بسم الله الرحمن الرحيم

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Sector of Mathematical Modeling of Radiation Induced Effects

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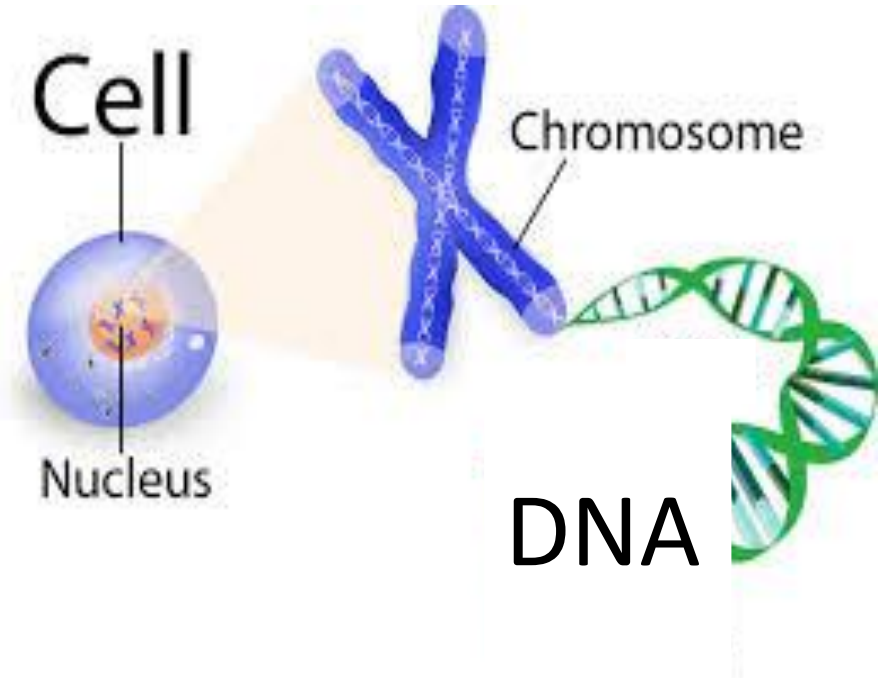# *Geant4 applications for computational radiation biology:* **Calculation of DNA strand breaks**
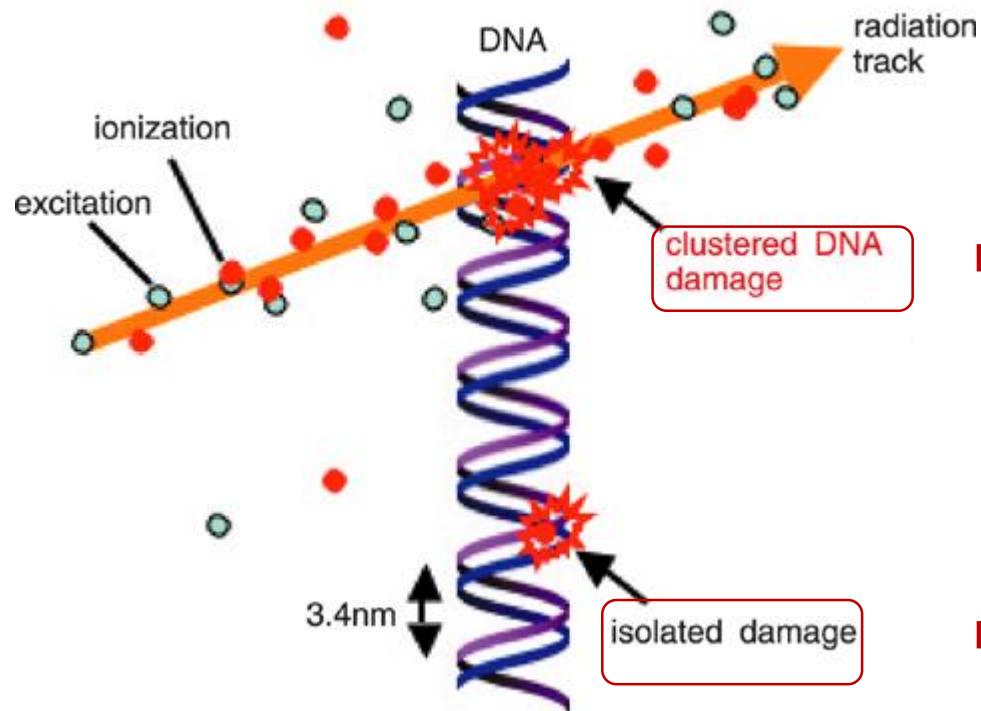
Outline

➤ *Purpose of this project*

➤ *Background*

➤ *Methods*

➤ *Results*

➤ *Conclusions*

Purpose of this project

Precise estimation of DNA damage induced by ionizing radiation with different qualities, as it is one of the main issues of space radiobiology and radiotherapy.

DNA is cell`s sensitive structure!

– two or more strand breaks of DNA molecule

– single strand break of DNA molecule

Background

Types of ionizing radiation:

- X-rays
- Gamma rays
- Beta particles
- Alpha particles
- Neutrons & **protons**
- **Heavy charged particles (^{12}C ions)**

Sources:
- Radioactive isotopes
- Sun and Cosmic rays
- Particle accelerators

# Initial effects of ionizing radiation in biological medium

Initial **physical** (direct) and **chemical** (indirect) of **ionizing radiation** events in biological medium are produces direct and indirect damages of DNA molecules.

