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

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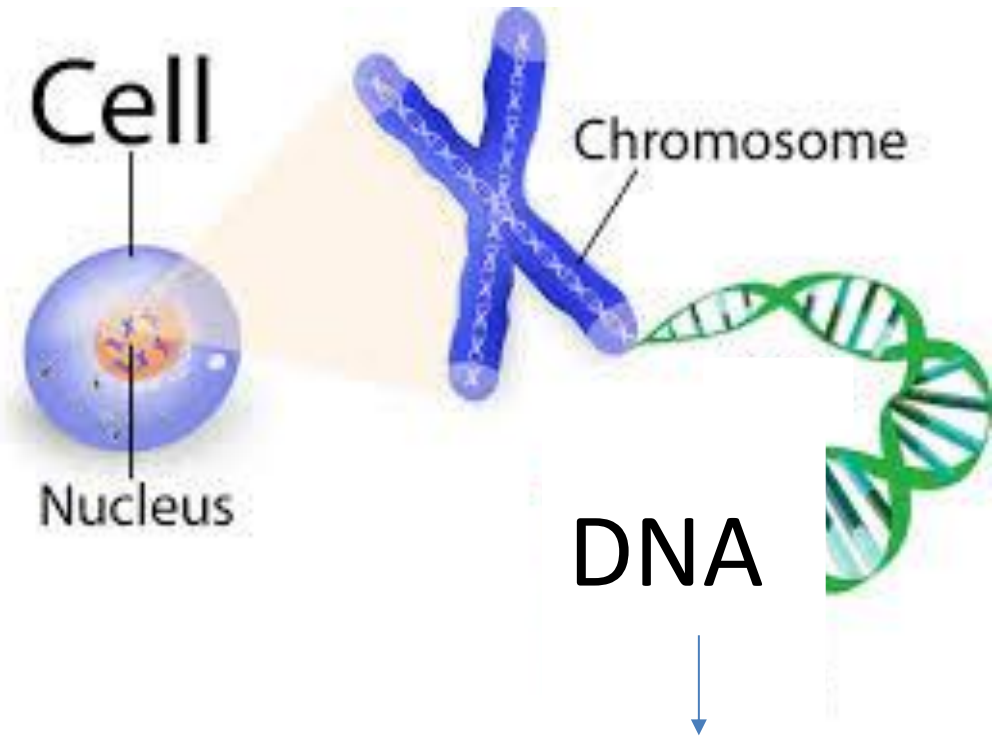
NRF National Research Foundation
iThemba LABS Laboratory for Accelerator Based Sciences

OUTLINE

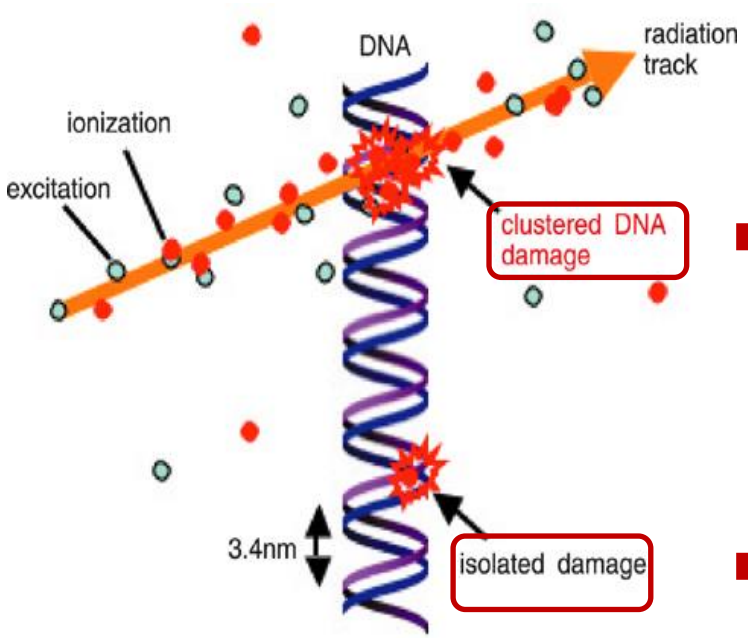
- ✓ Aim of the project
- ✓ Background
- ✓ Methods.
- ✓ Results
- ✓ Conclusion



most sensitive structure of cells

AIM 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.



