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

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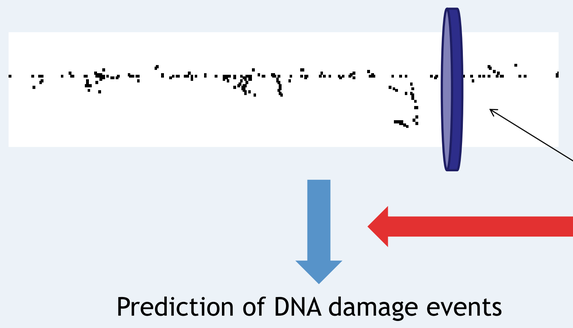
INTRODUCTION

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 => G_0G_1 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)

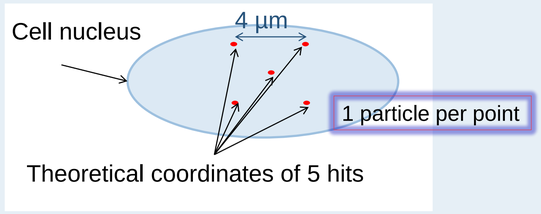
Alpha particles	Proton
8 MeV (170 keV/µm)	3 MeV (19 keV/µm)
10 MeV (85 keV/µm)	
20 MeV (36 keV/µm)	

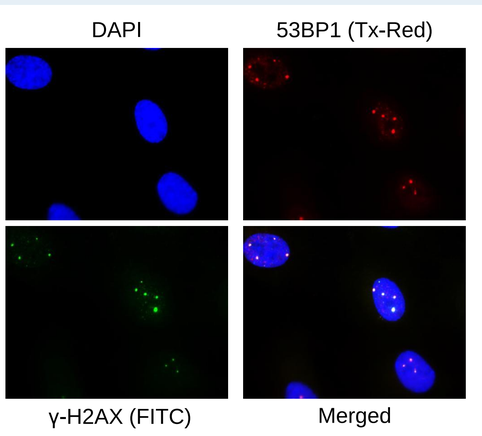
Analysis: Statistical evaluation of nuclear foci formation (53BP1 and γ-H2AX) related to a particle traversal was undertaken in a large population of cells.

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

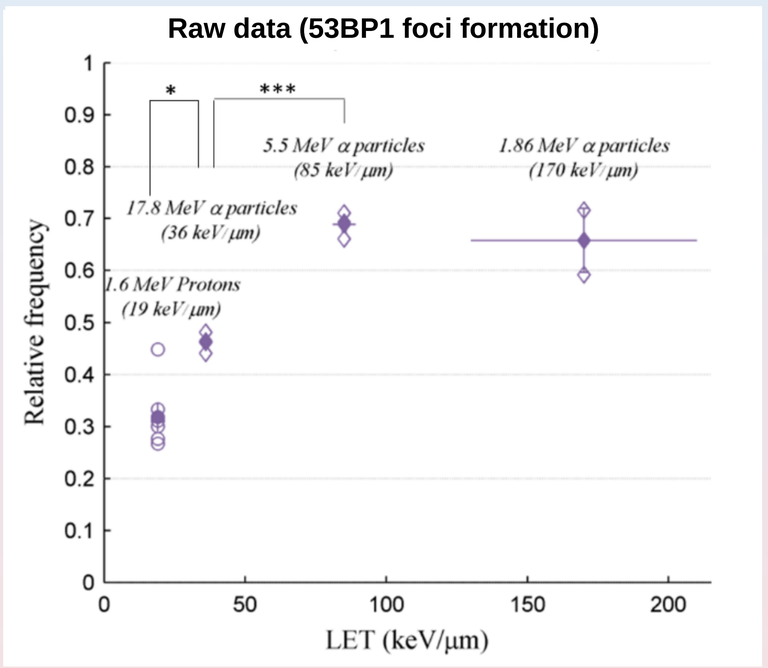
$$\text{Ratio} = \frac{Number\ of\ foci}{Theoretical\ number\ of\ particle\ hits}$$

Definition of square pattern of irradiation





Raw data (53BP1 foci formation)



❑ BIOLOGICAL DATA ADJUSTED FOR FACTORS LEADING TO EXPERIMENTAL BIAS

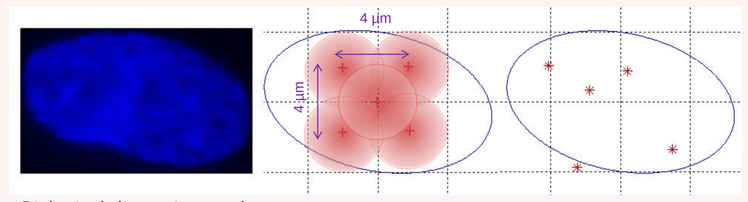
1- Foci background

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

2- Estimated number of particle hits reaching each cell nucleus

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

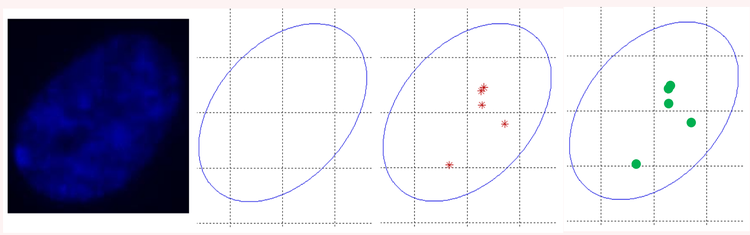
=> Irradiation characteristics influence the number of hits per nucleus in 10-15 % of cell nuclei