Incident & secondary particles interacts with biological medium (liquid water)

Generate physico-chemical processes (ionization, excitation and radiolysis)

Created species interacts with the crucial sites of DNA structure

Produce isolated and clustered DNA damages
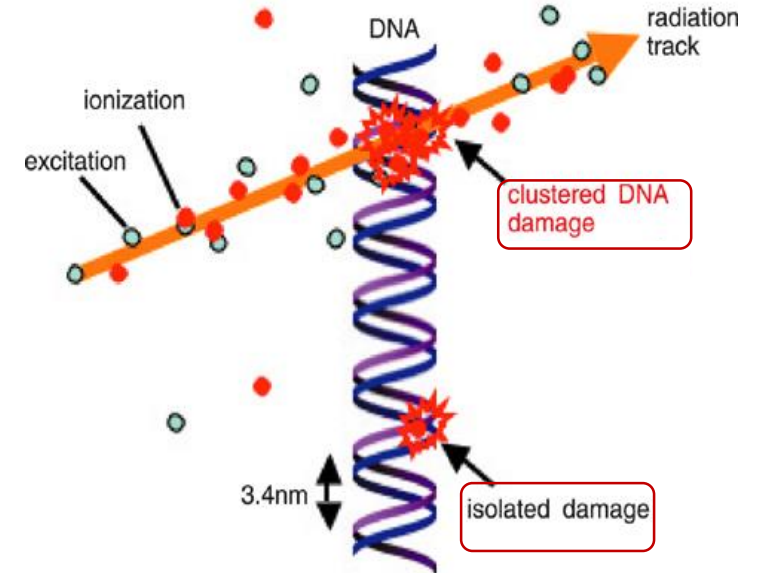
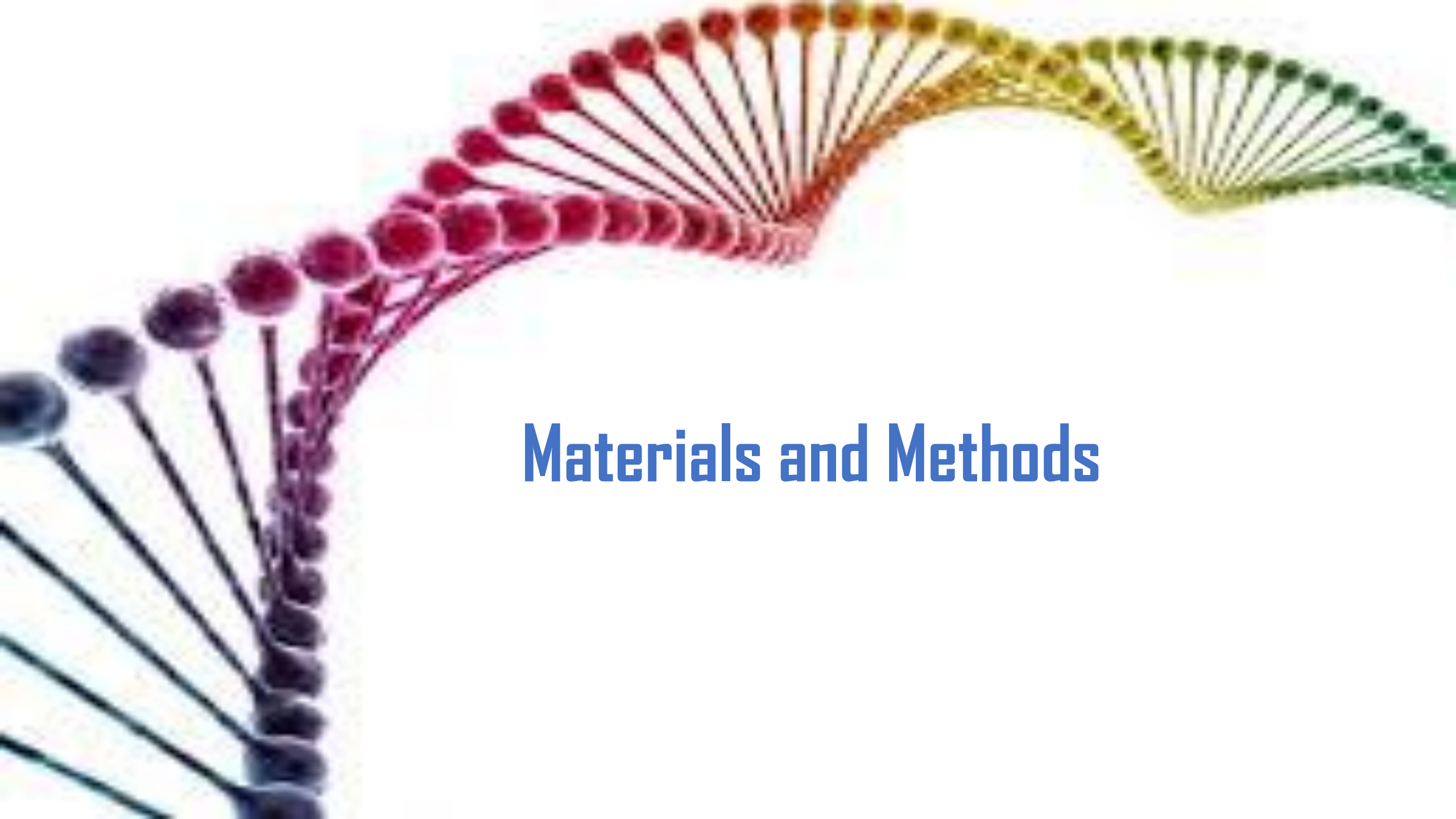killing tumour (cancer) cells as clustered damage sites are difficult to repair

