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Biological measure of DNA damage after single-ion microbeam irradiation and Monte Carlo simulations

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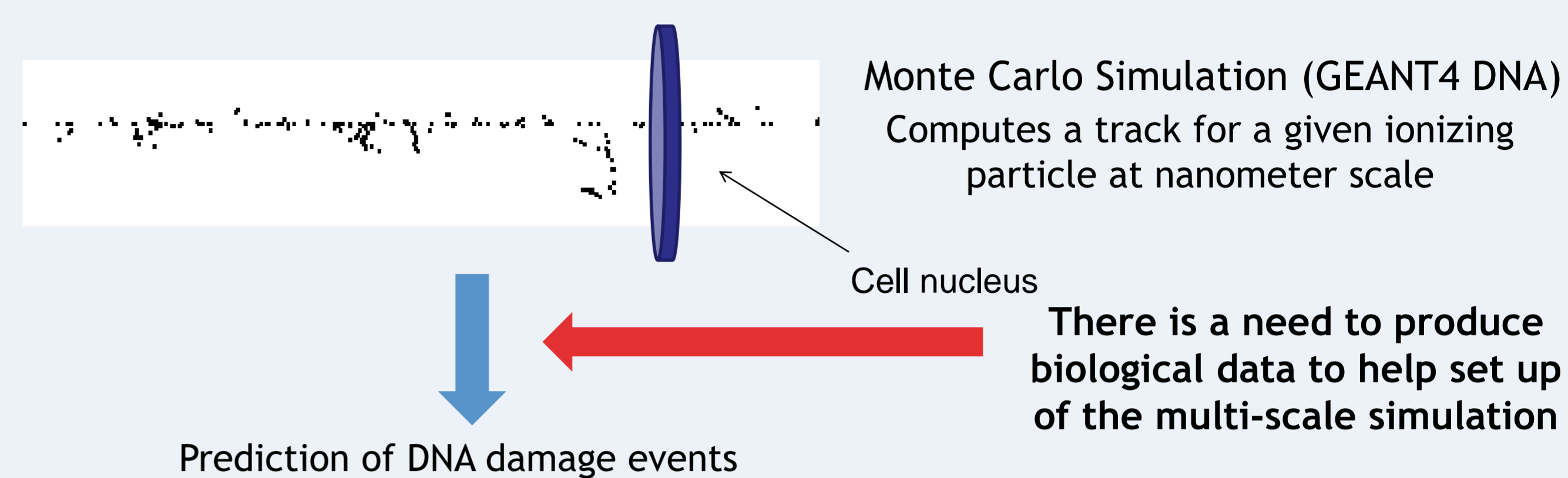
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INTRODUCTION

The growing use of hadrons in oncology entails the need to establish more specific dosimetry concepts adapted to their biological efficacy. This requires more information on the likelihood of subcellular effects, mainly DNA damage, according to how energy is deposited within cells by ionizing particle tracks. Monte Carlo track structure simulation provides a powerful tool for investigating such relation. However, the reliability of simulation results can only be assessed by comparison with dedicated biological data.

What type of biologic data may be relevant and how to produce them?

Link between track structure and biological effects of ionizing radiation



BIOLOGICAL DATA

Target: Cultures of primary Human Umbilical Vein Endothelial Cells (HUVEC) with homogeneous DNA density (controlled cytogenetic state and cell cycle stage => G₀G₁ phase)

Irradiation: Single ion microbeam facility at the PTB allows to control the energy and the number of particles. A pattern of 5 particles per nucleus was chosen (Number of foci per nucleus > Background)

