

Calculation of DNA damage probabilities of helium and carbon ion beams: A Geant4-dna study

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Introduction

+ Radiation-induced DNA strand breaks:

+ 1. Single Strand Breaks (**SSB**)

+ 2. Double Strand Breaks (**DSB**)

+ 3. Complex DSB (**cDSB**)

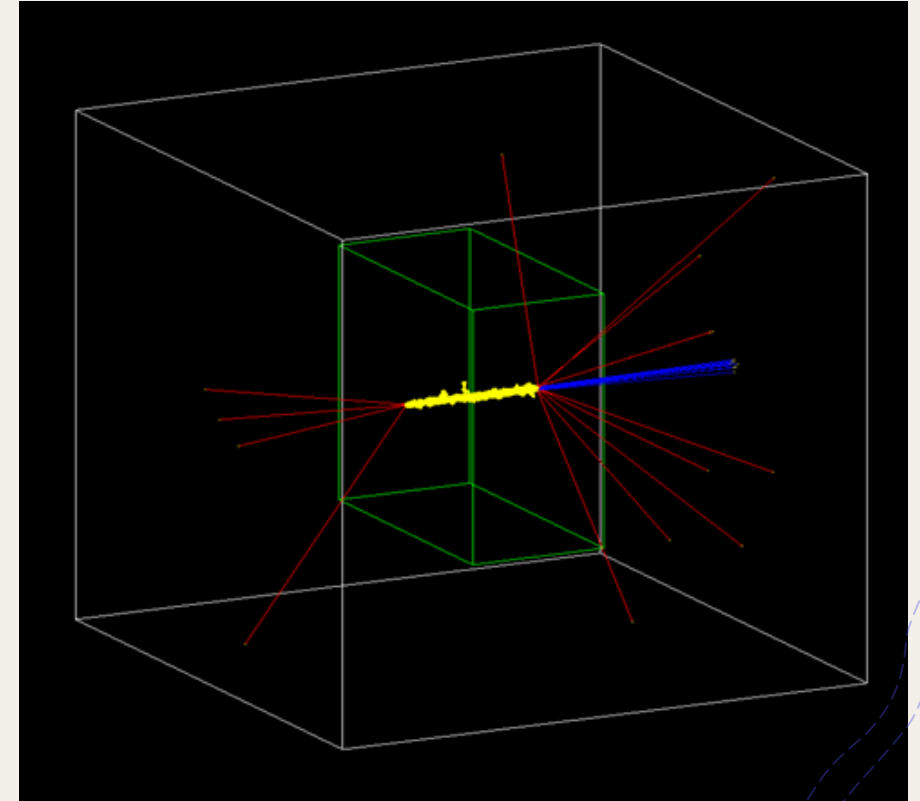
+ These result in mortality or mutagenesis depending on the damage quality and the cell repair ability

+ The energy deposited by the ionizing radiation crossing the cells is directly or indirectly responsible for the SSB and DSB

+ **DSB/SSB ratio** quantifies cell damage capability

Simulation Geometry

- + $1 \times 1 \times 0.5 \mu\text{m}^3$ filled with unit density water
- + The particle beam (pencil beam) is perpendicular to the $1 \mu\text{m} \times 1 \mu\text{m}$ surface
- + Target thickness is $0.5 \mu\text{m}$ and the particle's energy change is neglected through this distance
- + energy deposition on event-by-event basis using Geant4-dna track structure code
- + Energy deposition and the co-ordinate of interaction are stored in the output file



Geant4-dna physics

Geant4-dna : low energy extension of Geant4 toolkit

Ionizing radiations: photons, e^- , hadrons, α -particles, set of heavy ions

The physics interactions:

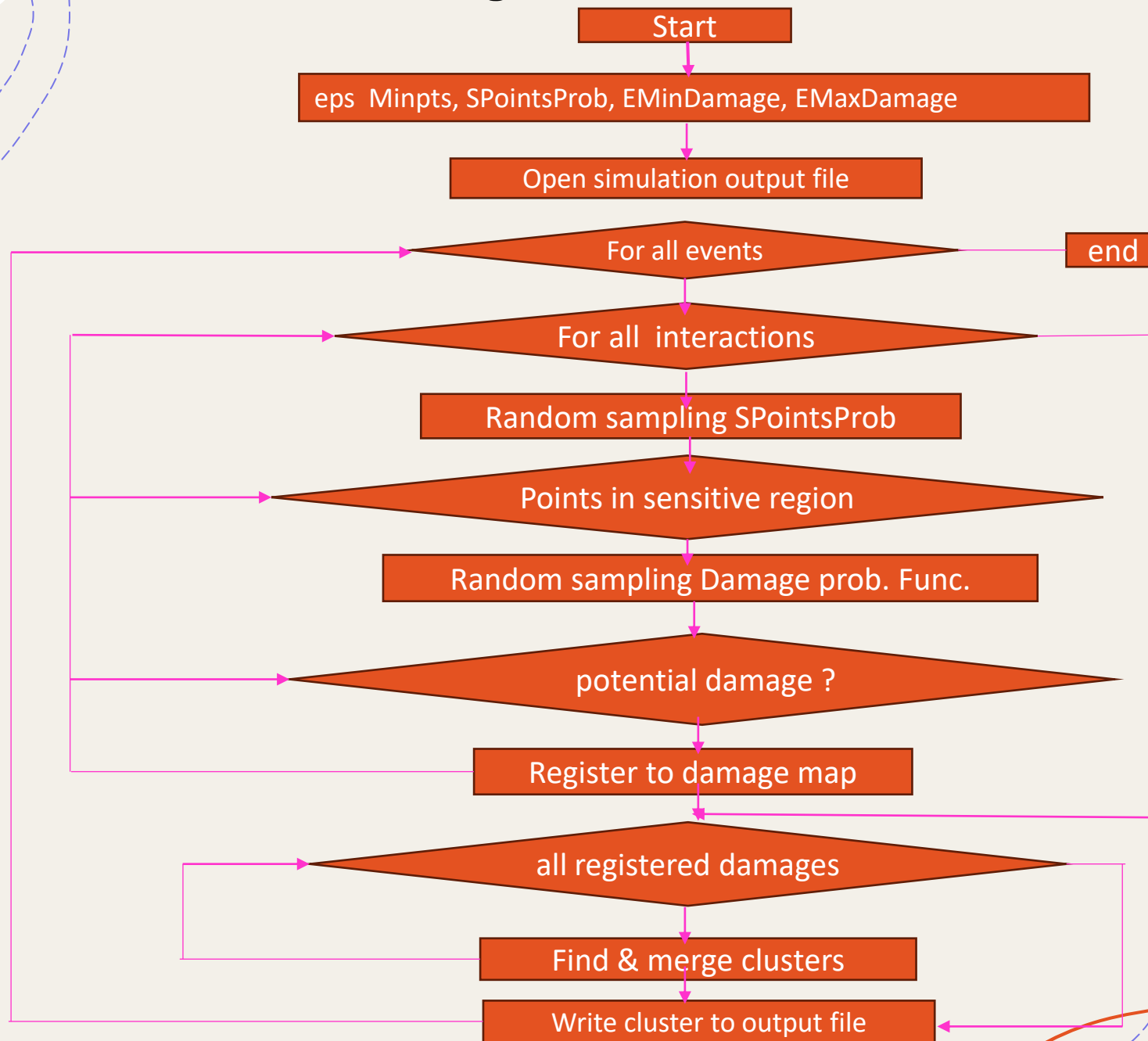
- ionization, excitation and charge transfer for proton and alpha
- ionization, excitation and elastic collisions for delta electrons
- Ionization for heavy ions