Virtual Experiments with Monte-Carlo simulation

Monte Carlo numerical simulation based on experimental data (cross section) is a suitable technique for understanding the fundamental mechanisms of radiation-induced biological damage.
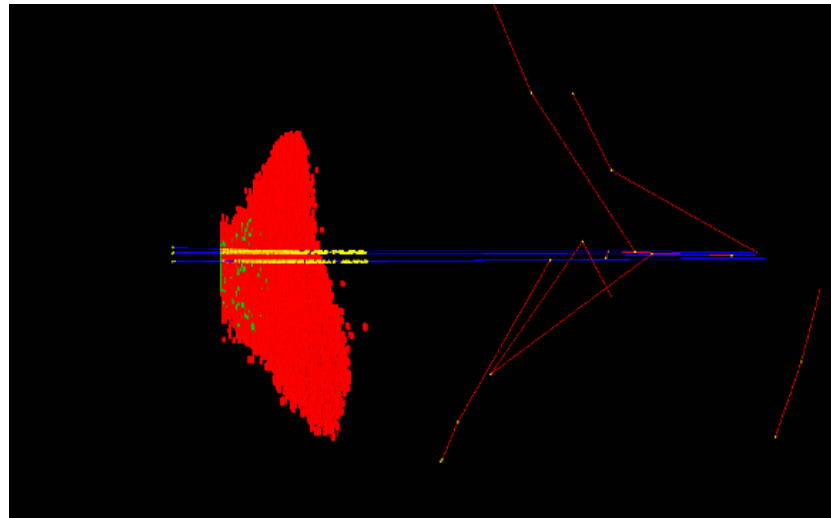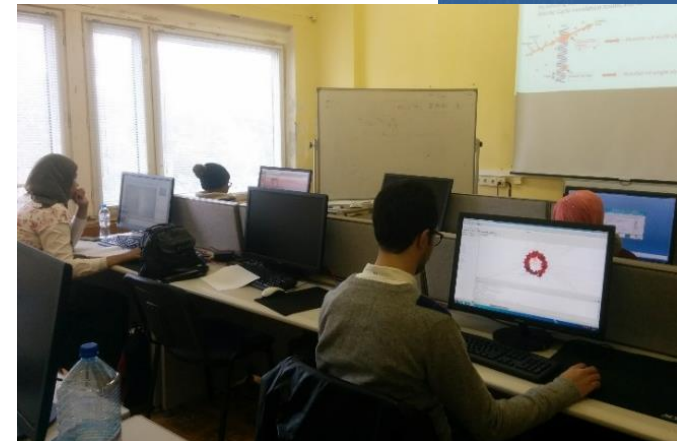

Geant4 modeling of microbeam at CENBG

Materials and Methods

The numerical simulation tools for virtual experiment:

1. Geant4/Geant4-DNA Monte Carlo simulation toolkit
2. QT visualization tool
3. C++ programming language
4. Clustering algorithms and pdb libraries
5. ROOT data-analysis software
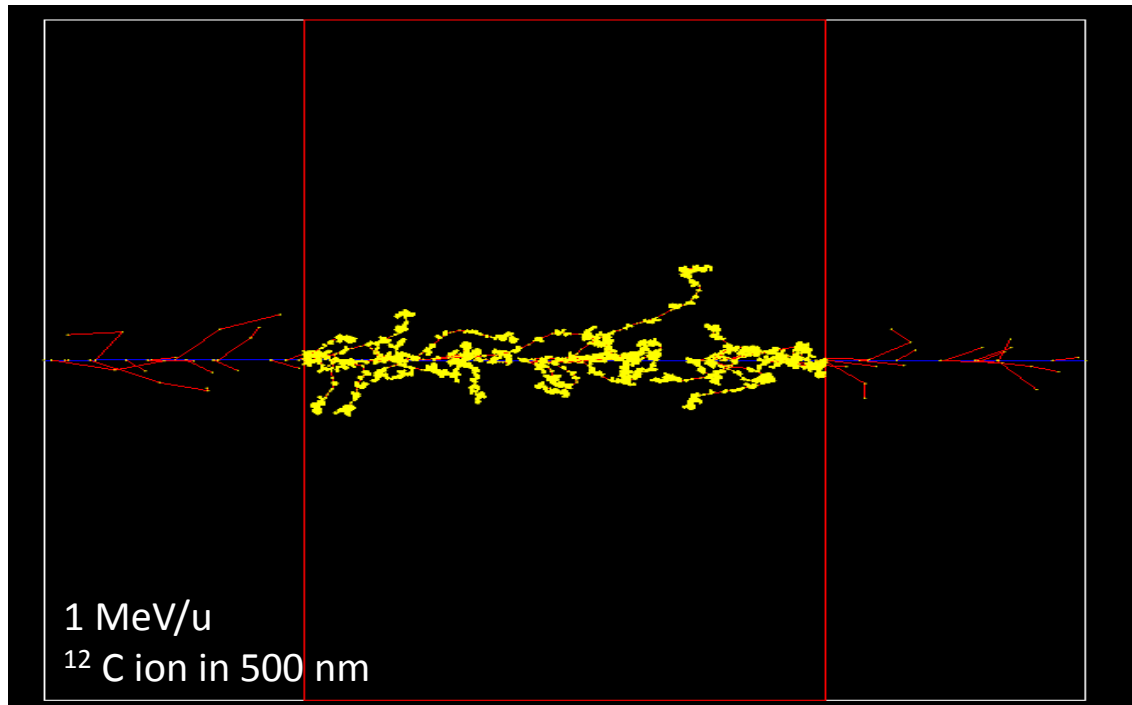6. Cluster computers at JINR