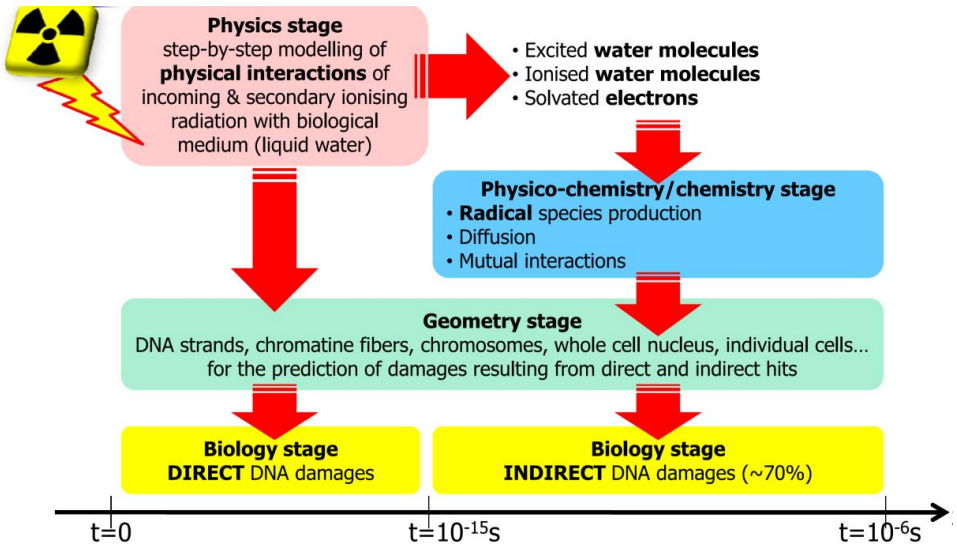
DNA is cell`s sensitive structure!

→ – multiple strand breaks of DNA molecule

→ – single strand break of DNA molecule

Initial biological effects of ionizing radiation

Initial **physical** (direct) and **chemical** processes (indirect) of ionizing radiation events in biological medium are main part of **radiobiological mechanisms.**



Types of ionizing radiation:

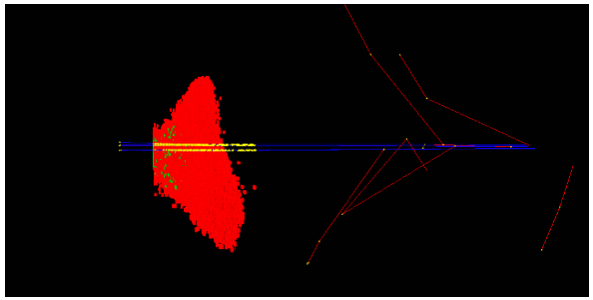
- X-rays
- Gamma rays
- Beta particles
- Alpha particles
- Neutrons & protons
- Heavy charged particles (^{12}C ions)

Sources:

- Radioactive isotopes
- Sun and Cosmic rays
- Particle accelerators

THEORETICAL MODELING AND COMPUTER SIMULATION

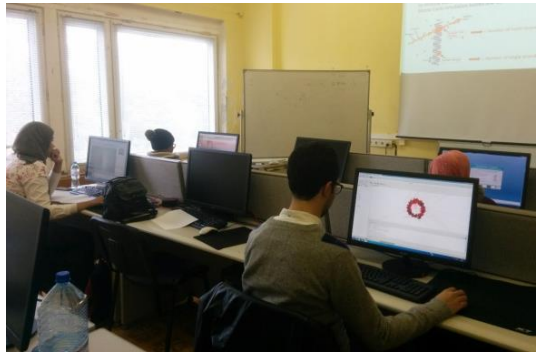
Study on the biological effect of ionizing radiation, in particular heavy ions requires not only experimental facilities (particle accelerators), but also a complete theoretical assessment. Numerical simulation based on Monte Carlo techniques is a suitable tool in studying initial radiation transport in biological medium.