Energy range:

- e^- : Up to 1 MeV
- Proton: 100 eV - 100 MeV
- α -particles : 1 keV - 400 MeV
- Heavy ions: 0.5 - 10^6 MeV/u

Ref: Review of Geant4-dna simulation toolkit for Radiobiological applications at cellular and DNA level.
Kyriakou et al (2021)

DBSCAN algorithm: Flow chart



Density Based Spatial Clustering of Applications with Noise (DBSCAN)

- + **SPointsProb**: Uniform probability that an interaction point is situated in a sensitive location where it can directly or indirectly reach the DNA.
- + **Sensitive area**: volume of DNA double helix plus a virtual aura surrounding this latter
- + every particle-DNA interactions does not lead to DNA damage
- + **Damage induction caused by < 5 eV energy deposits is still an open debate**

Possible events by 5 eV energy deposits:

- + do not correspond to ionizing collisions
- + only to different excitation modes,
- + excited water molecule can disintegrate into reactive chemical species damaging indirectly the DNA molecule

DBSCAN Algorithm

+ damage probability = 0 for energy deposits < 5 eV ($E_{\text{MinDamage}} = 5 \text{ eV}$)
= 1 for energy deposits > 37.5 eV ($E_{\text{MaxDamage}} = 37.5 \text{ eV}$)

+ increases linearly between $E_{\text{MinDamage}}$ & $E_{\text{MaxDamage}}$

+ DBSCAN algorithm runs over all the points testing the distances between every pair of SSBs

Condition for considering as potential SSB damage:

- + interaction should be located in a sensitive area
- + Must succeeds the random sampling of damage induction in DBSCAN