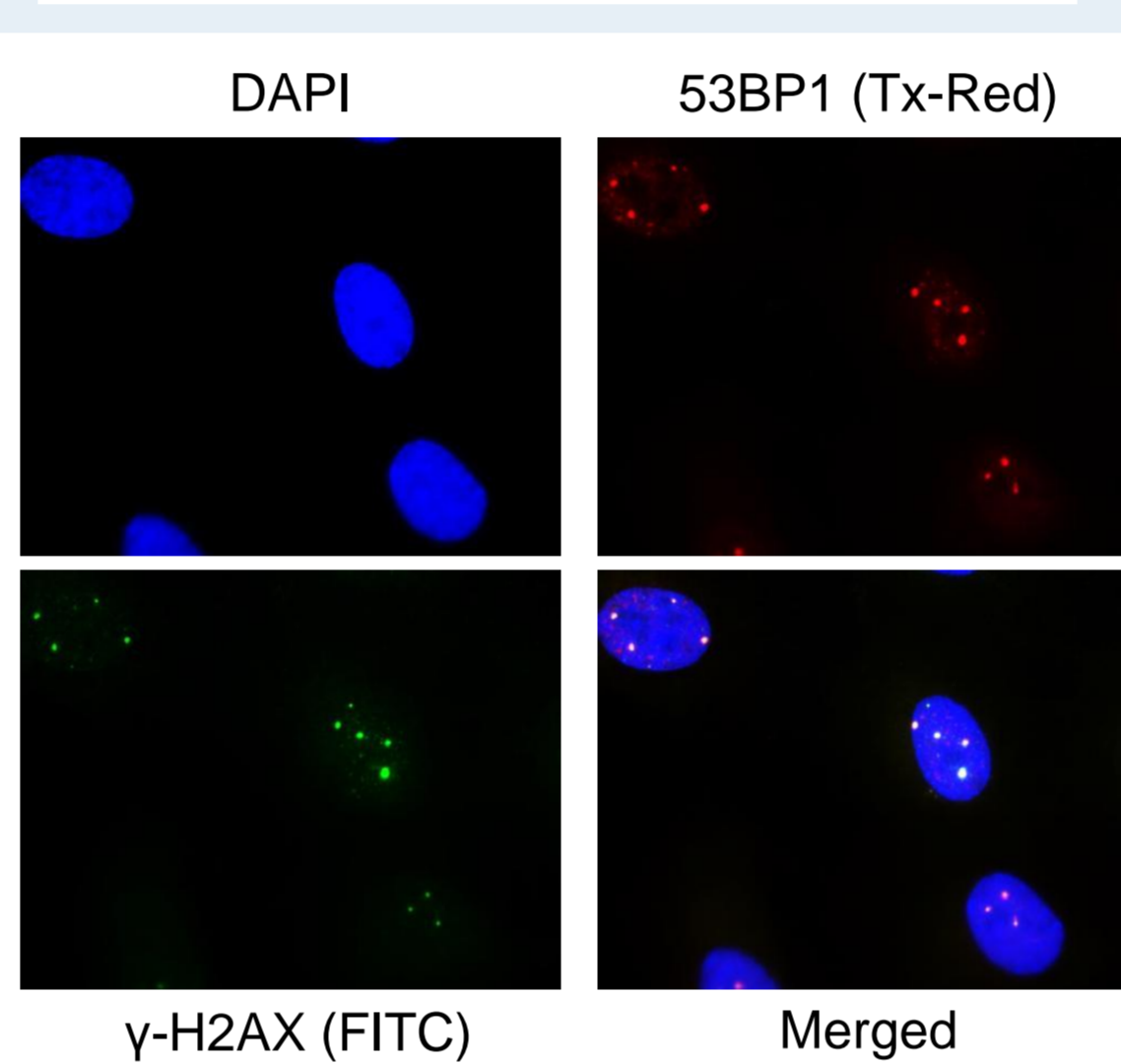
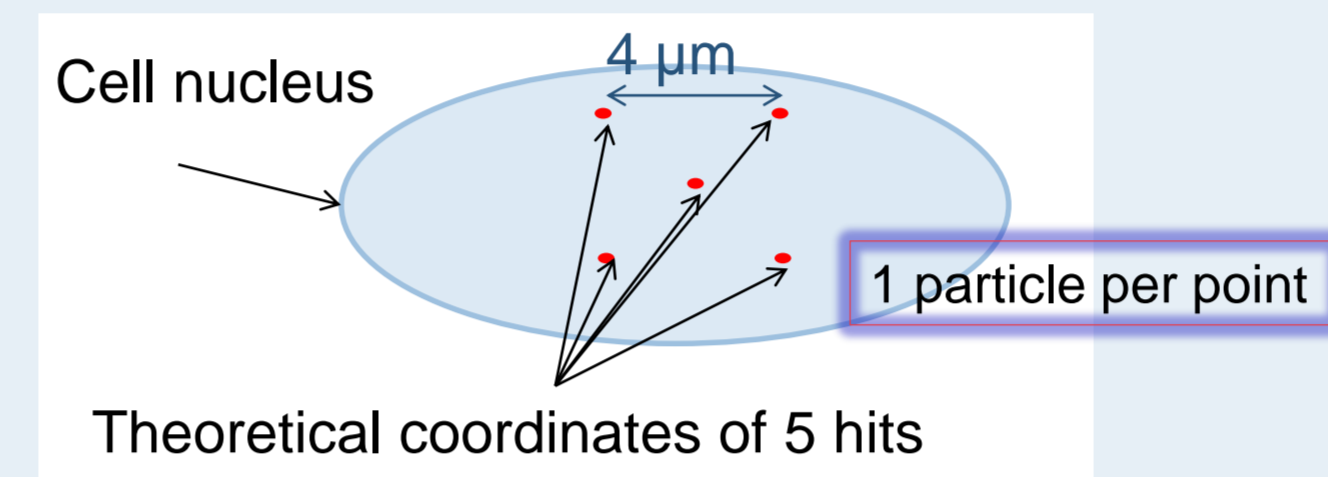
Alpha particles	Proton
8 MeV (170 keV/μm)	3 MeV (19 keV/μm)
10 MeV (85 keV/μm)	
20 MeV (36 keV/μm)	

