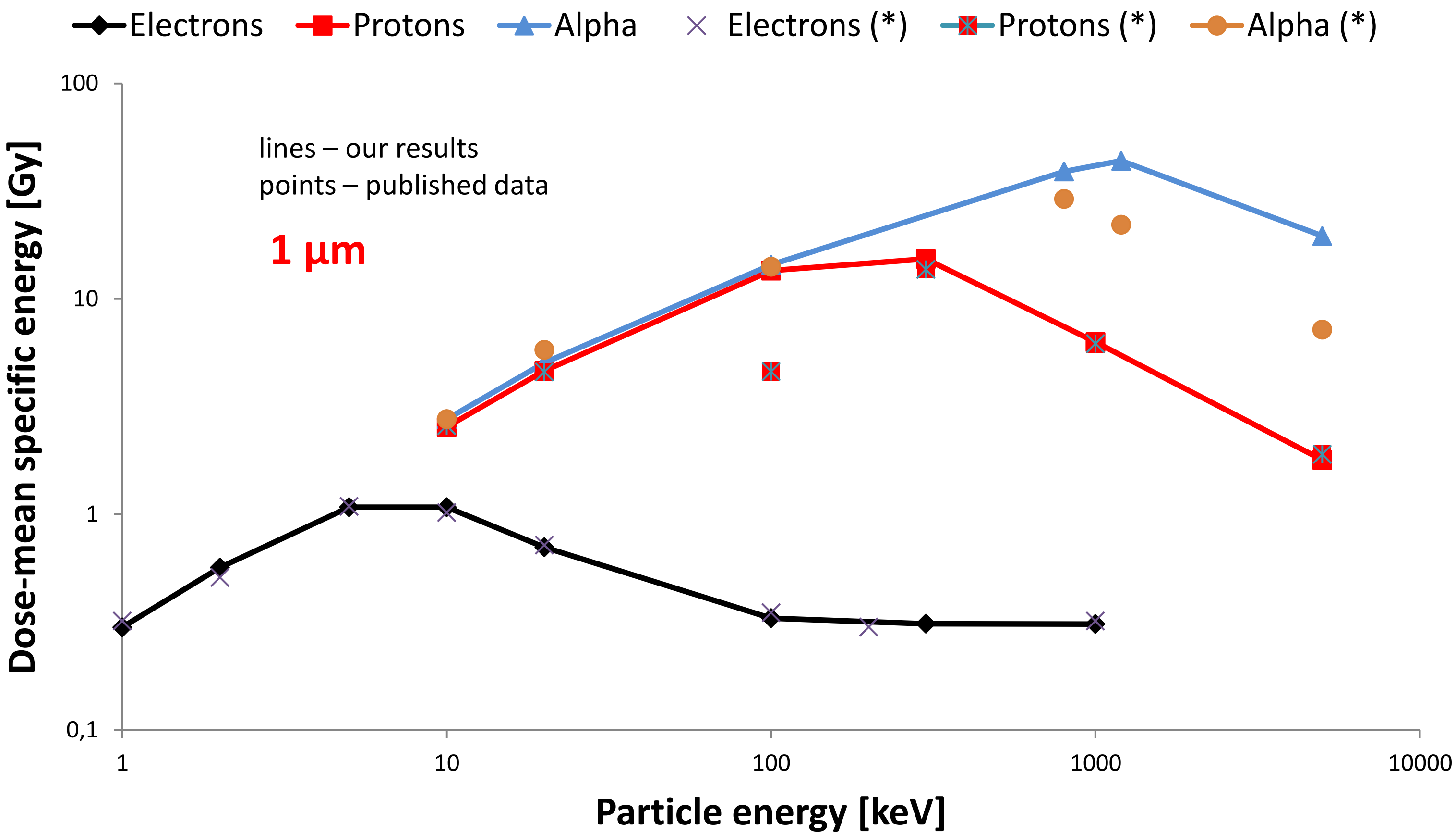


Comparision of numerical simulation results and published data

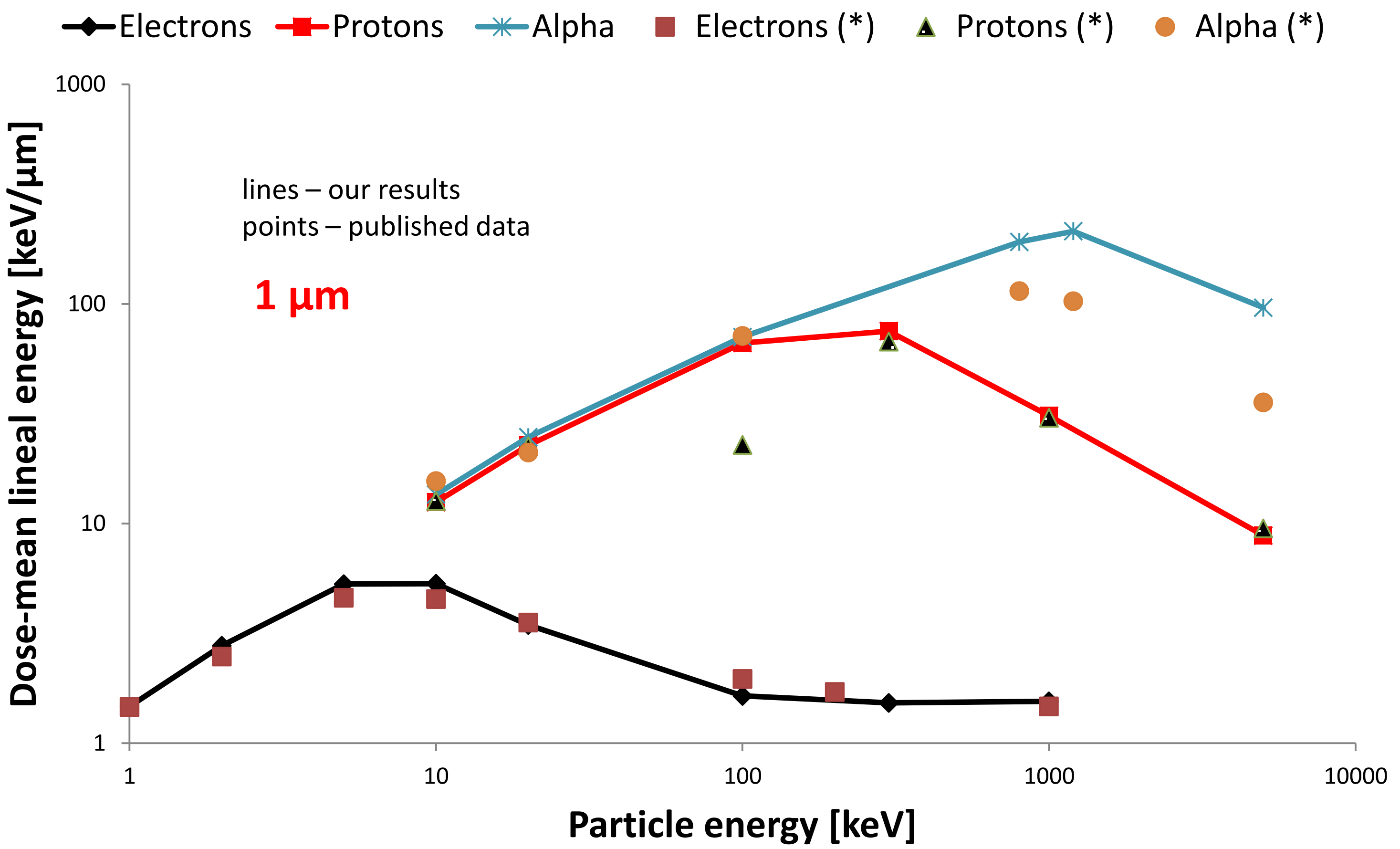
- Electrons: 1,2,5,10,20,100,300,999 [keV]
- Protons: 10,20,100,300,1000,5000 [keV]
- Alpha: 10,20,100,300,800,1200,5000 [keV]

Ploting the graph for particle energy vs. lineal energy and comparing with previous work done by Famulari and Nikjoo

Comparison of numerical simulation results and published data



Comparison of numerical simulation results and published data

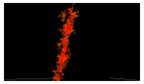


lines – our results
points – published data

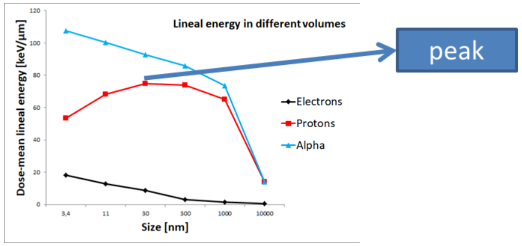