Geant4 modeling of microbeam at CENBG

The numerical simulation tools used in this project:

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

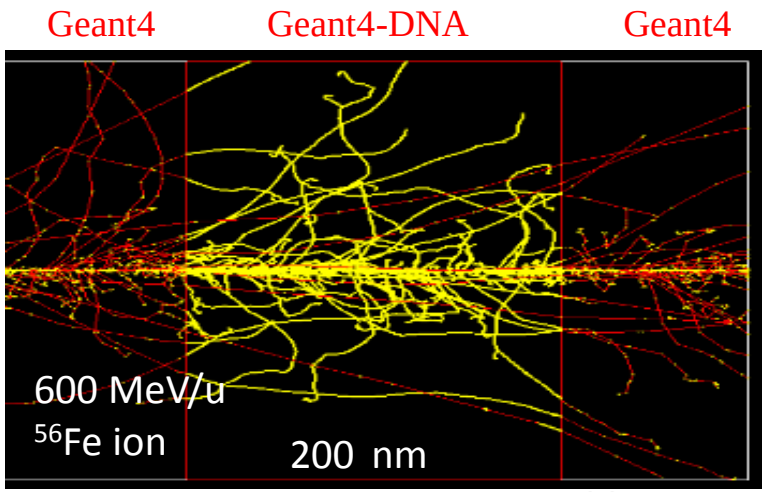


Methods (1): Track Structure Simulation

Monte-Carlo based 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.

One of the most powerful tools for Monte-Carlo simulation of low- and high-energy radiation transport is **Geant4 toolkit**,
which includes **Geant4-DNA** models for micro- and nano-dosimetry simulations.

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



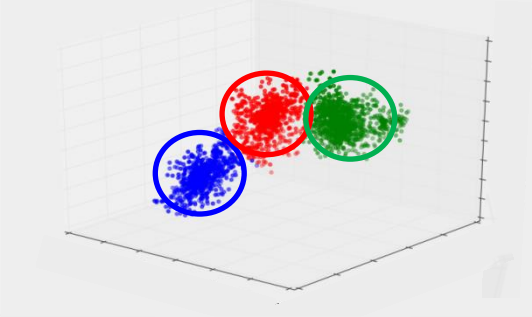
M.Batmunkh 2013

METHODS (2): CLUSTERING APPROACH FOR DNA DAMAGE CALCULATION

In order to estimate precise number of DNA strand breaks along the track structure we used **clustering algorithms** such as K-means and DBSCAN.

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



Input parameters:

- Coordinates of interaction points and energy depositions
- Threshold value of energy deposition for SSB (isolated) is 8.22 eV
- Cluster radius is 3.4 nm (~10 bp for DSB)

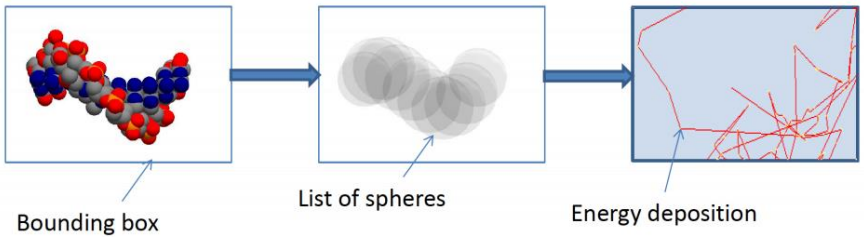
H. Späth, Cluster Analysis Algorithms for Data Reduction and Classification of Objects (Halsted Press, New York, (1980), p. 226.
J. A. Hartigan and M. A. Wong, "A Kmeans clustering
algorithm," Appl. Stat. 28, 100–108 (1979).
Batmunkh et al., 2013 // K-means
Francis et al., 2012 // DBSCAN

METHODS (3): ATOMISTIC APPROACH FOR DNA DAMAGE CALCULATION

In order to estimate precise number of DNA strand breaks in atomistic model of DNA molecule we used pdb4dna application of Geant4-DNA

Definition of mathematical algorithm:

- Generate energy depositions along particle track in water
- Construct DNA molecule from PDB file
- Each atoms representing as spheres and considering Van der Waals radii
- Find the closest atom from the energy deposition
- Count DNA hit when allocated values in sugar-phosphate group more than threshold values



Input parameters:

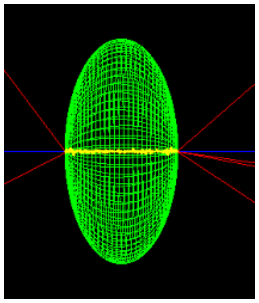
- Coordinates of interaction points and energy depositions;
- Coordinates of atoms in DNA molecule
- Threshold value of energy deposition for SSB (isolated) is 8.22 eV
- Threshold distance for DSB is 10 bp (3.4 nm)

M.A. Bernal, et al., Comp. Phys. Comm. 184, 2840-2847 (2013)
E. Delage, et al., Comp. Phys. Comm. 192, 282-288 (2015)

RESULTS

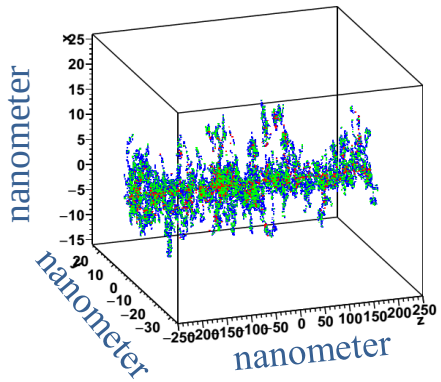
TIME AND SPACE EVOLUTION OF PARTICLE TRACK STRUCTURE AT PHYSICAL AND CHEMICAL STAGE

Track structure of 0.5 MeV proton in 500 nm water volume



Bacteria and mitochondria, which are about 500 nm (0.5 μm) in wide.

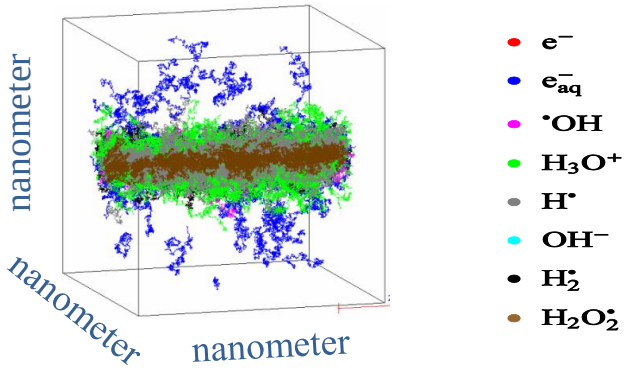
Physical stage of particle track at 1 fs (10^{-15} s)



For protons and secondary electrons:

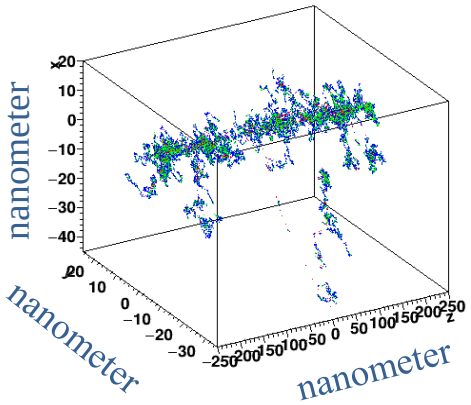
Ionisation
Excitation
Elastic scattering

Chemical stage of particle track at 100 ns (10^{-7} s)

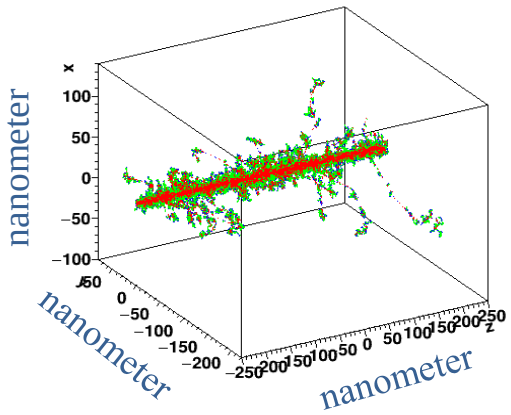


TRACK STRUCTURE OF PROTON AND CARBON ION WITH SAME KINETIC ENERGY (1 MeV/u)