Analysis: Statistical evaluation of nuclear foci formation (53BP1 and γ-H2AX) related to a particle traversal was undertaken in a large population of cells.

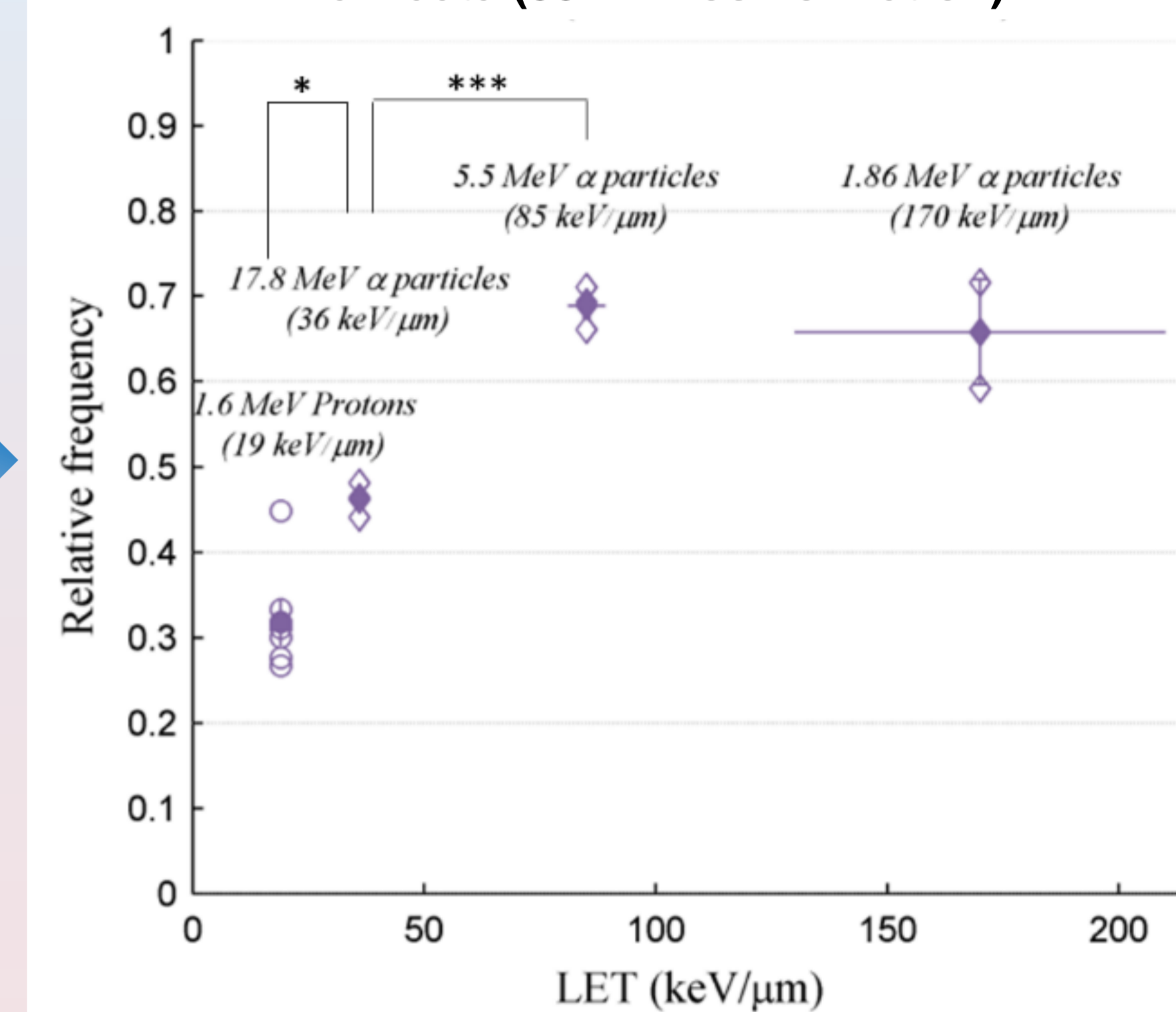
Aim: Estimate the relative frequency of radiation-induced foci formation following a single particle track in cell nuclei