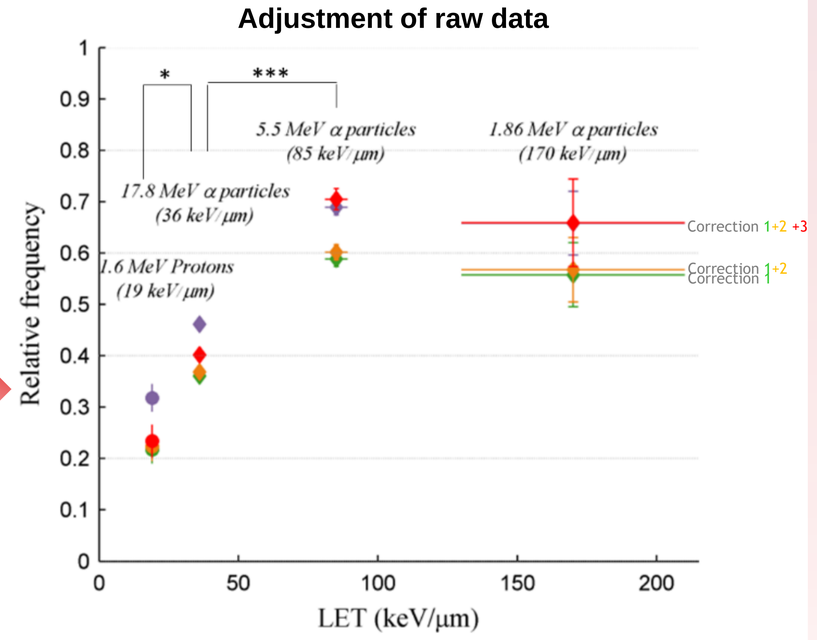
Biological dimensions and orientation of each nucleus is specific

… but the orientation of the pattern does not change

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



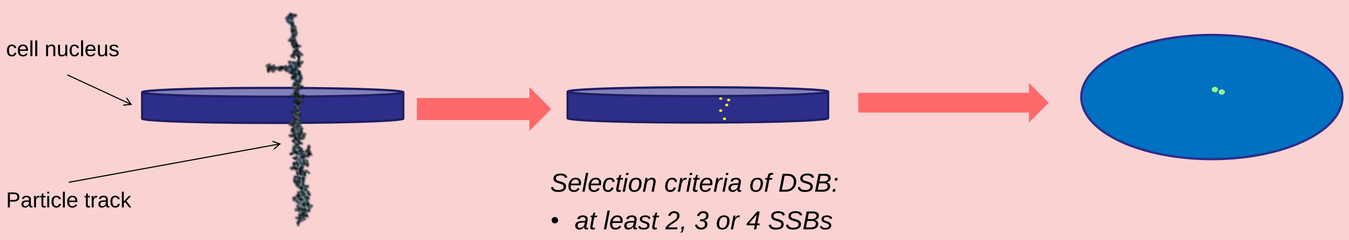
❑ SIMULATION OF PARTICLE INTERACTIONS WITH DNA

- Monte Carlo Simulation with Geant4-DNA

Simulation of physical and chemical interactions of the particle with DNA

Definition of DNA DSB *taking into account the geometry of DNA model*

2D projection to obtain a number of simulated foci that would be observed by microscopy

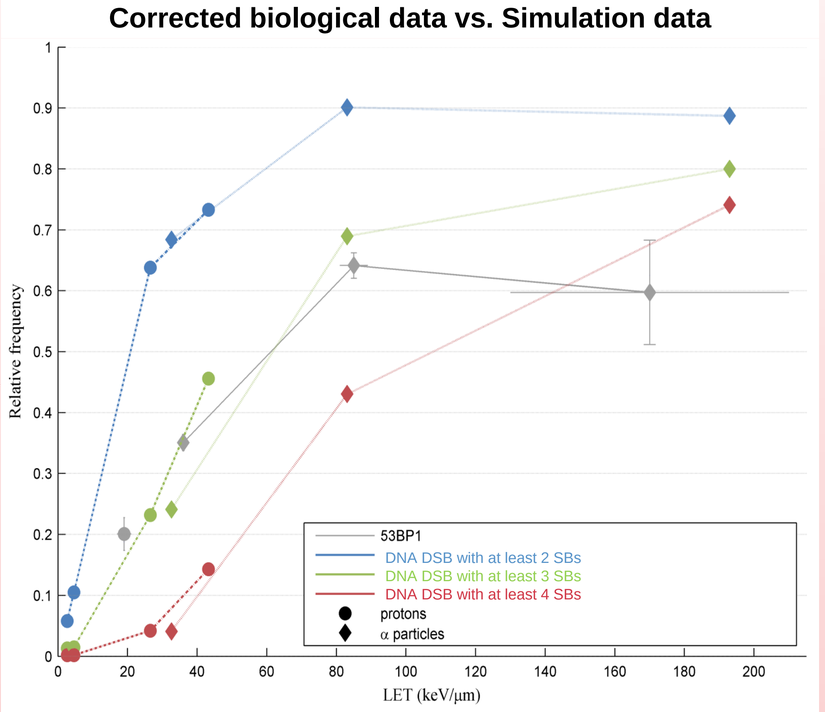


Selection criteria of DSB:

- *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.

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