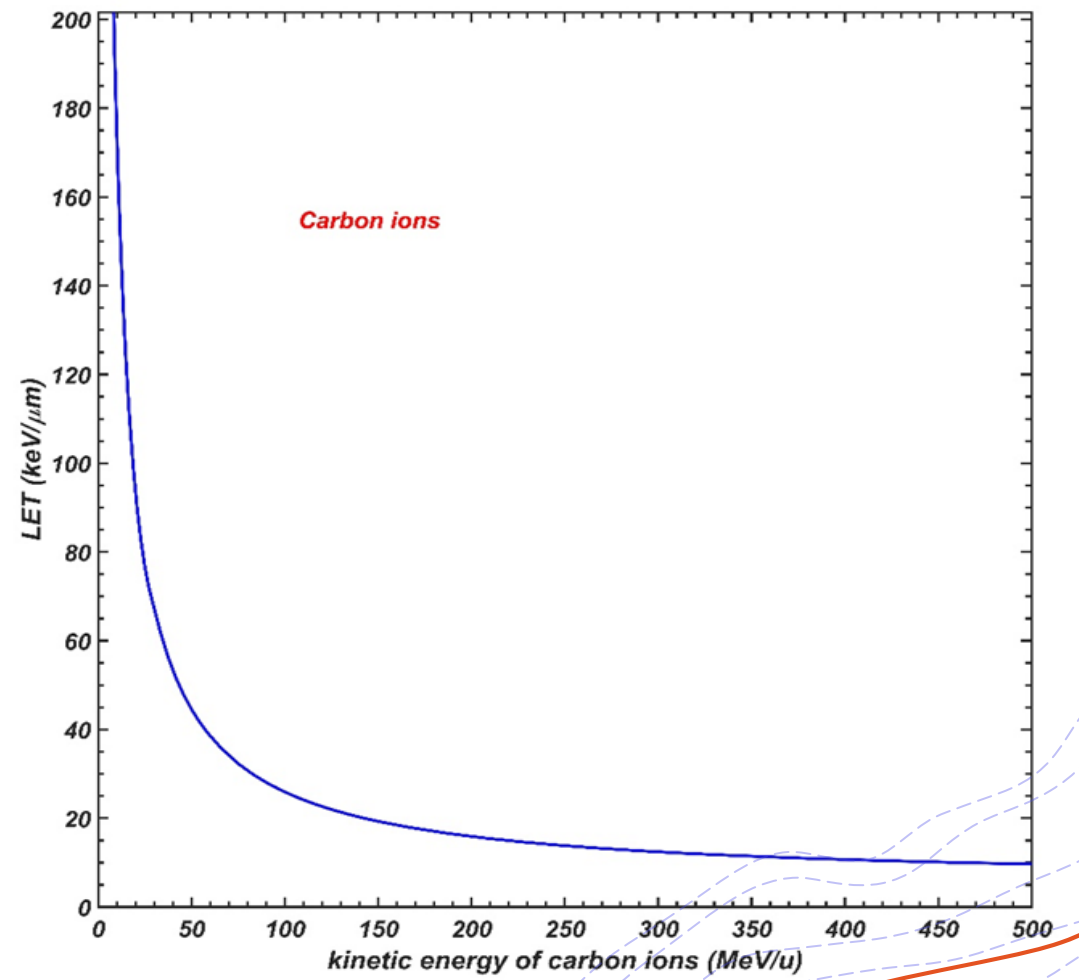
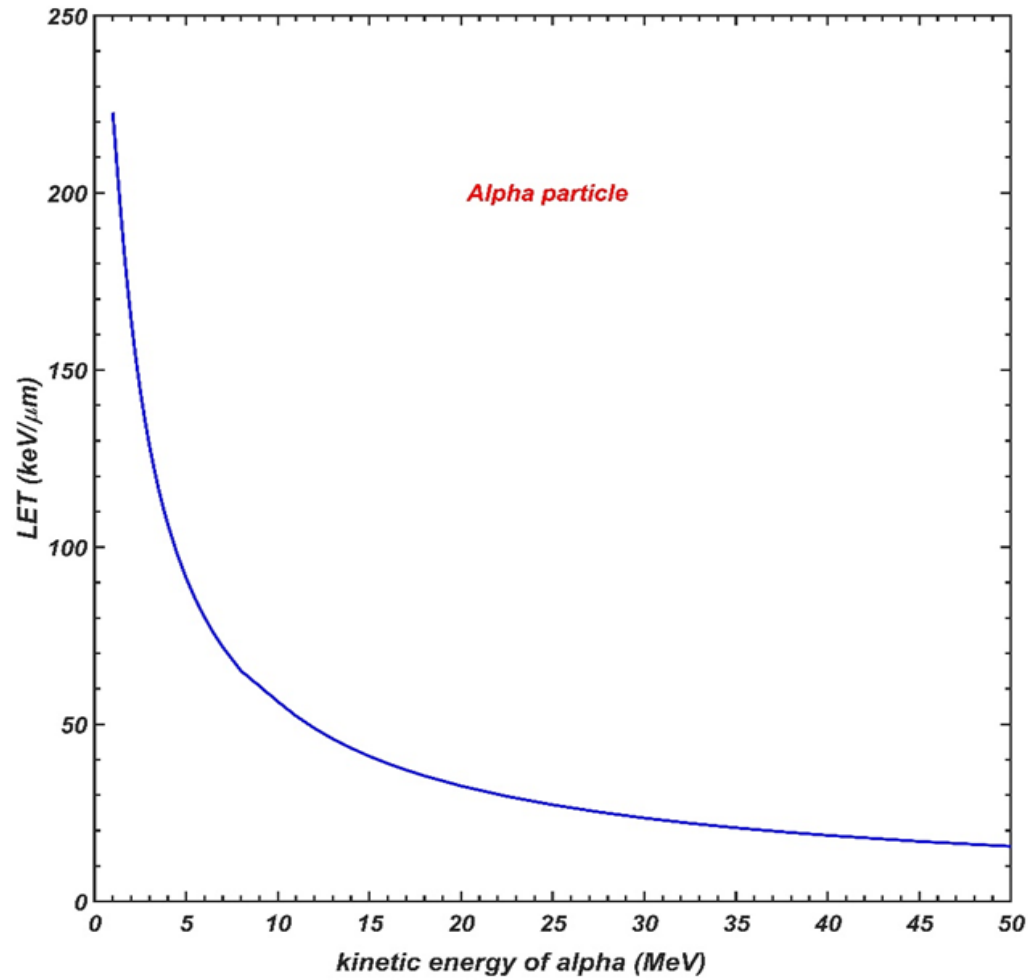
DBSCAN Algorithm

- + If two SSBs are located within a certain radius, they form a cluster
- + maximum radius to form a cluster (eps) = 3.2 nm
- + In radiobiology, two SSBs are considered a DSB if they are separated by less than 10 base pairs corresponding distance (~3.2 nm)
- + **DSBs**: Clusters containing 2 or more SSBs where at least one SSB is located on an opposite strand