1 µm

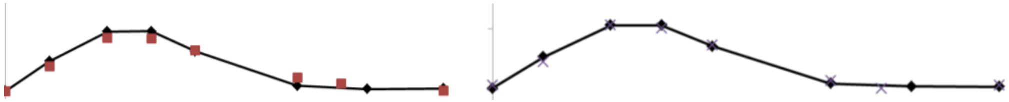
Microdosimetry - conclusions

- For small targets (<1µm) we can estimate with high precision the particle enegy deposition
- Using the GEANT4 we simulated the track of 1 e-, p+, alpha with different energies (10 keV, 100 keV, 1000 keV) and we observed that alpha has the highest energy deposited



- We calculated the lineal energy and specific energy for e-, p+ and alpha
- 30 nm → chromatine model that is more sensitive to protons
- Compared our results with published data
- For e- →good agreement





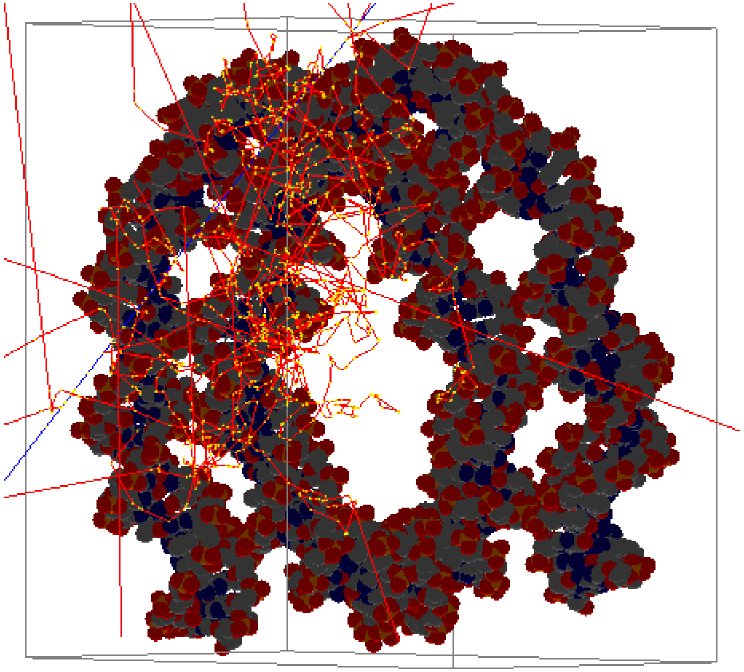
DNA damage
by Sevestrean Vasile

Aim:

- To simulate interaction between radiation (electrons, protons and alpha particles) and DNA
- To score the energy deposition in DNA
- To calculate the DNA damage: SSB and DSB

Modeling & Scoring of E deposition in DNA nucleosome

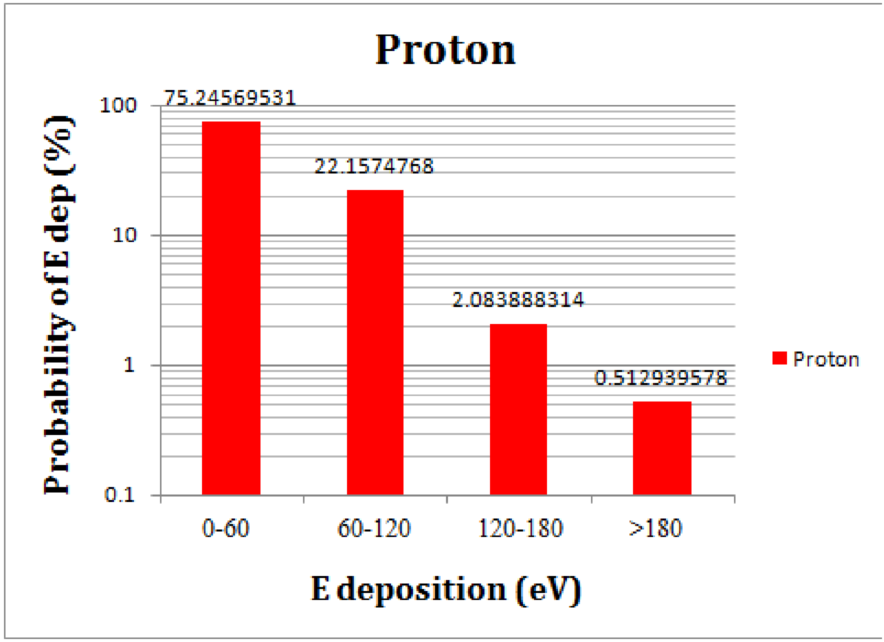
Atoms	Van der Waals radius (nm)	Simulted Color
H	0.12	White
C	0.17	Gray
N	0.155	Blue
P	0.18	Orange
O	0.152	Red

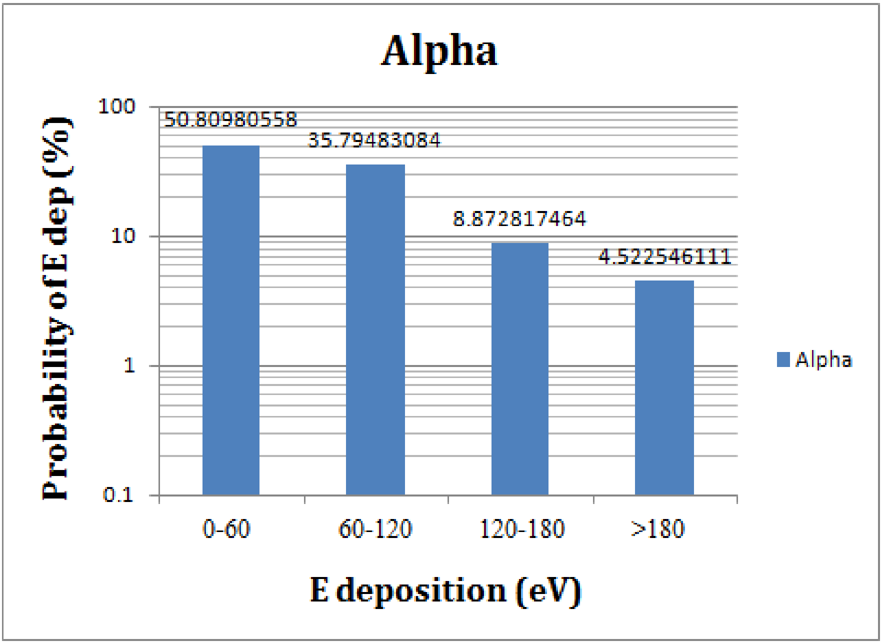


1AOI.pdb: 146 bp

The measurement of energy deposition was as follows: we simulated the path of the incoming particle around the DNA nucleosome. The atoms are represented by spheres and if the particle will deposit energy inside of them it will be scored.