Geant4/Geant4-DNA particle track structure simulation provides exact nature of stochastic energy depositions and free-radical species following the physico-chemical stages of radiation action on matter.
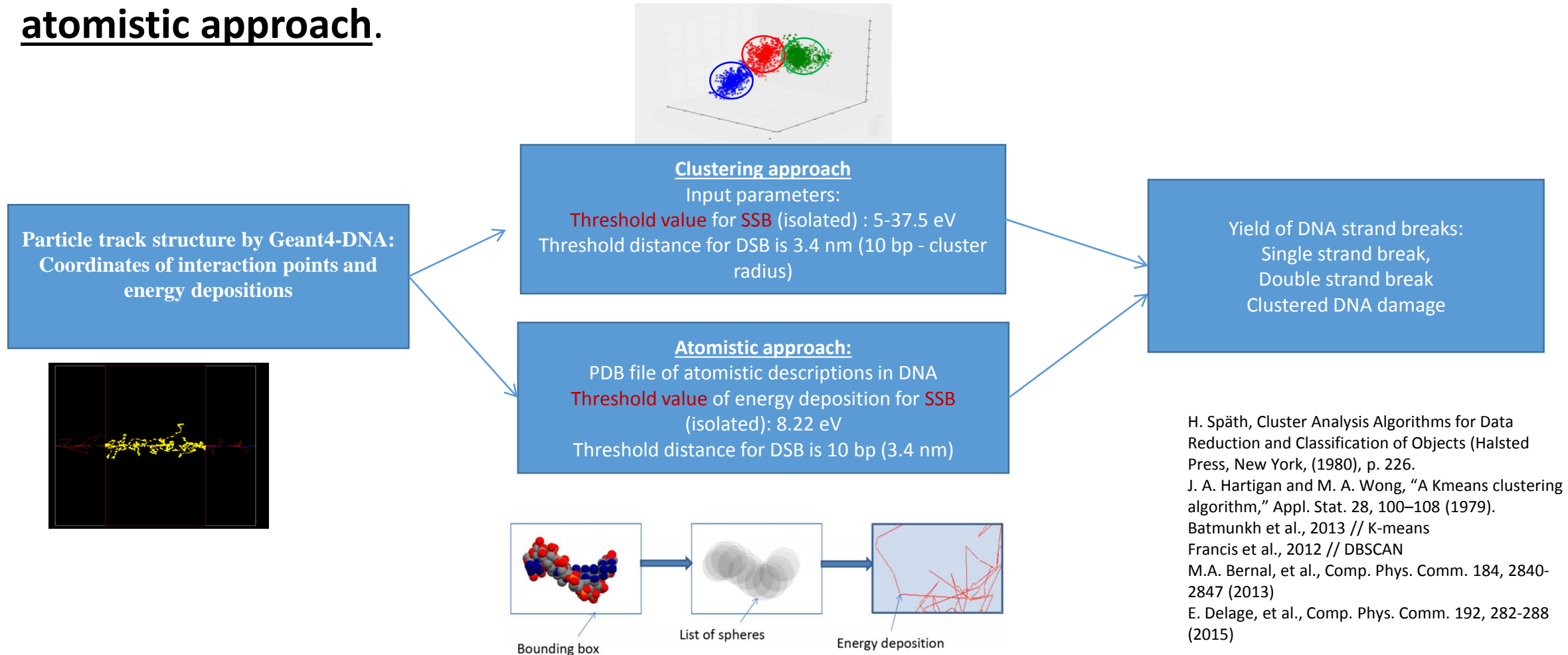
Geant4   **Geant4-DNA**   *Geant4*

1 MeV/u
^{12}C ion in 500 nm

Geant4 (http://geant4.cern.ch/)
Geant4-DNA (http://geant4-dna.org/)

Methods (2): *Numerical methods for DNA damage calculation*

In order to estimate precise number of DNA strand breaks along the track structure in biological medium we used **clustering algorithms** (K-means and DBSCAN) and **atomistic approach**.

Particle track structure by Geant4-DNA:
Coordinates of interaction points and energy depositions

Clustering approach
Input parameters:
Threshold value for SSB (isolated) : 5-37.5 eV
Threshold distance for DSB is 3.4 nm (10 bp - cluster radius)

Atomistic approach:
PDB file of atomistic descriptions in DNA
Threshold value of energy deposition for SSB (isolated): 8.22 eV
Threshold distance for DSB is 10 bp (3.4 nm)

Yield of DNA strand breaks:
Single strand break,
Double strand break
Clustered DNA damage

Bounding box   List of spheres   Energy deposition

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).
Batmunkh et al., 2013 // K-means
Francis et al., 2012 // DBSCAN
M.A. Bernal, et al., Comp. Phys. Comm. 184, 2840-2847 (2013)
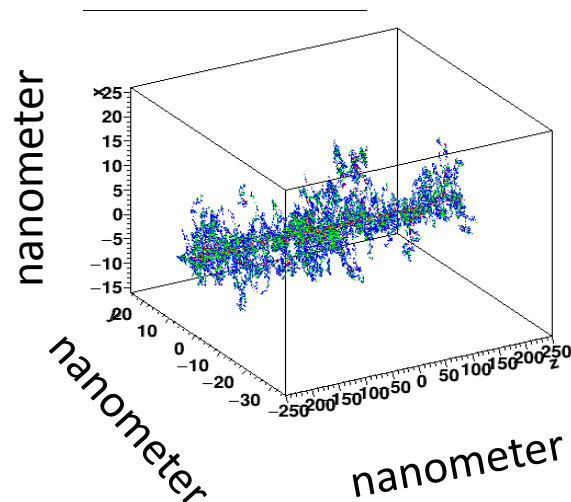E. Delage, et al., Comp. Phys. Comm. 192, 282-288 (2015)

Results

1) Time and space evolution of particle track structure at physical and chemical stage

