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INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

MINAS TIRITH: A GEANT4-DNA-BASED TOOL FOR MODELING DAMAGE AT THE CELL POPULATION SCALE

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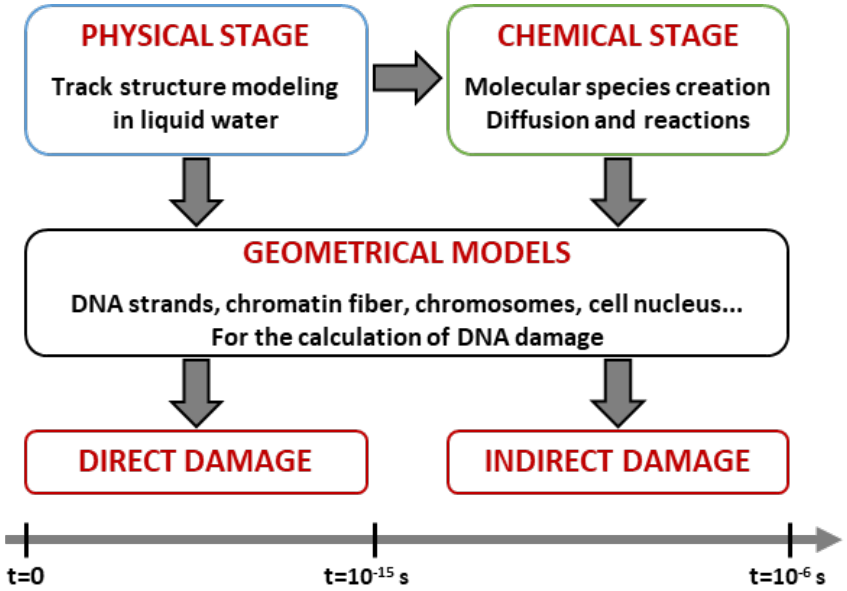
IV Geant4 International User Conference

MEMBRE DE ETSON

UNDERSTANDING RADIATION-INDUCED EFFECTS

MODELING THE RADIATION INDUCED DNA DAMAGE AT THE CELL NUCLEUS SCALE *

A nanodosimetric simulation chain based on GEANT4-DNA to model the early radiation-induced DNA damage at the cell nucleus scale.



Calculation of early radiation-induced damage in modeling

* Meylan *et al.*, Sci. Rep. (7) **2017**

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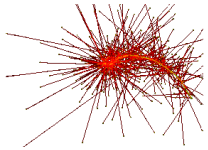

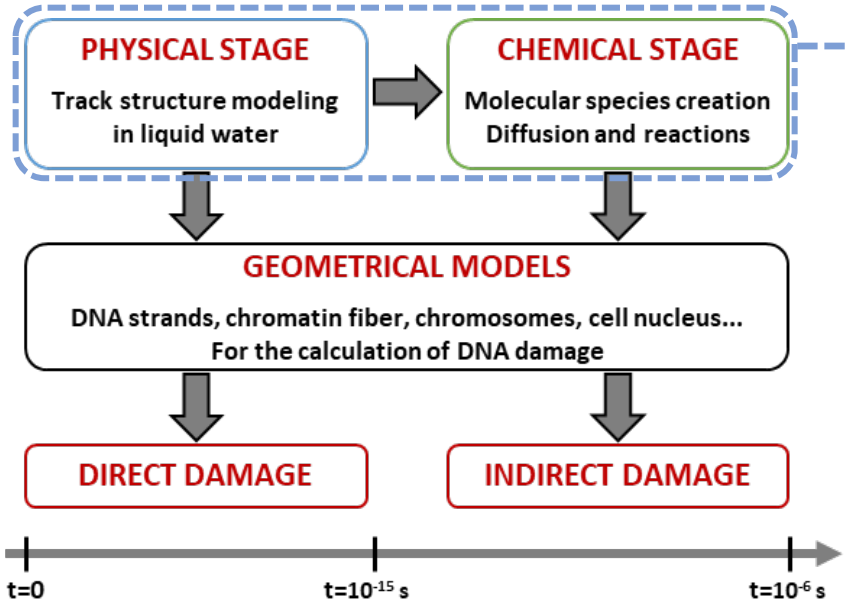

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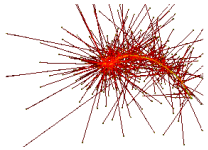