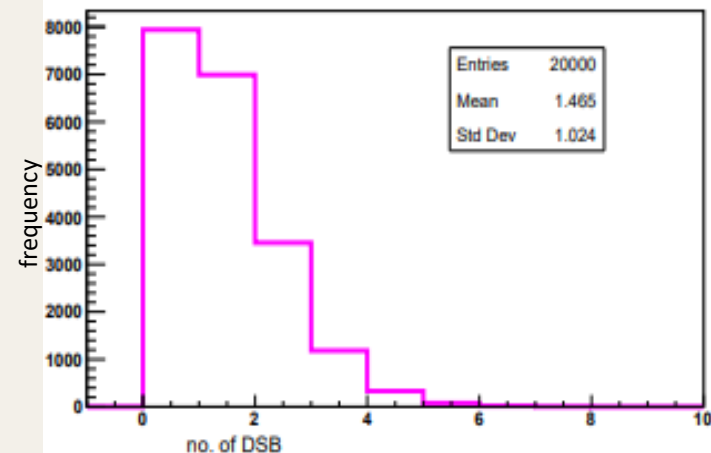
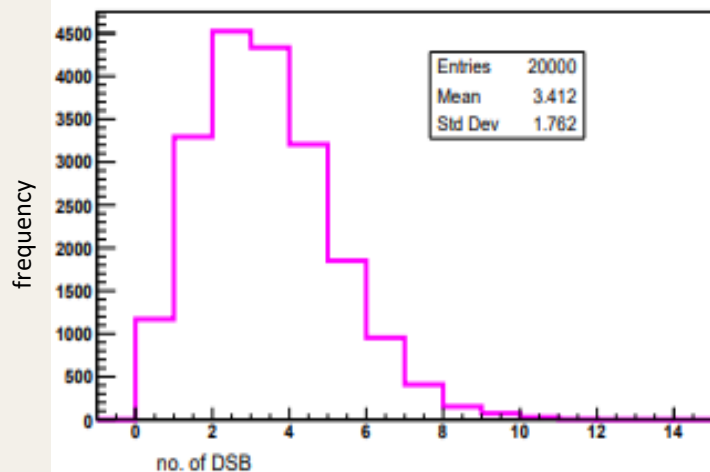
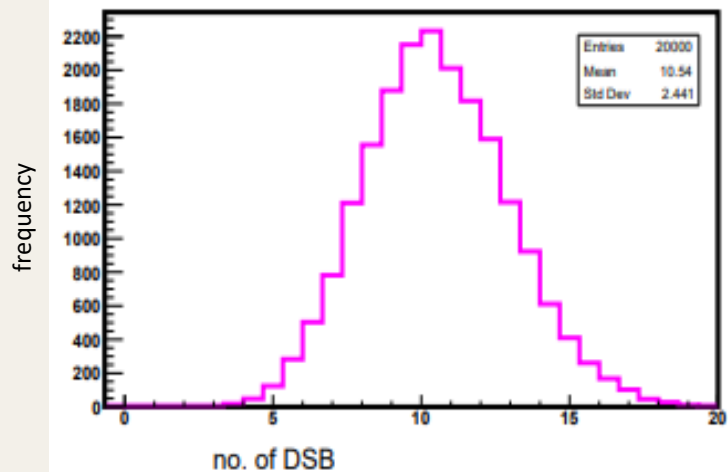
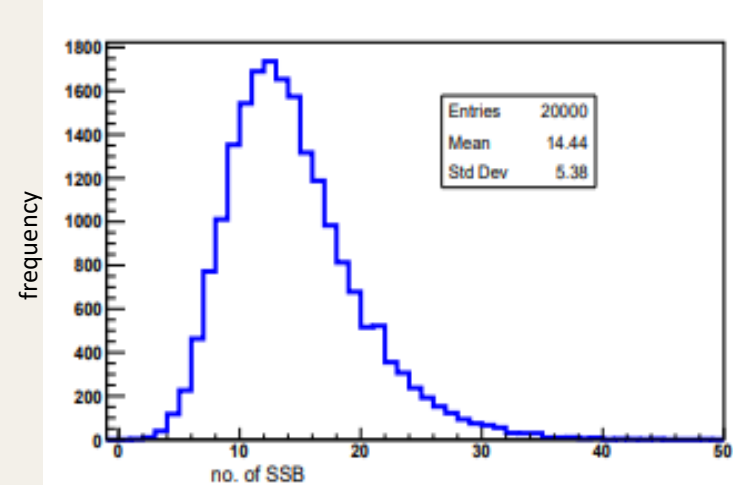
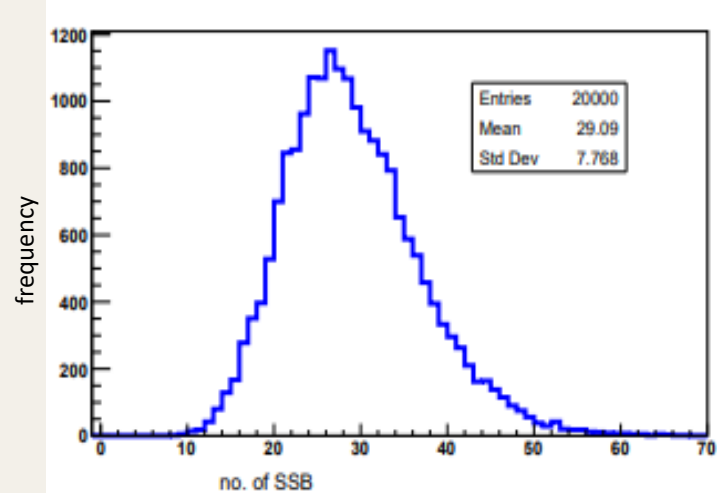
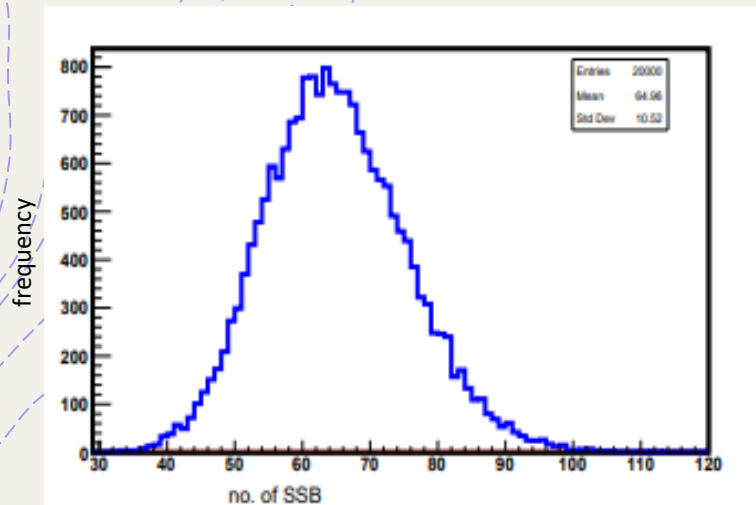
DBSCAN Algorithm

- + minimum number of points to form a DSB cluster (**MinPts**) = 2
- + **simple DSBs**: formed by only 2 SSBs located on 2 opposite strands
- + **complex or clustered DSBs**: formed by 3 or more SSBs with at least one SSB located on an opposite strand