- **Track structure of 0.5 MeV proton in 500 nm water volume**
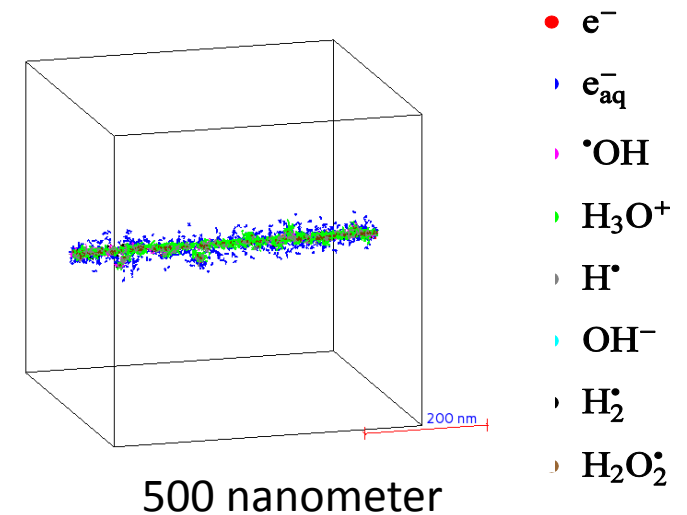
Physical stage of particle track at 1 fs

Chemical stage of particle track at 10 ns

For protons:
Ionisation
Electronic Excitation
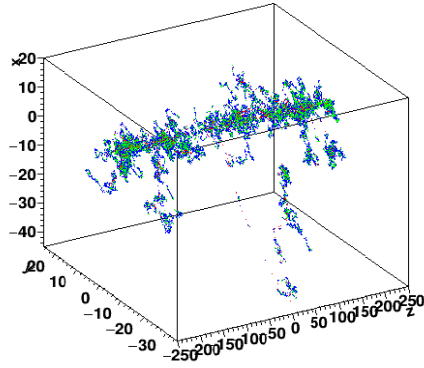Elastic scattering
ChargeDecrease

For secondary electrons:
Ionisation
Electronic Excitation
Vibrational Excitation
Elastic scattering
Attachment

- e^-
- e^-_{aq}
- $^\cdot OH$
- H_3O^+
- $H^\cdot$
- OH^-
- $H_2^\cdot$
- $H_2O_2^\cdot$

500 nanometer

2) Compare track structure of proton and carbon ion with same kinetic energy (1 MeV/u)

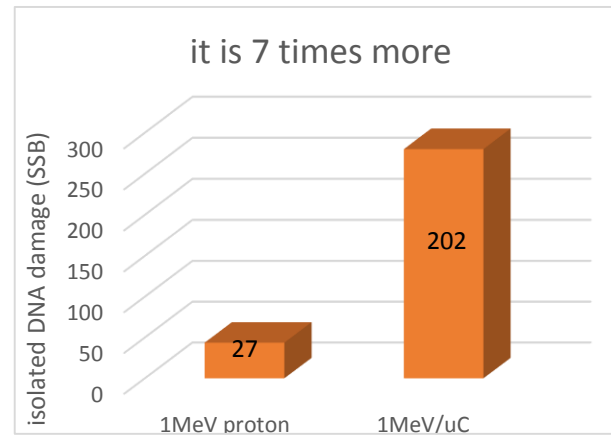**Track structure of 1 MeV proton**
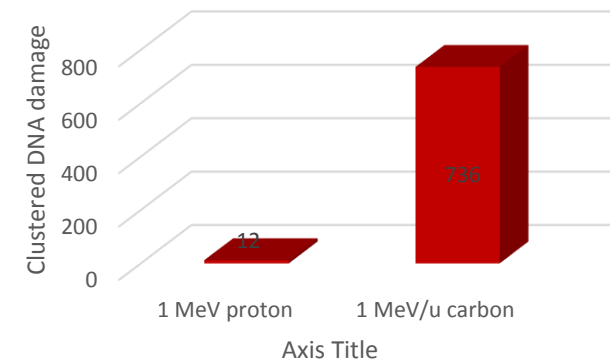
Track structure of 1 MeV/u carbon
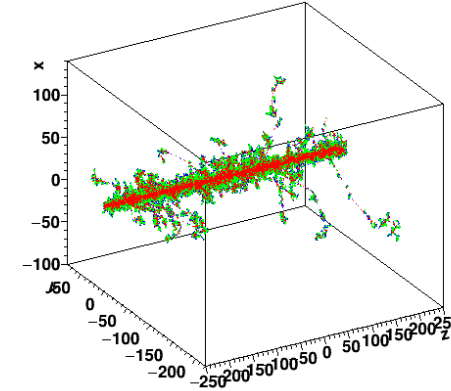
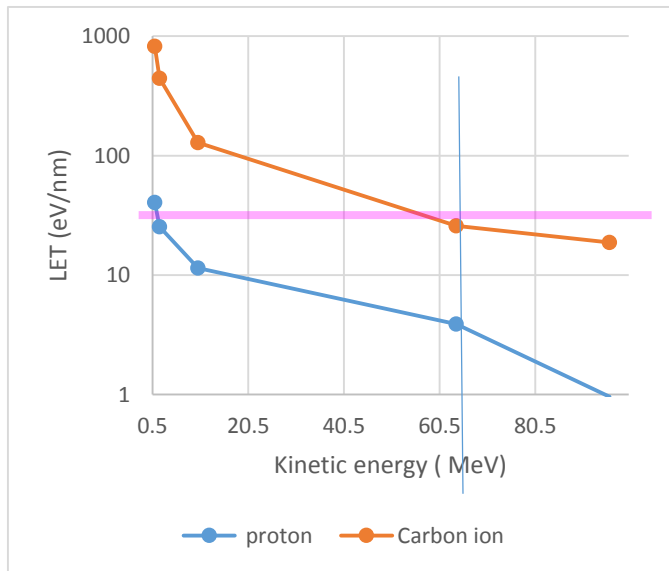
it is 23 times more
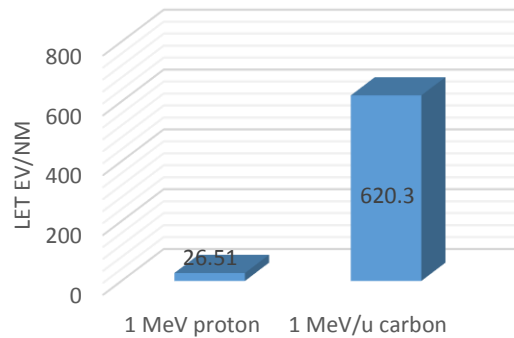
it is 7 times more