1) Analysis of energy deposition in DNA nucleosome





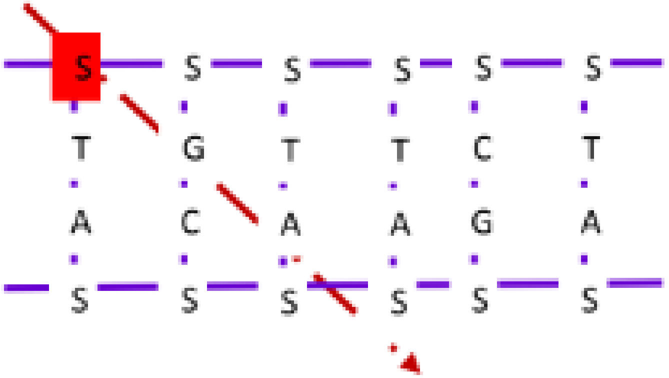
For protons about 75% of the total energy deposition in DNA is less then 60 eV, which is more the alpha particle.

For alpha particle about 50% of the total energy deposition in DNA is less then 60 eV, which is less then the proton.

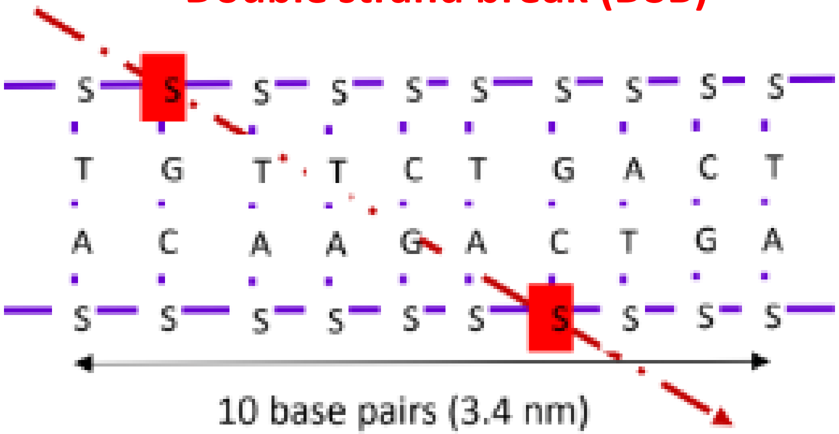
Also the alpha particle tends to deposit energy in higher values (>60 eV) in comparison with the protons.

Counting DNA Breaks

Single Strand Break (SSB)



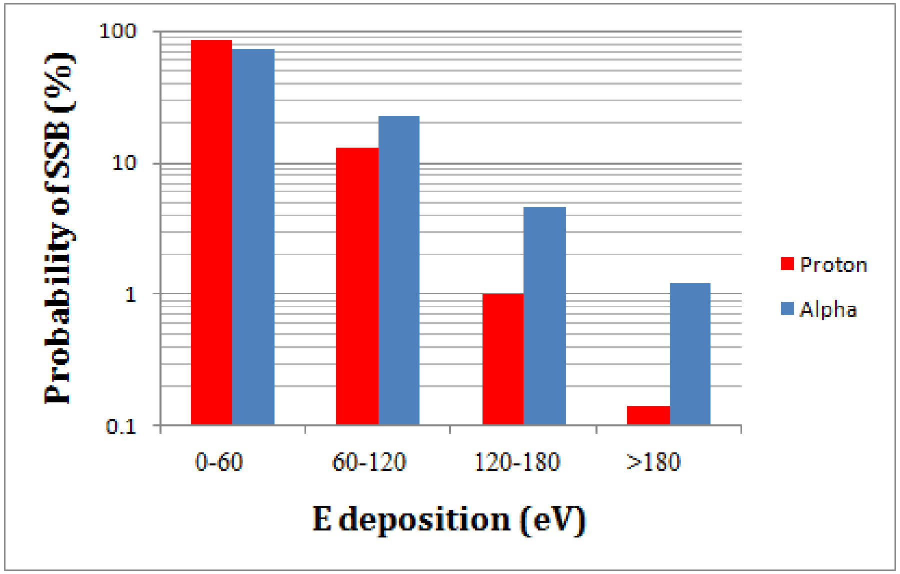
Double strand break (DSB)

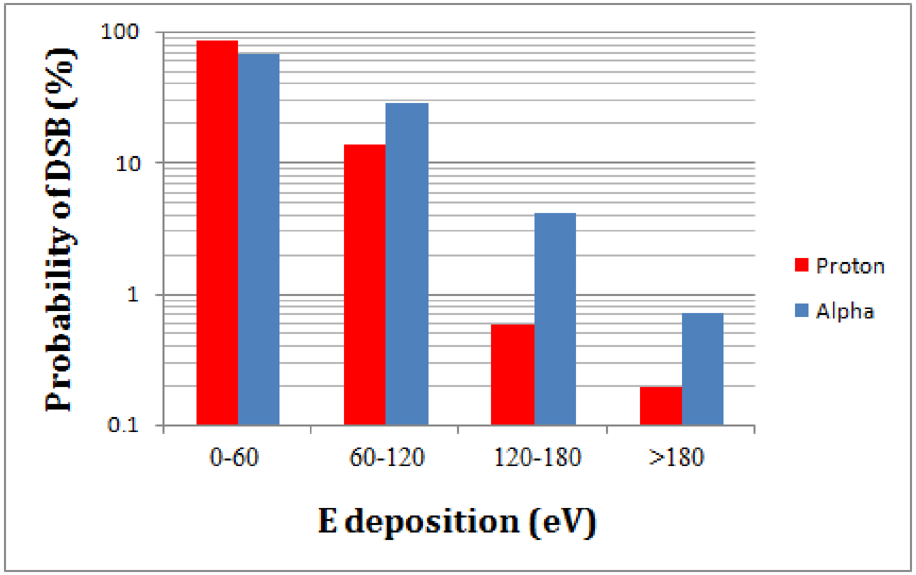


The counting of breaks was done like so:

- If energy deposition in the single strand of DNA > 8 eV then we have a SSB
- If there is a SSB on each strand and the distance between them < 10 base pairs (3.4 nm) then we have a DSB

2) Comparison of SSB and DSB for Proton and Alpha with different energy deposition in DNA



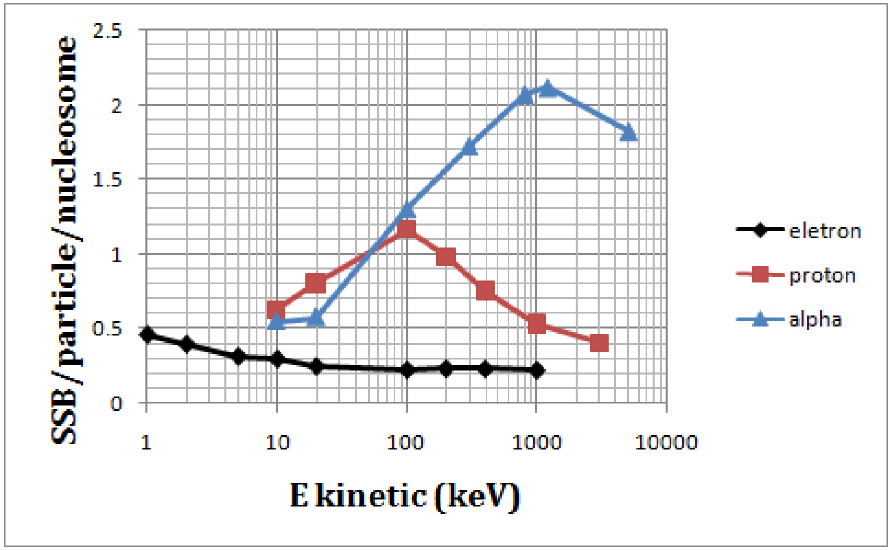


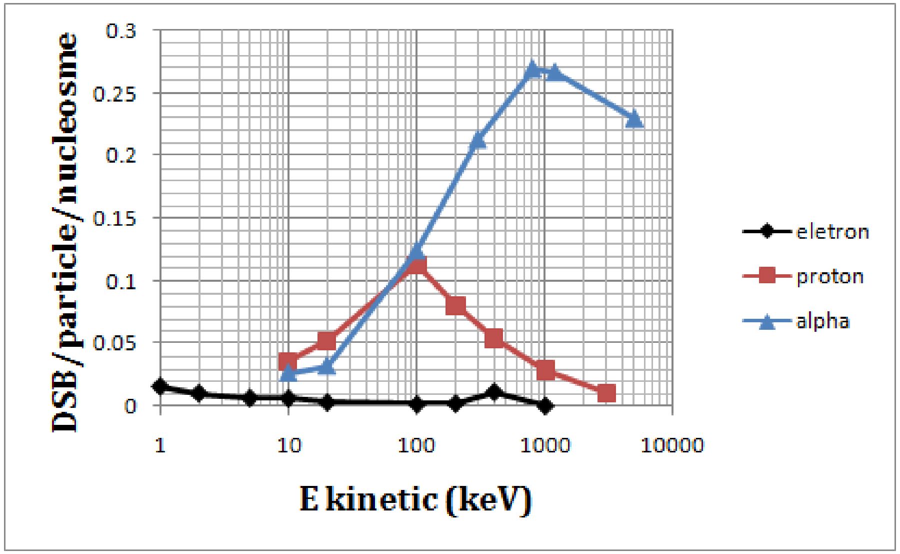
Probability of SSB is about 85% of total SSB damage for proton and 70% for alpha particle for energy deposition lower then 60 eV.

For alpha particle DSB is more efficient when energy deposition more then 60 eV.

As before the alpha particle tends to deposit energy in higher doses compared to the proton, which deposits more in doses lower then 60 eV.

3) Comparison of SSB and DSB for Electron, Proton and Alpha with different energies





With the increase of the energy of the particle, the number of SSB decrease for electron; it increase, hits a peak and decrease for proton and alpha particle.

With the increase of the energy of the particle, the number of DSB decrease for electron; it increase, hits a peak and decrease for proton and alpha particle.

For proton and alpha exist a energy for which the SSB and DSB hits a peak doing more damage then for any other energies from the range we studied.