$$\text{Ratio} = \frac{\text{Number of foci}}{\text{Theoretical number of particle hits}}$$

Definition of square pattern of irradiation



Raw data (53BP1 foci formation)



BIOLOGICAL DATA ADJUSTED FOR FACTORS LEADING TO EXPERIMENTAL BIAS

1- Foci background

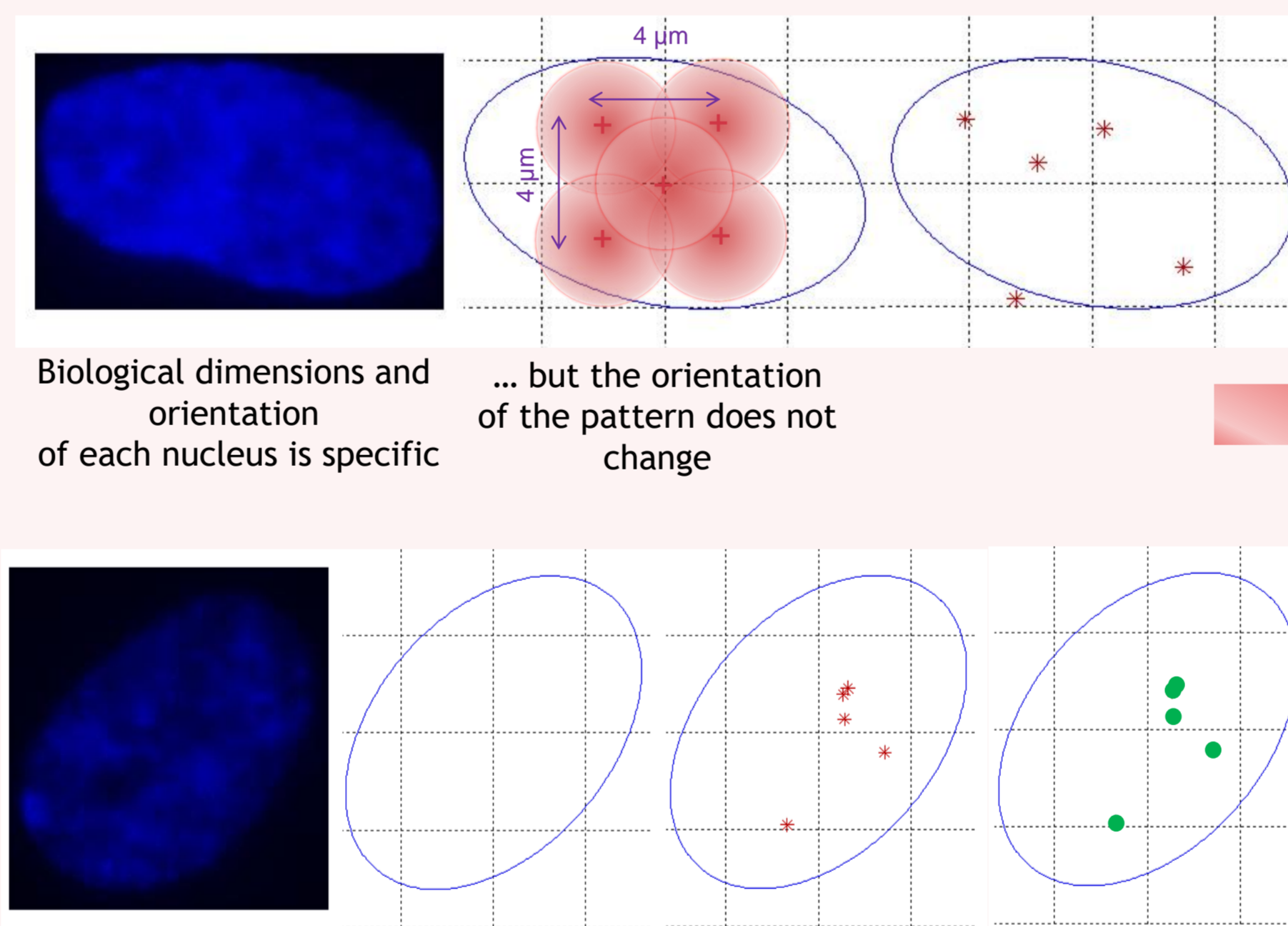
$$\frac{\text{Number of foci} - \text{background foci}}{\text{Theoretical number of particle hits}}$$