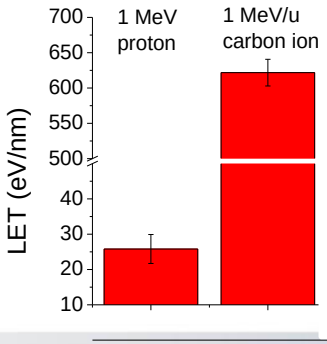
1 MeV proton



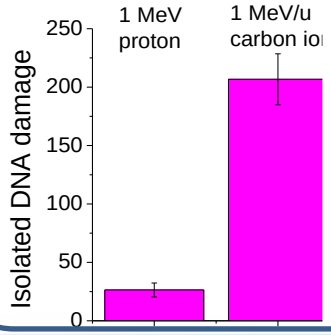
1 MeV/u carbon ion



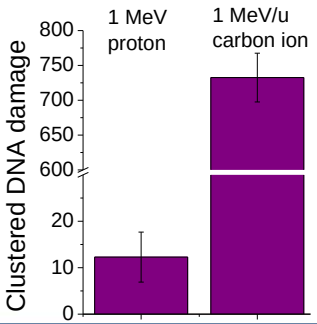
23 times more



7 times more

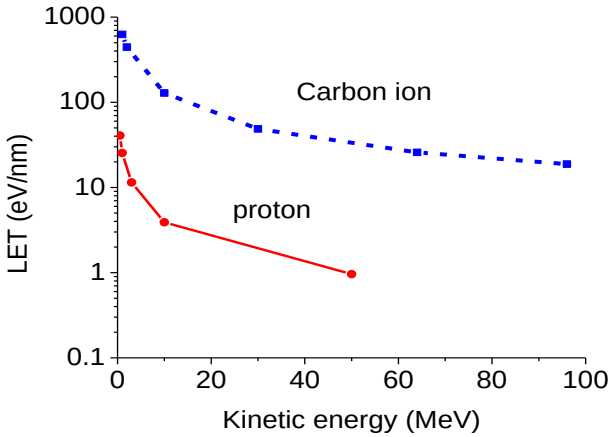


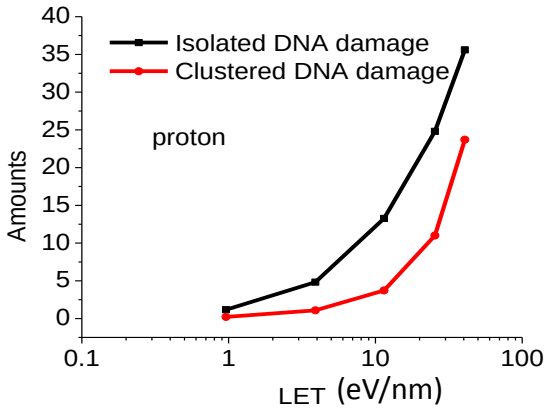
60 times more

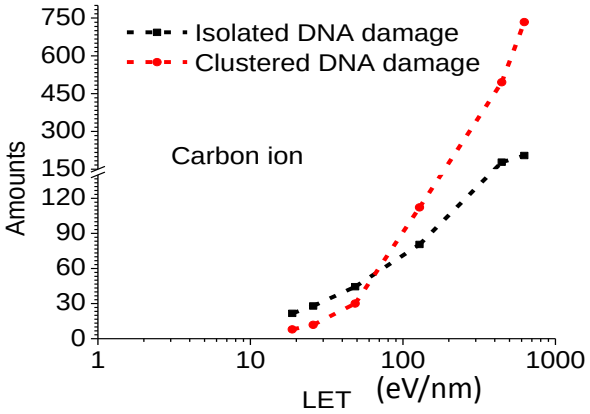


YIELDS OF DNA STRAND BREAKS FOR PROTONS AND CARBON IONS WITH DIFFERENT ENERGIES

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







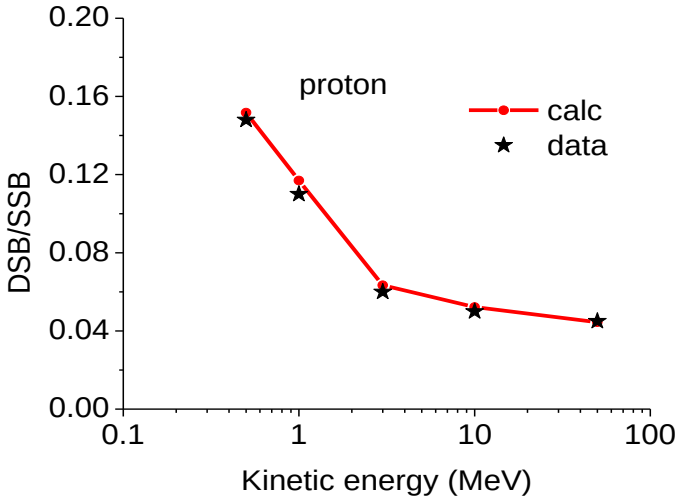
Large energy deposition (LET) is scored when kinetic energy is lower than 10 MeV