Conclusions of DNA damage

1)We simulated energy depositon in realistic geometry of DNA nucleosome with atomic resolution

- For proton, more than 75% of total energy deposition in DNA nucleosome is less then 60 eV and about 50% for alpha
- Alpha tends to do SSB and DSB with higher energy deposition compared to proton
- For energy deposition more then 60 eV alpha particle is dominant over proton DNA damage

2)Then we calculated SSB and DSB for different particles and different energies

- Simulation result were analysed by using Microsoft Excel

Cluster analysis by Ioana Kuncser

Cluster analysis

Track structure of different particles

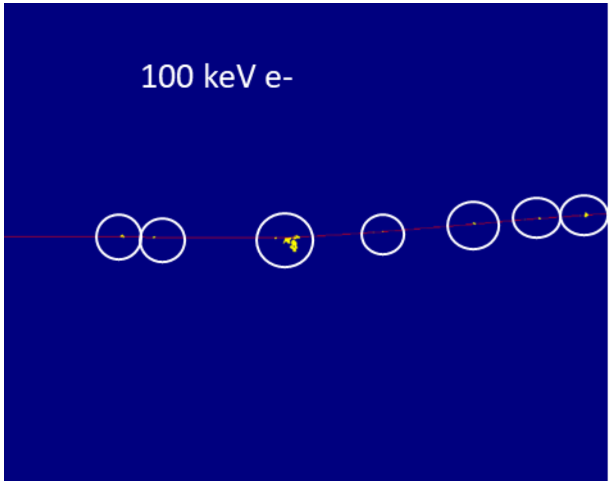
Probability of clustered and isolated DNA damage

SSB and DSB per track and per micrometer

Clustering Algorithms and energy depostion clustering?

K-MEANS and DBSCAN

H. Späth, Cluster Analysis Algorithms for Data Reduction and Classification of Objects (Halsted Press, New York, (1980), p. 226.
J. A. Hartigan and M. A. Wong, “A Kmeans clustering algorithm,” Appl. Stat. 28, 100–108 (1979).



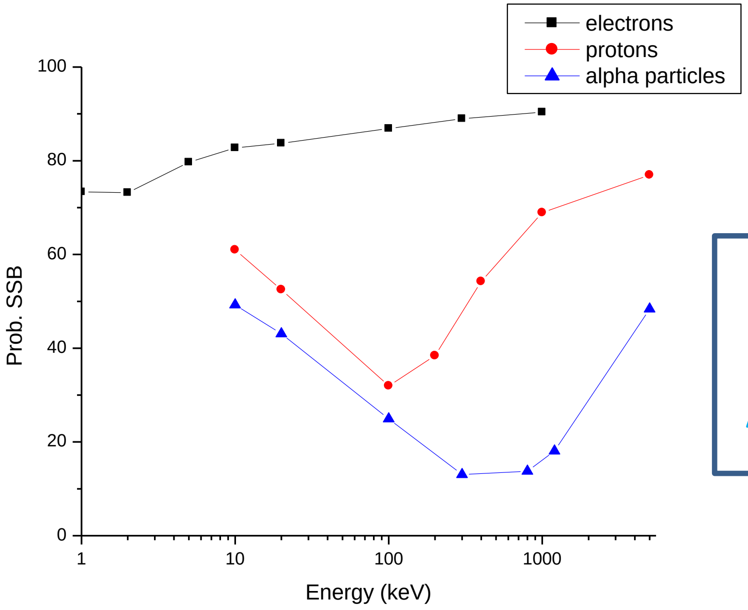
➢ **Definition of Clustering Algorithm:**

- Input cluster radius, R
- Detect groups of neighbor points if EuclideanDist() < R
- Generate center of clusters
- Append each energy deposit point to the closest center
- Recalculate new clusters positions from the clustered point positions
- Count clusters when allocated values in clusters more than threshold values

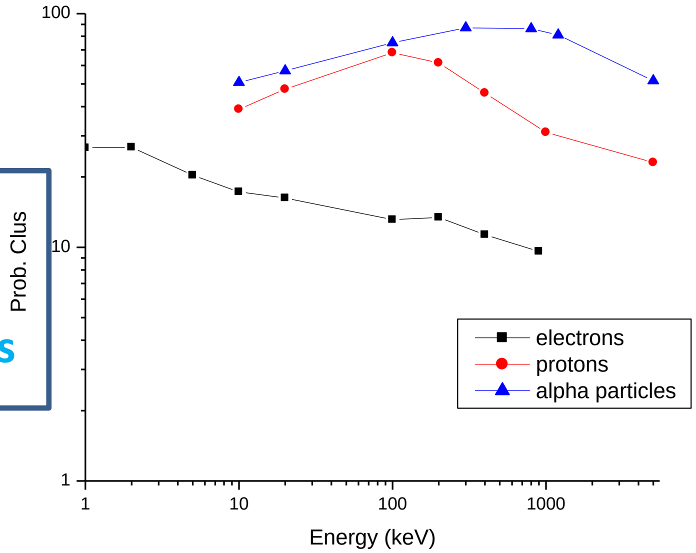
Batmunkh et al., Cluster analysis of HZE particle tracks as applied to space radiobiology problems, (2013)
Francis et al., Simulation of DNA damage clustering after proton irradiation using an adapted DBSCAN algorithm, (2012)

Cluster Analysis in track structure of different particles

Isolated damage



Clustered damage



Electrons
Protons
Alpha particles

Probability of isolated damage is about 80% of the total damage for electrons

When you increase the electron energy the probability of isolated damage is increasing. For protons and alpha particles this probability is first decreasing and after increasing

Probability of clustered damage is about 20% of total damage for electrons

When you increase the electron energy the probability of clustered damage is decreasing. For protons and for alpha particles this probability is first increaing and after decreasing .