it is 60 times more

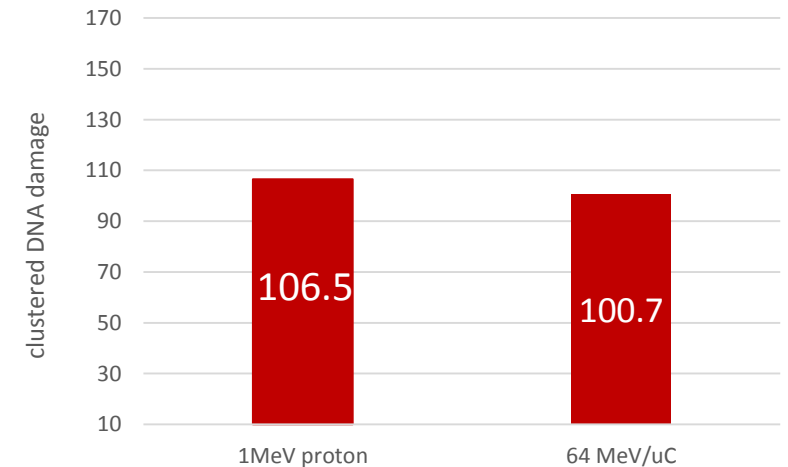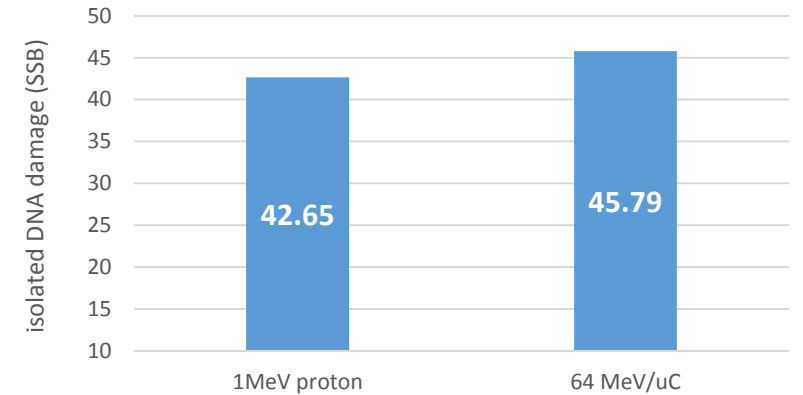# 3) Comparison of DNA strand breaks for protons and carbon ions with different energies (at same LET)

Proton: 0.5, 1, 3, 10, 50, 80 MeV
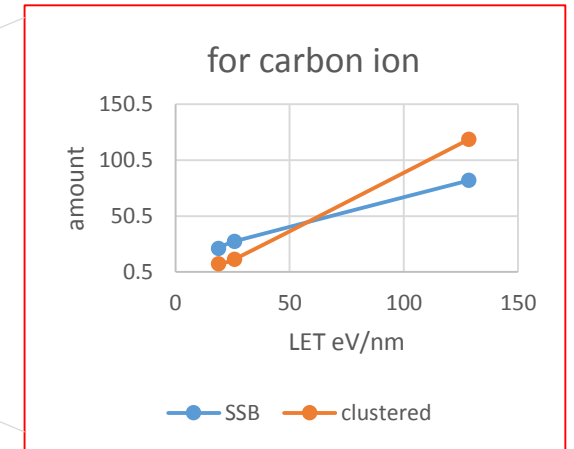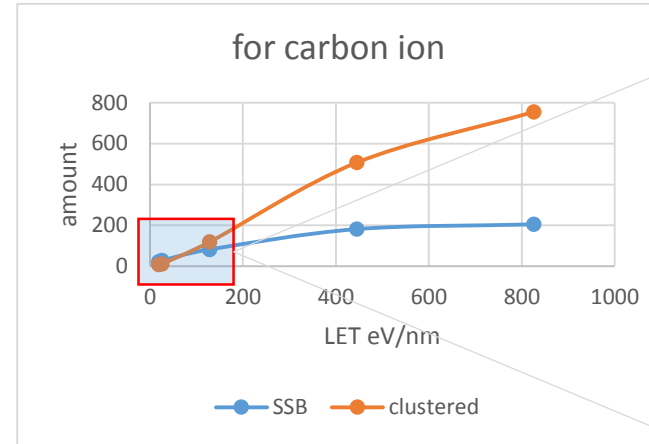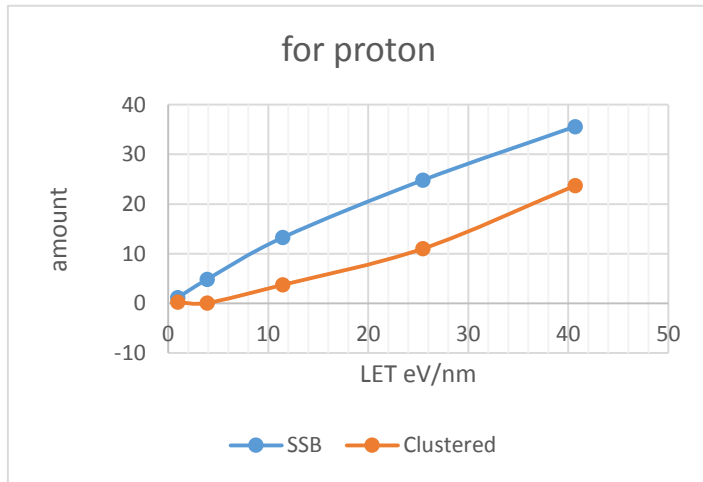
Carbon ion: 1, 2, 10, 30, 64, 96 MeV

Same LET (26 eV/nm) at 1 MeV proton, 64 MeV/u carbon.