LET vs energy : helium & carbon ions



SSB & DSB histograms: helium ions

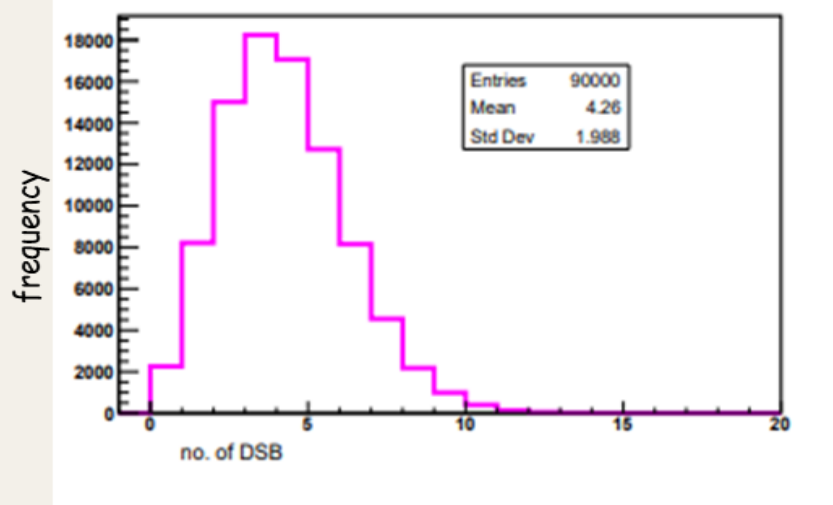
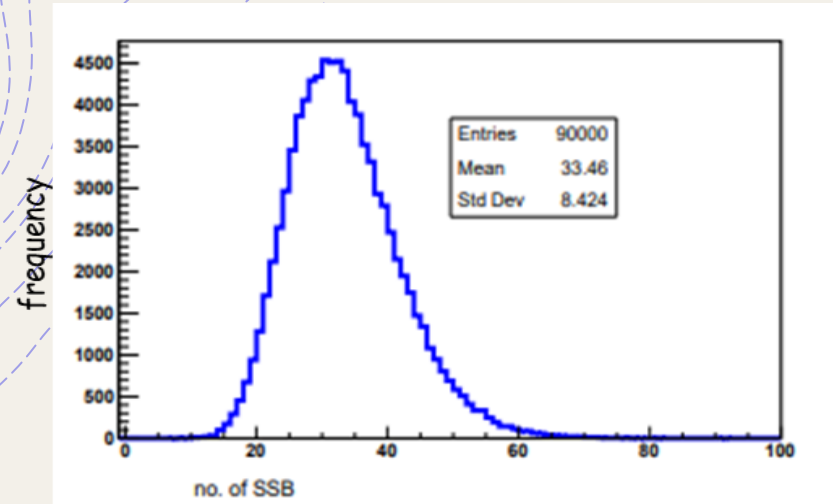


5 MeV

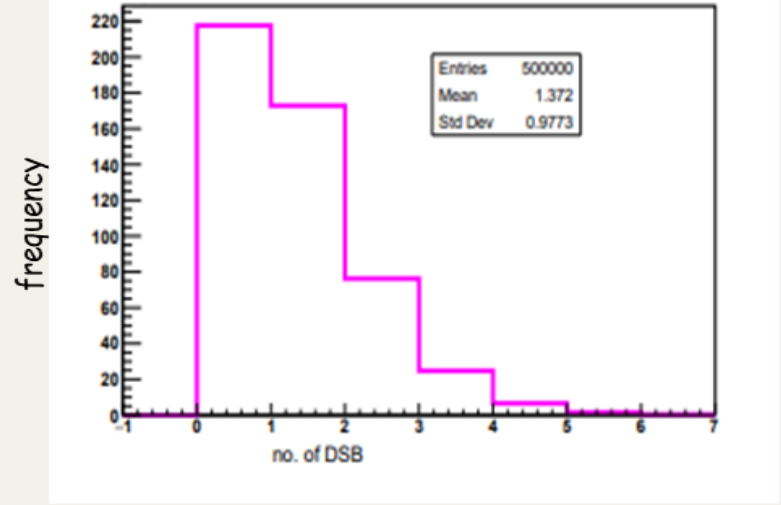
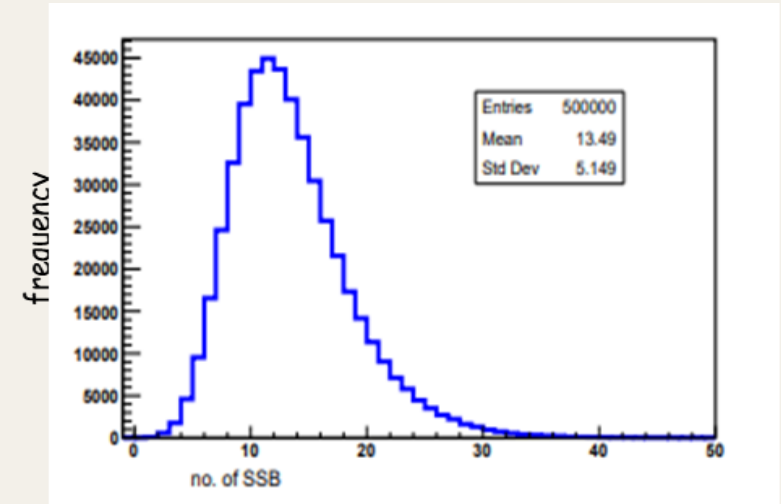
20 MeV

50 MeV

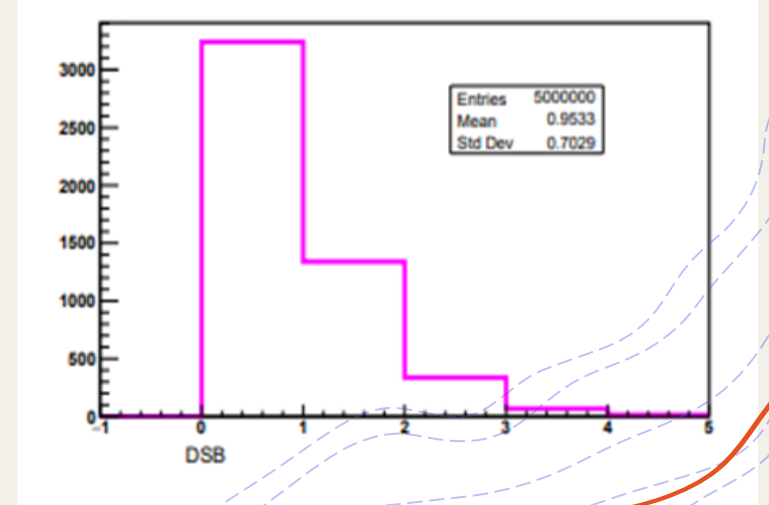
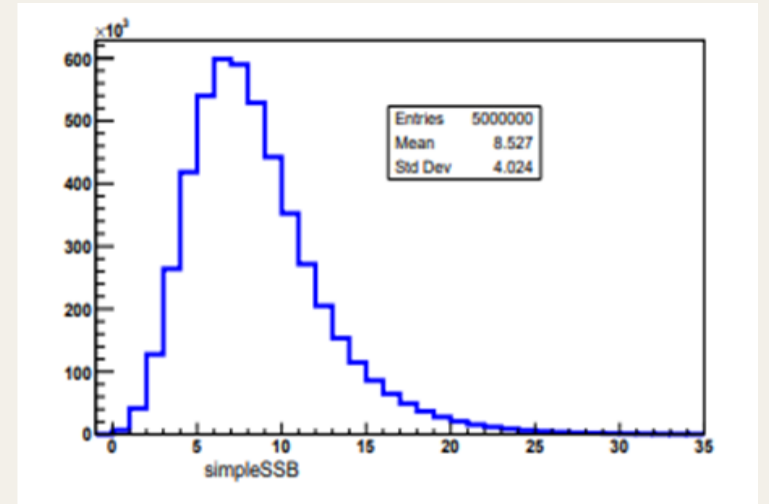
SSB & DSB histograms: carbon ions