Electrons
Protons
Alpha particles

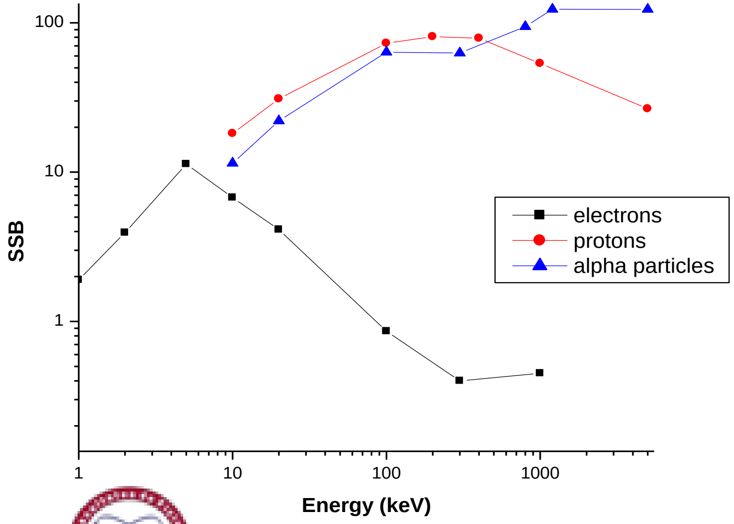
- **Single Strand Breaks** and **Double Strand Breaks** per track per micrometer depends on particle energy
  - **When increase energy of particles, Single Strand Breaks and Double Strand Breaks per track per micrometer are increasing and decreasing**
  - **Peaks for SSB:**

Electrons: 5 keV (SSB=11.28), Protons: 400 keV(SSB=81.44), Alpha particles: 1.22 MeV(SSB=121.9)

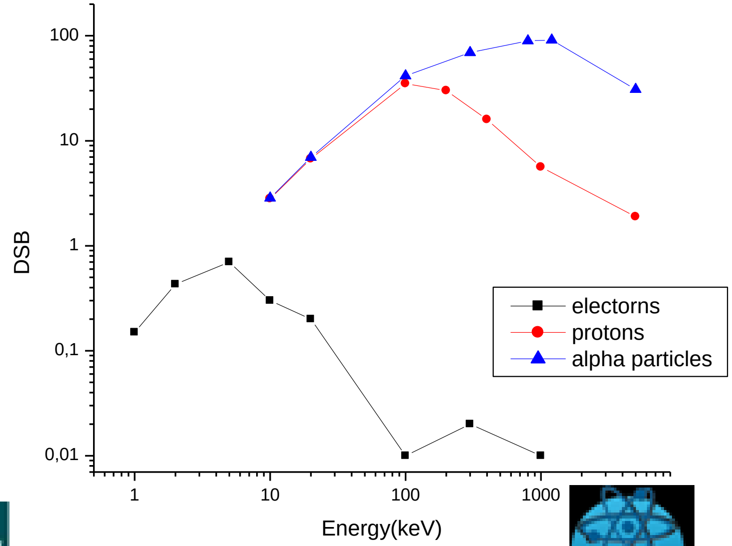
- **Peacks for DSB:**

Electrons: 4.66 keV(DSB=0.7), Protons:105 keV(DSB=33.77),Alpha particles: 1,13 MeV(DSB=81.84)

Single Strand Breaks for electrons, protons and alpha particles

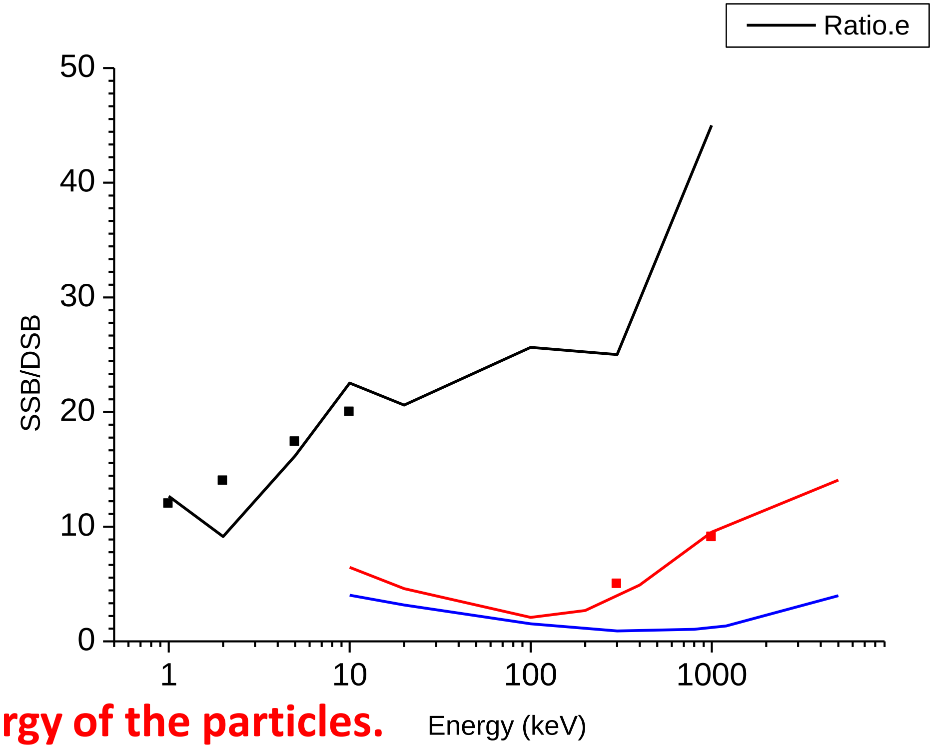


Double Strand Breaks for electrons, protons and alpha particles



SSB/DSB Ratio

The ratio between Single Strand Breaks and Double Strand Breaks for electrons, protons and alpha particles