2- Estimated number of particle hits reaching each cell nucleus

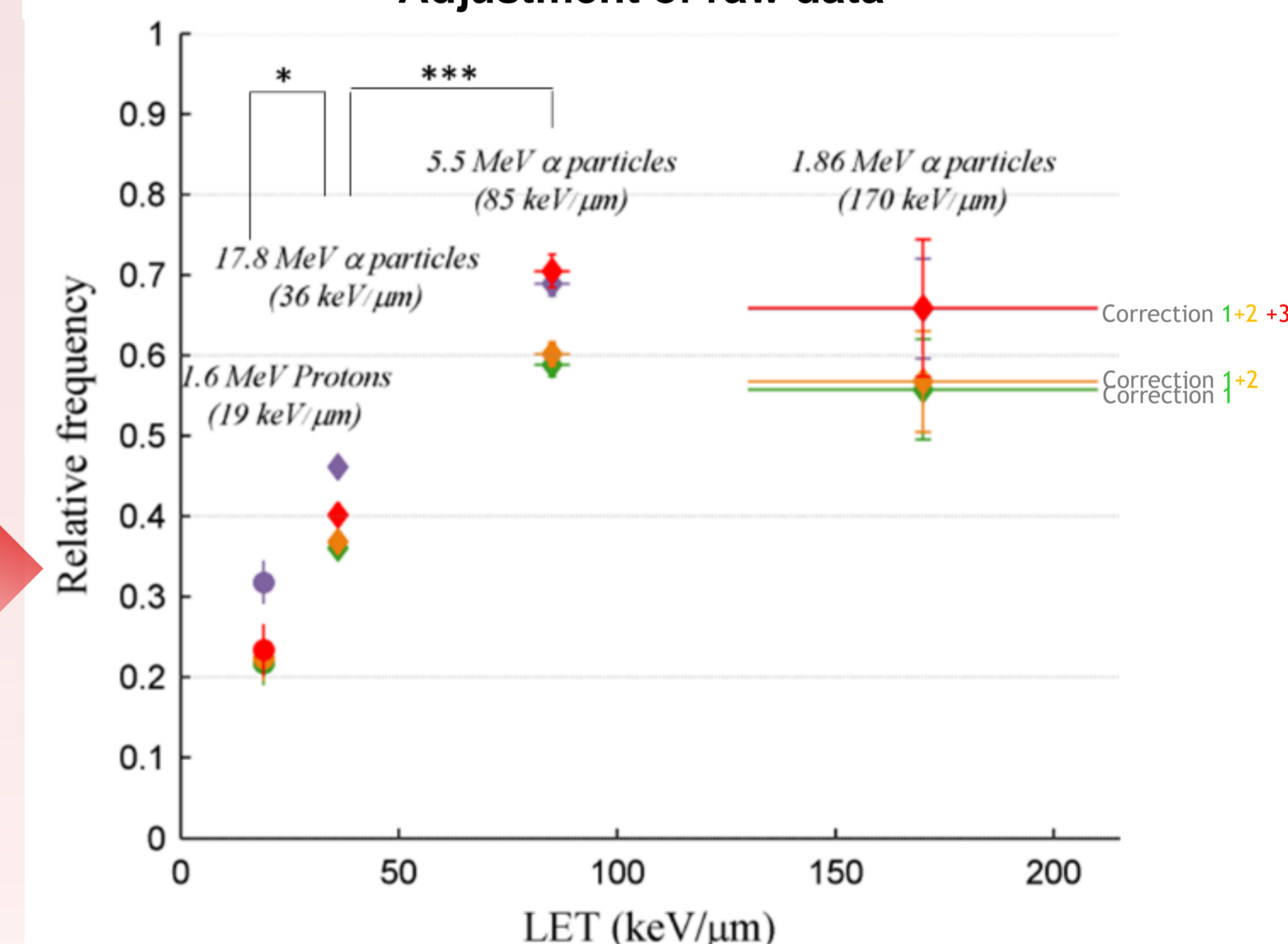
$$\frac{\text{Number of foci} - \text{background foci}}{\text{Estimated number of particle hits}}$$