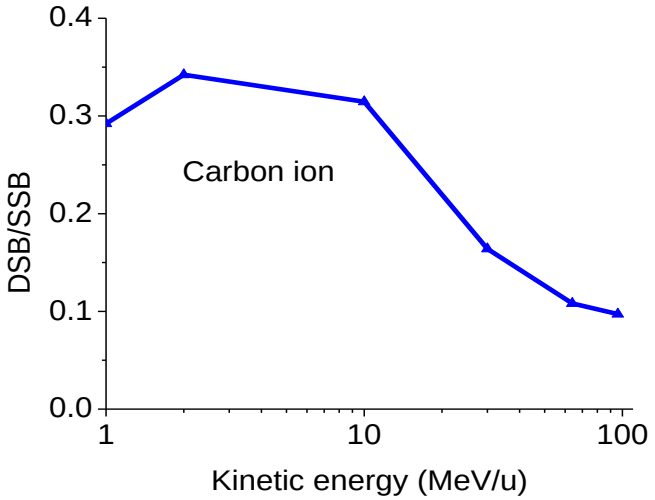
For protons, isolated DNA damage is always more than clustered DNA damage

For carbon ion, isolated DNA damage is more than clustered DNA damage when lower-LET. Large amount of clustered DNA damage is counted when higher-LET.

COMPARISONS OF DSB/SSB RATIO WITH PUBLISHED DATA

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



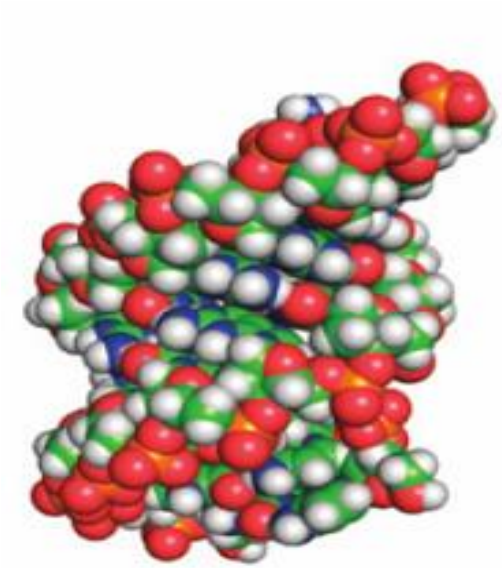


❖ Experimental and calculation data of published literature (Francis et al., 2012)

In the case of carbon ion, DSB/SSB ratio more than protons. We calculated that large energy deposition generated when kinetic energy lower than 10 MeV (DSB increases).