Large energy deposition (LET) is scored when kinetic energy is lower than 10 MeV

4) Comparison of DNA strand breaks for protons and carbon ions with different energies

Proton: 0.5, 1, 3, 10, 50, 80 MeV
Carbon ion: 1, 2, 10, 30, 64, 96 MeV

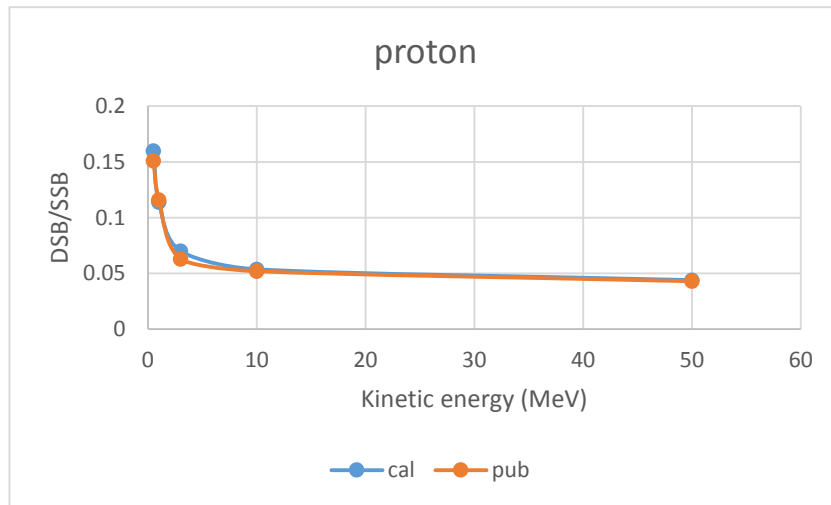For protons, isolated DNA damage is always more than clustered DNA damage

For carbon ion, isolated DNA damage is more than clustered DNA damage when low-LET. Large amount of clustered DNA damage is counted when high-LET
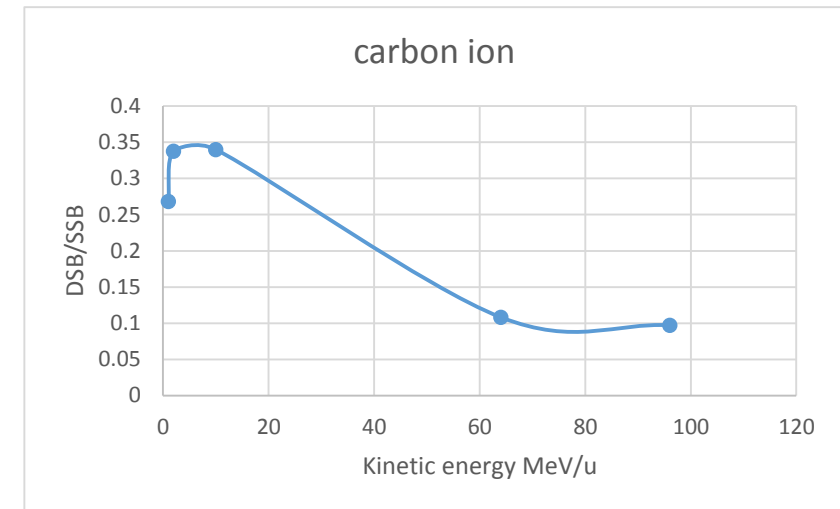
5) Comparisons of DSB/SSB ratio with published data

Proton: 0.5, 1, 3, 10, 50 MeV
Carbon ion: 1, 2, 10, 30, 64, 96 MeV

* Experimental and calculation data of published
literature (Francis et al., 2012)

In the case of proton, DSB/SSB ratio decreases when energy increasing. Calculation results good agreement with published data.

In the case of carbon ion, DSB/SSB ratio more than protons. At 1 MeV/u, ratio lower than 2 MeV/u energy. Than ratio decreases when energy increasing.

6) Simulation of atomistic model of DNA molecules with different forms

Form of **A-DNA** double helix

Form of **B-DNA** double helix

Form of **Z-DNA** double helix
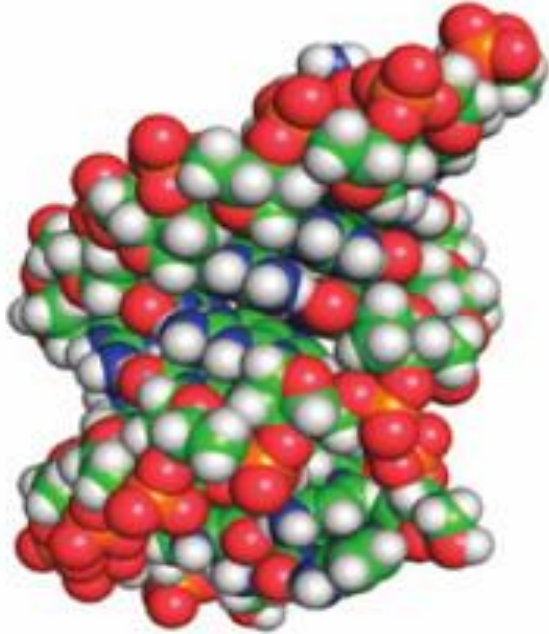
Short and broad
2d47.pdb