=> Irradiation characteristics influence the number of hits per nucleus in 10-15 % of cell nuclei

3- Correction due to two particle tracks generating two foci in close proximity to each other, so that it may be analyzed as one focus formation

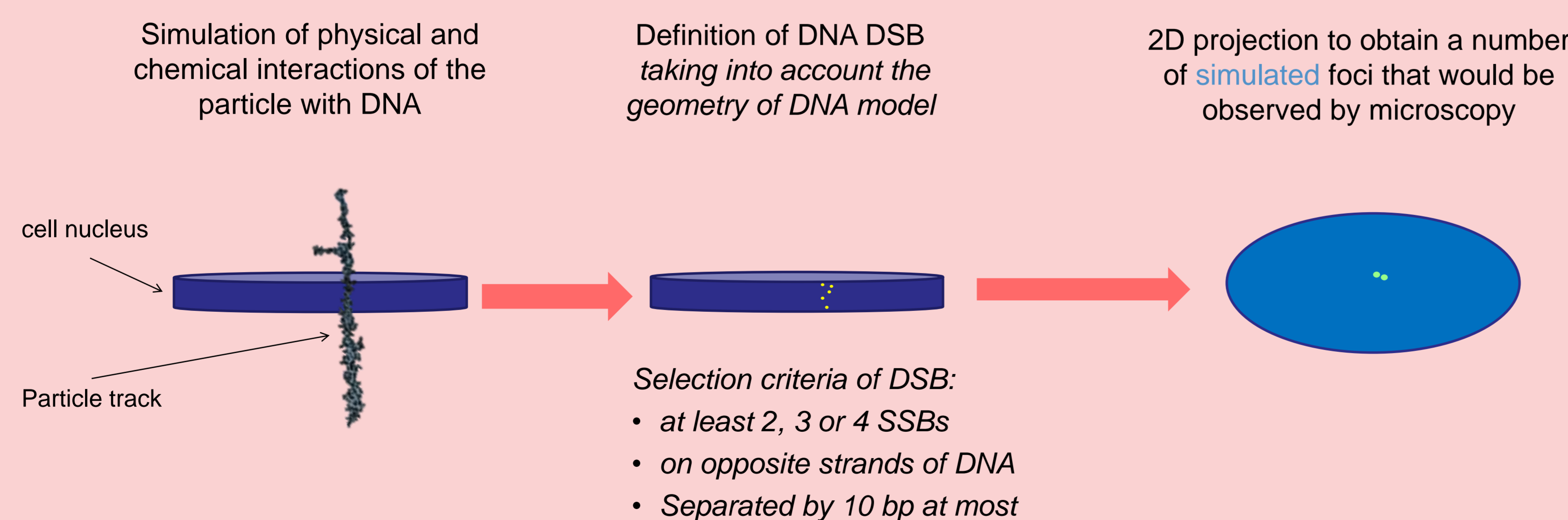


Adjustment of raw data



SIMULATION OF PARTICLE INTERACTIONS WITH DNA

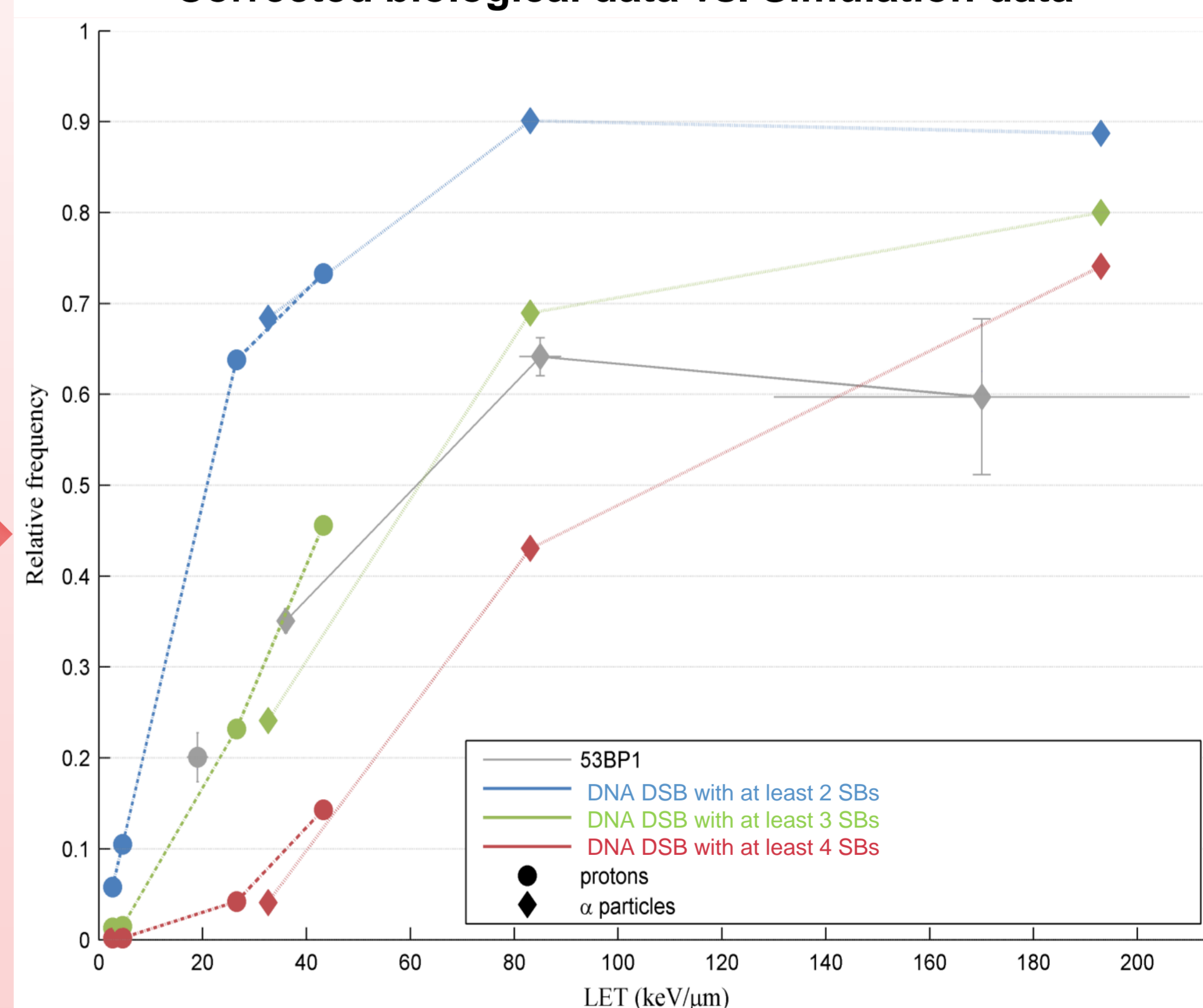
- Monte Carlo Simulation with Geant4-DNA



- Selection criteria of DSB:**
- at least 2, 3 or 4 SSBs
 - on opposite strands of DNA
 - Separated by 10 bp at most

=> This is performed thousands of times at different positions of the target in order to take into account the variation of DNA density inside the simulated nucleus.

Corrected biological data vs. Simulation data



RESULTS AND CONCLUSION

Comparable to corrected biological data, the simulated relative frequencies of at least one radiation-induced focus formation per particle track increase gradually. For α particles of LET ranging from 80 to 170 keV·μm⁻¹, a constant DNA damage-induction frequency was found, where 10-30% of the particle traversals did not lead to foci formation.

These findings will allow for a better comprehension of the relationship between the topology of energy deposition from particles of different LET and early cell damage. They will also help obtain an accurate estimate of the probability of particle interaction to induce foci formation at DNA damage sites.