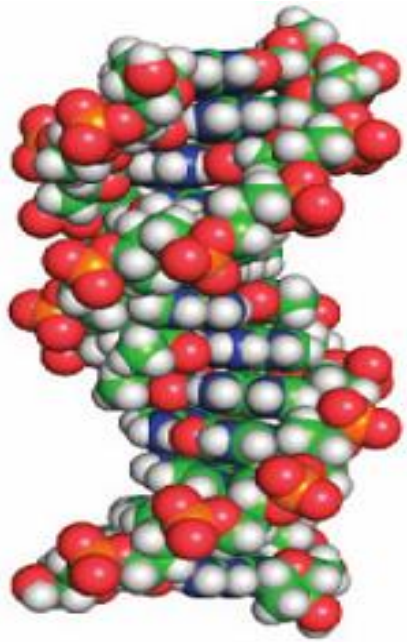
SIMULATION OF ATOMISTIC MODEL OF DNA MOLECULES WITH DIFFERENT FORMS

Form of **A-DNA** double helix



Short and broad

Form of **B-DNA** double helix



Longer and thinner

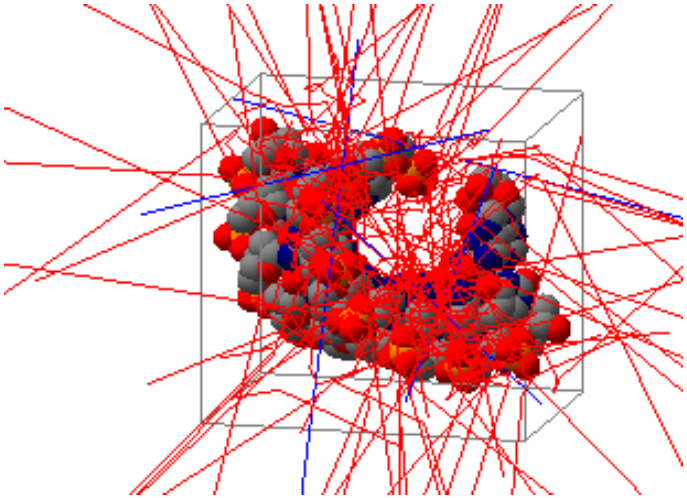
Form of **Z-DNA** double helix

Elongated and slim

SIMULATION OF ATOMISTIC MODEL OF DNA MOLECULES UNDER IRRADIATION WITH 1 MeV/u CARBON ION

5 particles

Screenshot of A-DNA (10 bp)

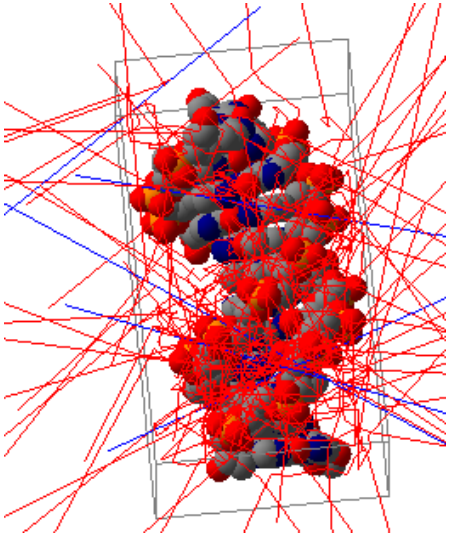


440d.pdb

Total number of atoms = 404

Number of SSB = 4
Number of DSB = 1

Screenshot of B-DNA (12 bp)

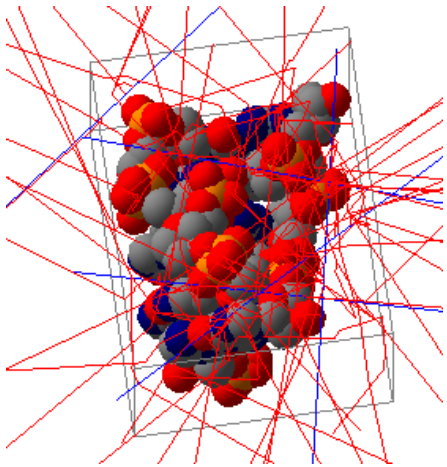


1bna.pdb

Total number of atoms = 486

Number of SSB = 3
Number of DSB = 0

Screenshot of Z-DNA (6 bp)



4r15.pdb

Total number of atoms = 291

Number of SSB = 3
Number of DSB = 2

CONCLUSIONS

- We have simulated nanoscopic track structure of proton and carbon ions with different energies at physical and chemical stages using the Geant4-DNA Monte Carlo code.

- We have calculated isolated and clustered DNA damage along the track structure of proton and carbon ion using the clustering algorithms.
- Obtained results were compared with published data. Also simulation was performed for calculation of DNA strand breaks in realistic model of DNA molecules with different forms (A-DNA, B-DNA, Z-DNA).
- Simulation results were analyzed using the ROOT software.

- Finally, we obtained practical experience with precise calculation method of DNA damage and gain an advanced understanding of early molecular radiobiological mechanisms using the Geant4-DNA extension of Geant4 Monte Carlo simulation toolkit.

APPRECIATION

- *Dr M.Batmunkh for supervising us*
- *South African co-ordinators in collaboration with the JINR*
- *NRF in collaboration with iThemba LABS.*

To

THANK YOU FOR YOUR ATTENTION

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