Electrons
Protons
Alpha particles

Ratio of SSB and DSB depends on energy of the particles.

electrons → Energy from 1 keV to 1000 keV → Ratio increase from 9.2 to 45.12

protons → Energy between 10 and 5000 keV → Ratio is between 2.3 and 14.3

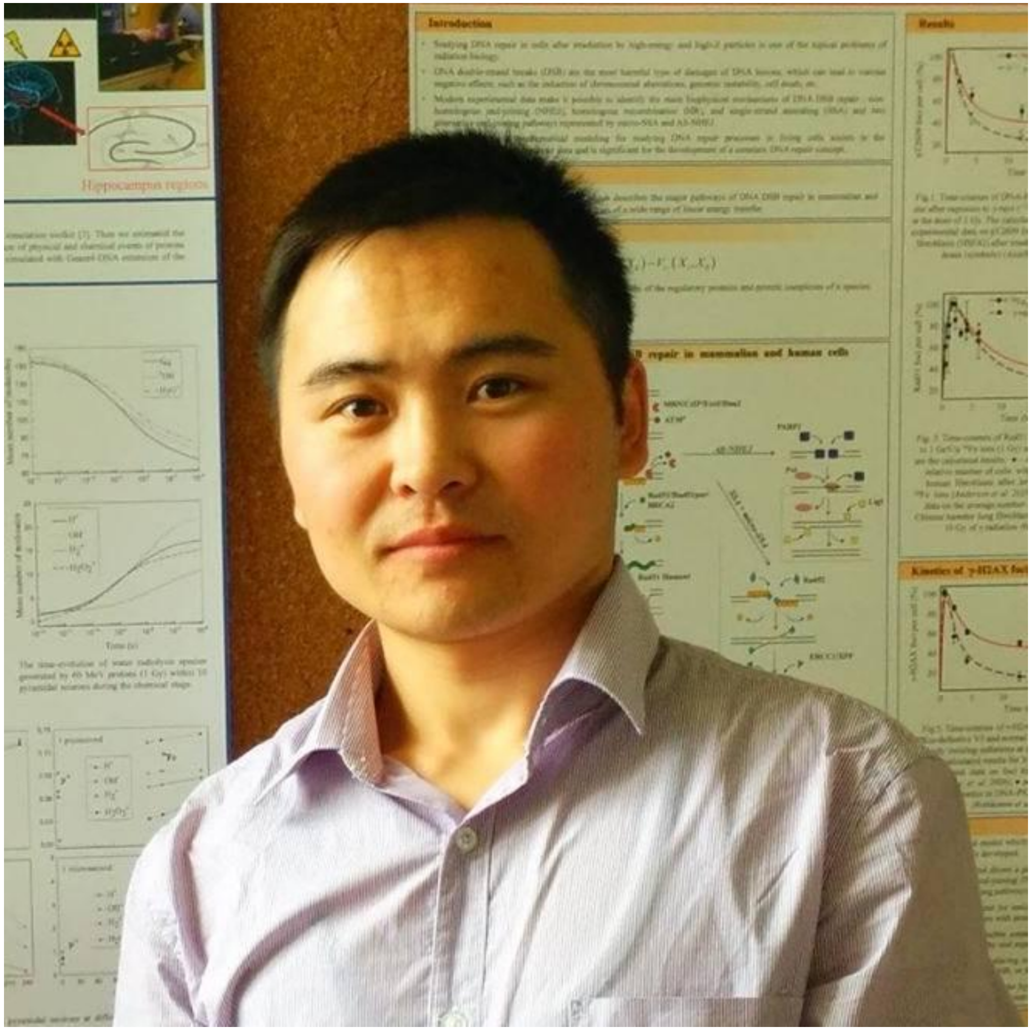
alpha particles → Energy between 10 and 10000 keV → Ratio is between 0.5 and 4.2

Conclusion of “Cluster analysis”

- The clustered and isolated damage were measured for energies between 1 keV and 1000 keV for electrons,between 10 keV and 5000 keV for protons and between 10 keV and 10000 keV alpha particles
- Simulation results were analyzed using the Wolfram Mathematica and Origin
- By plots it can be seen that isolated damage by electrons was more than by protons and alpha particles and clustered damage by alpha was more than by electrons and protons
- DNA damage was done comparing the simulated data with published data
- Finally, we obtained practical experience with numerical method of microdosimetry, nanodosimetry and DNA damage calculation using Geant4 Monte Carlo simulation toolkit and analyzing softwares.

Thank you for your attention!

Special thanks to our supervisor!



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