50 MeV



200 MeV



480 M

How to calculate yield from histogram ?⁺

- + total SSB or DSB or cDSB \longrightarrow Area under the histogram
- + **SetSelectionProb** = 0.16 : 16% of primary cluster is selected for further analysis
- + Effective number of SSB or DSB or cDSB = 0.16 x total number
- + Cumulative Absorbed dose in Gy is recorded
- + **Cell line:** Human Fibroblast (Diploid cell) \longrightarrow 6×10^9 base pairs (bp)

How to calculate yield from histogram ? ⁺

+ Volume of cell nucleus: $500 \mu\text{m}^3$

+ Density of bp: $6 \times 10^9 / 500 = 1.2 \times 10^7 \text{ bp} / \mu\text{m}^3$

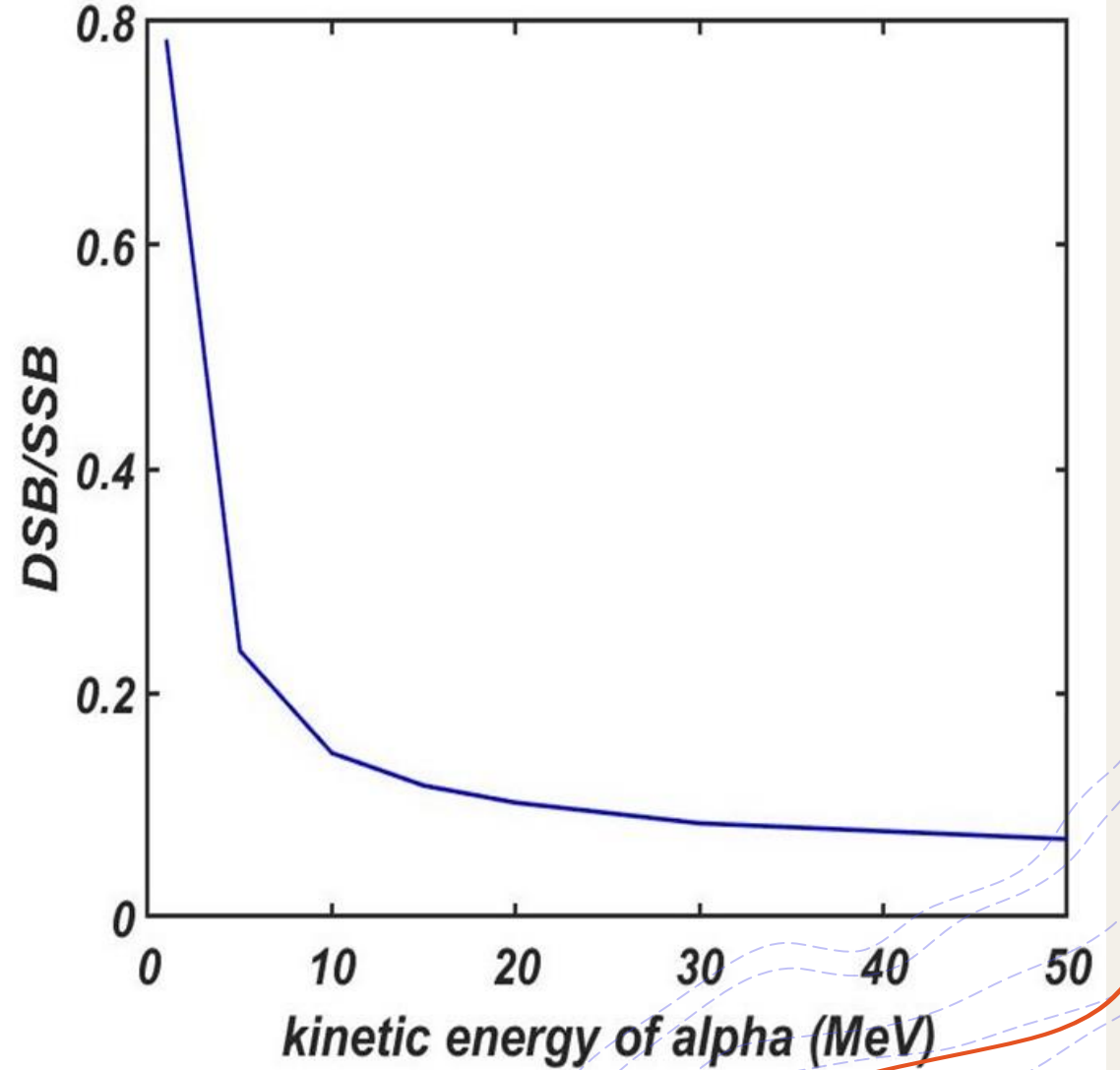
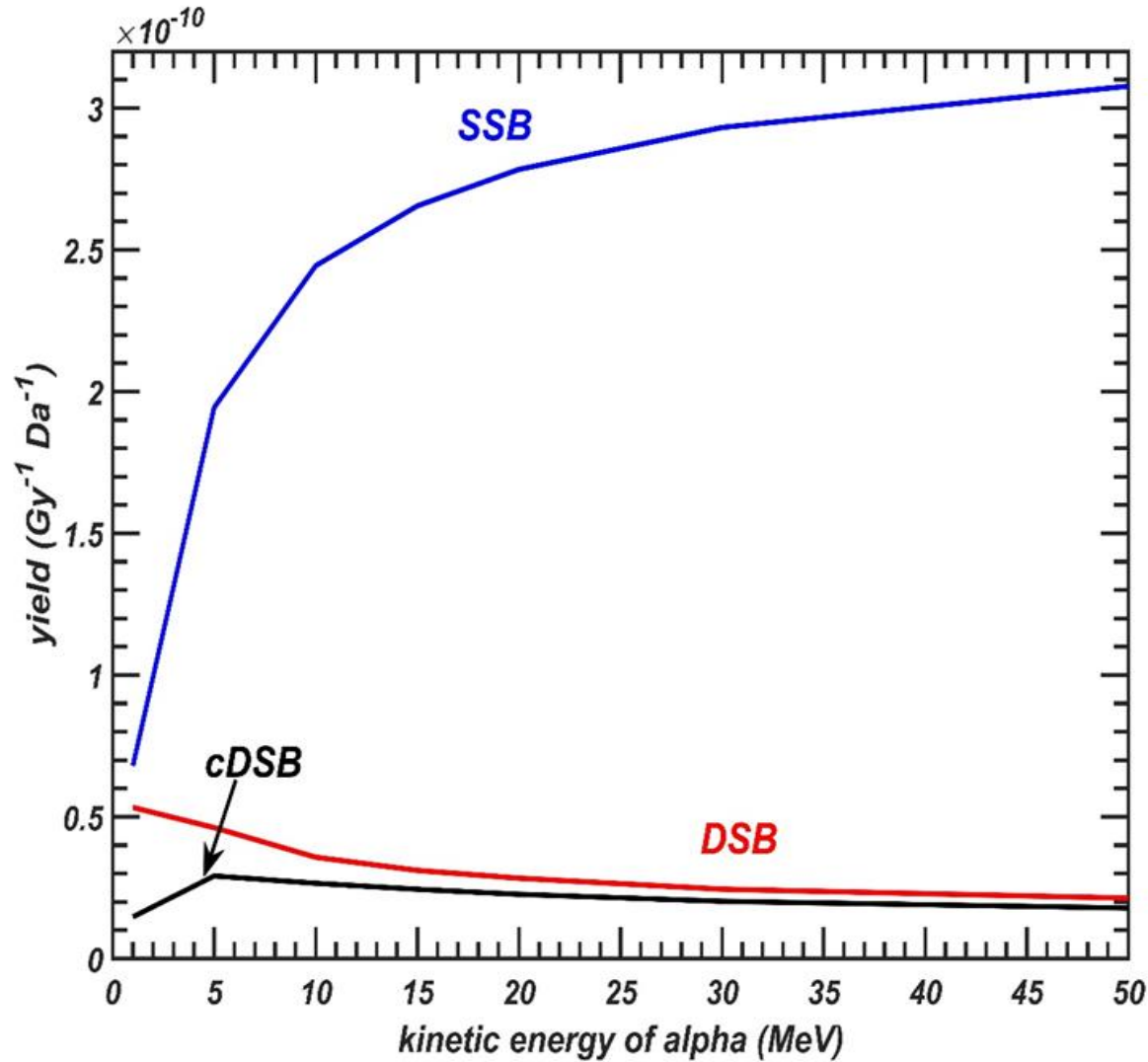
+ Mass of one bp: 650 Da