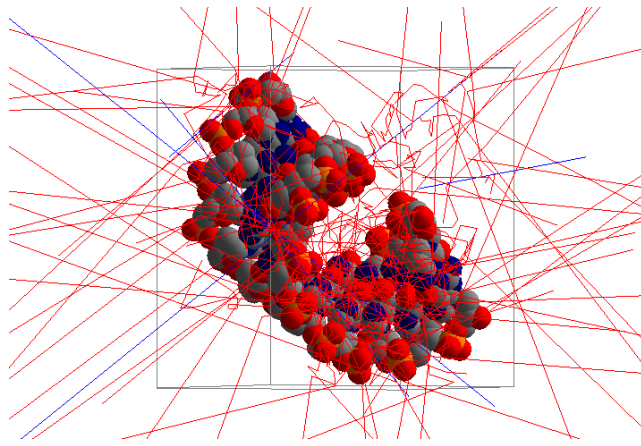Longer and thinner
355d.pdb

Elongated and slim
1dcg.pdb

R. H. Garrett (2016)

7. *Simulation of atomistic model of DNA molecules under irradiation with 1 MeV/u carbon ion*

5 particles

Screenshot of A-DNA (12 bp)

Screenshot of B-DNA (12 bp)
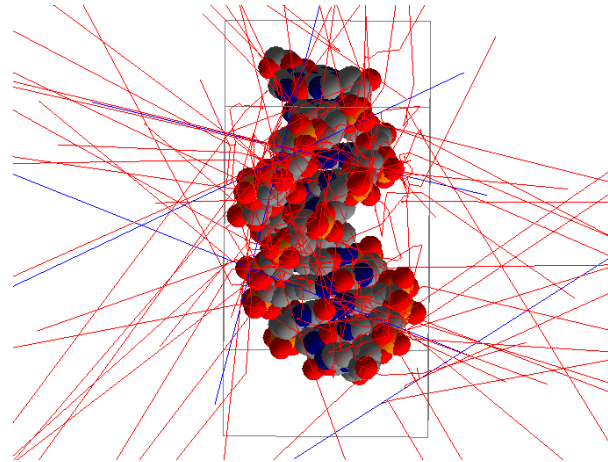
Screenshot of Z-DNA (6 bp)

2d47.pdb

Number of SSB = 7
Number of DSB = 0

355d.pdb

Number of SSB = 3
Number of DSB = 0
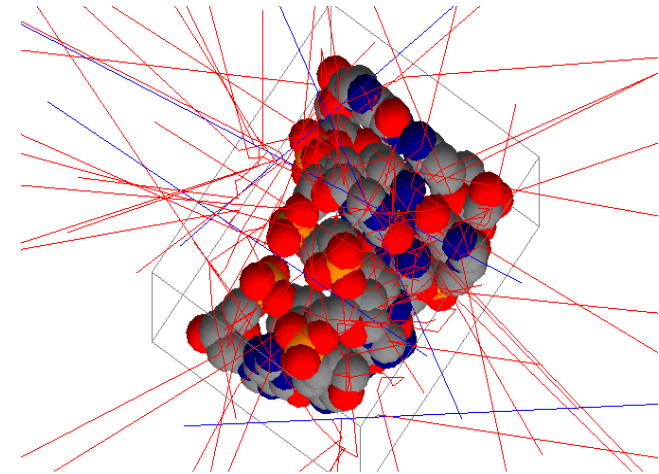
1dcg.pdb

Number of SSB = 2
Number of DSB = 2

Conclusions

➢We have simulated track structure of different LET particles in nanometer volume at physical and chemical stages using the Geant4-DNA Monte Carlo code.

➢We have calculated DNA strand breaks by proton and carbon ion using the clustering approach and atomistic approach.

➢Simulation results were analyzed using the ROOT software and MS Excel.

➢Obtained results were compared with published data. Also simulation performed for different form of DNA molecules.

➢Finally, we obtained practical experience with precise estimation method of DNA damage using Geant4 Monte Carlo simulation toolkit.

Appreciation
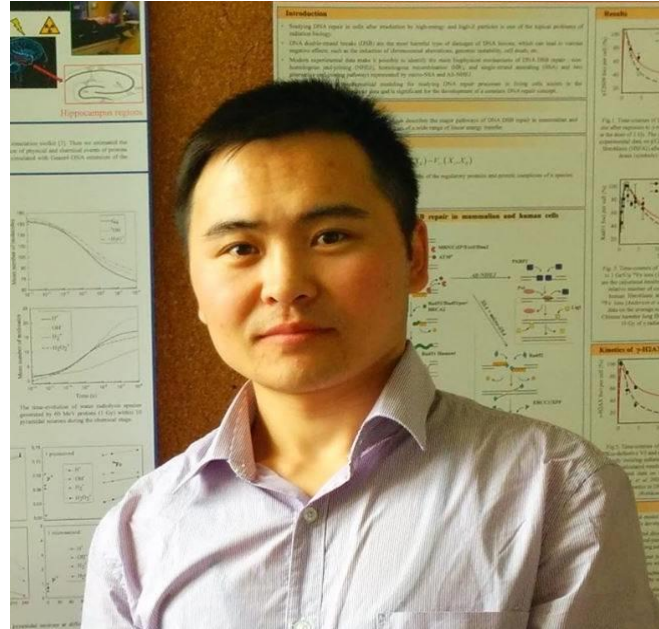
Dr .Batmunkh Munkhbaatar

thank you