+ Target volume : $0.5 \mu\text{m}^3$

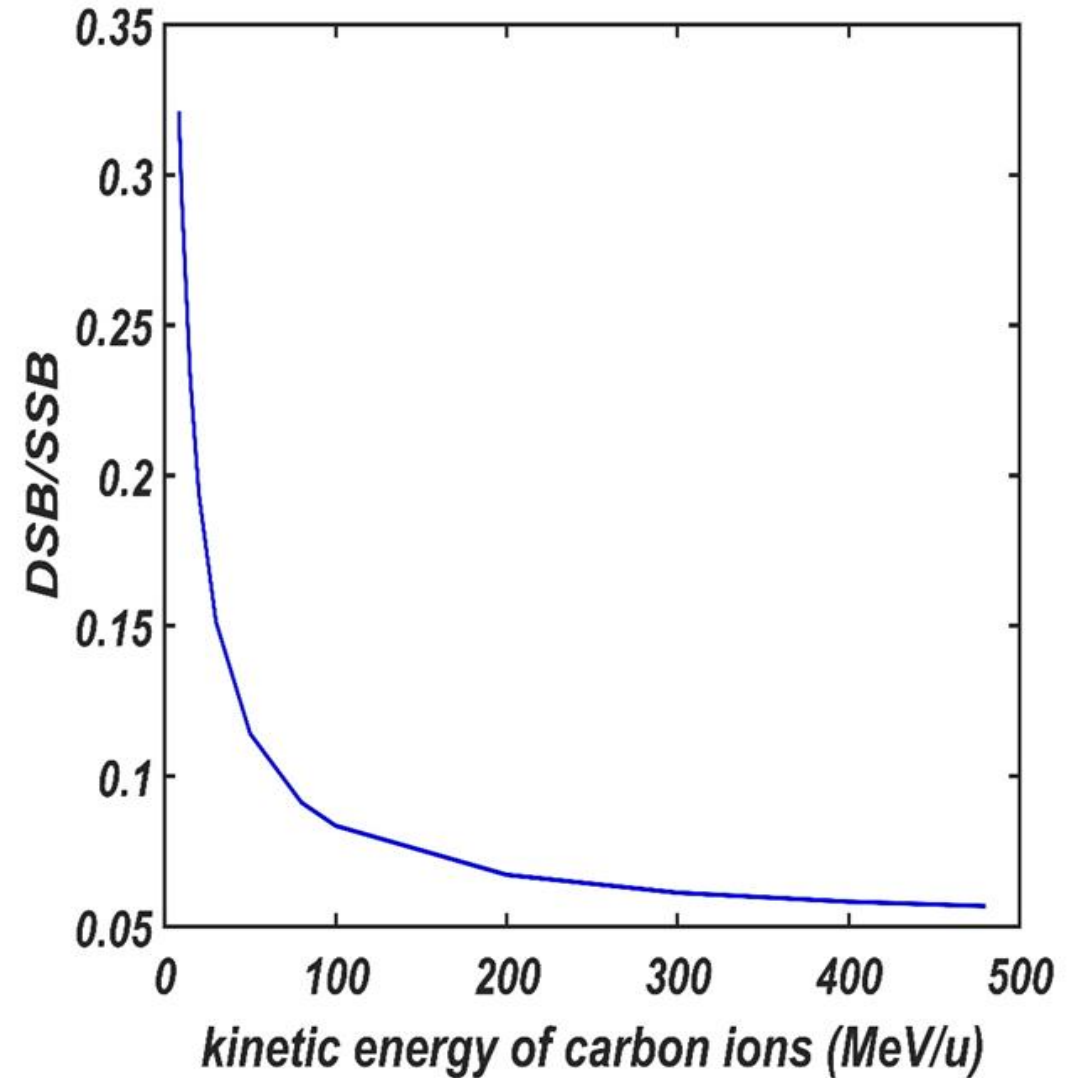
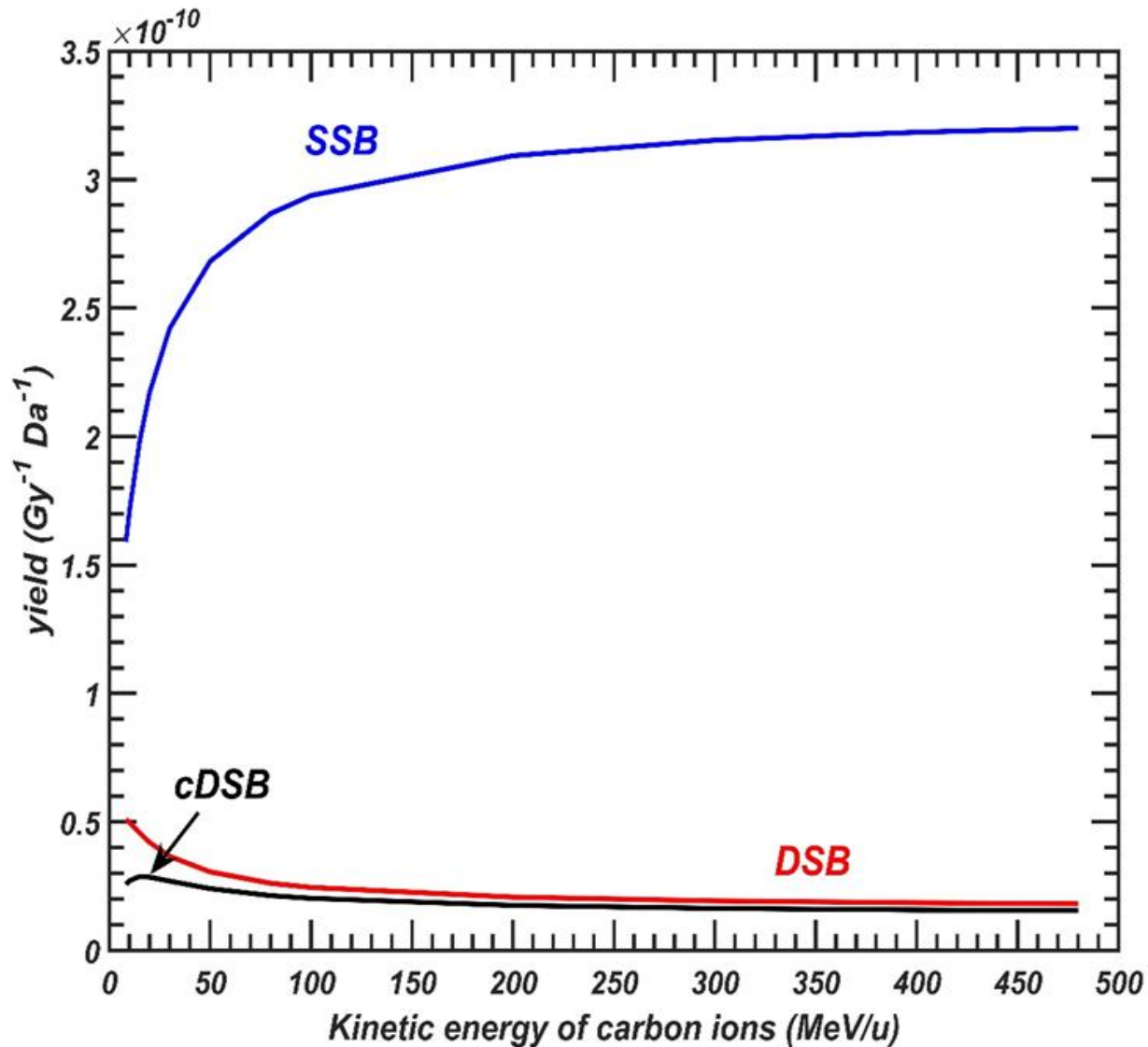
+ nuclear mass in target: $1.2 \times 10^7 \text{ bp} / \mu\text{m}^3 \times 0.5 \mu\text{m}^3 \times 650 = 3.9 \times 10^9 \text{ Da}$

$$\text{yield}(\text{Gy}^{-1}\text{Da}^{-1}) = \frac{\text{effective no. of SSB or DSB or cDSB}}{(3.9 \times 10^9 \text{ Da}) \times \text{tot. dose (Gy)}}$$

Yields of SSB, DSB and cDSB: helium ion



Yields of SSB, DSB and cDSB: carbon ions



Summary

- + Yields of SSB, DSB and cDSB are calculated as a function of kinetic energy of helium and carbon ions.
- + Geant4-dna track-structure code combined with DBSCAN algorithm is used
- + Calculated yields are inline with available experimental data ([Nikjoo et al, 2016](#))
- + Variation of yields and DSB/SSB ratio are more significant in high LET (low energy) region
- + Beyond 10 MeV of helium ion and 100 MeV/u of carbon ion, yields are insensitive to energy

Ref: Radiation track, DNA damage and response - a review. Nikjoo et al (2016)



Thank you