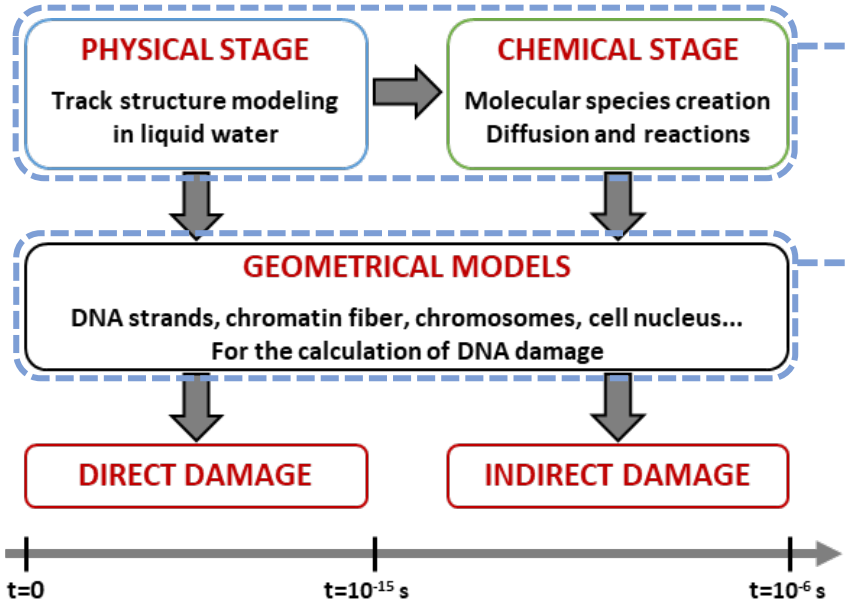

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- Entire cell nucleus geometry **
- Molecular level of detail
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https://bitbucket.org/sylMeylan/opendnafabric/src/master/ ** Meylan *et al.*, Comput. Phys. Commun. (204) **2016** / Tang *et al.*, Med. Phys. (46) **2019** / Thibaut *et al.*, Int. J. Mol. Sci. **2022**

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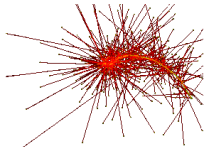

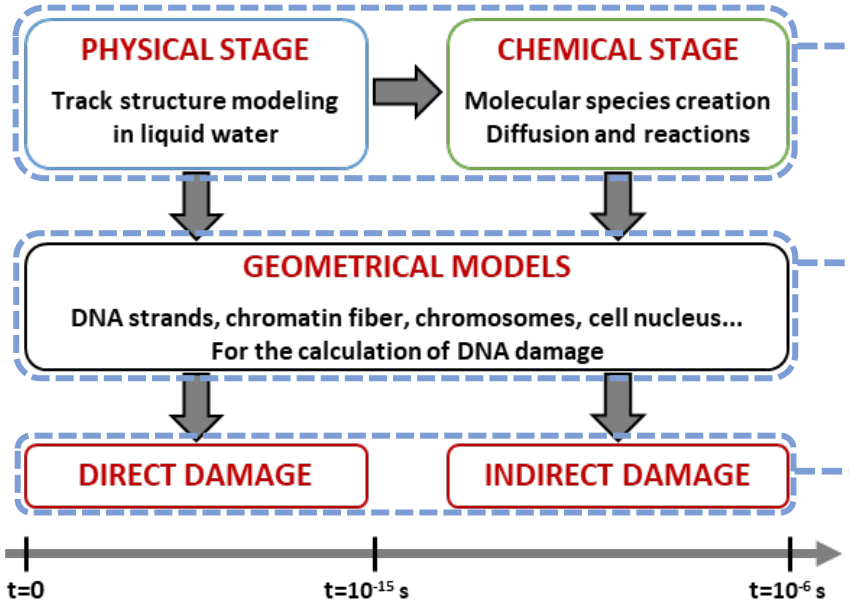

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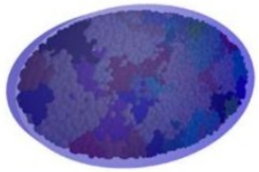

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- Direct SB: >17.5 eV deposits in a sugar-phosphate group
- Indirect SB: 42% of OH/deoxyribose interactions
- Clustering of SB less than 10 bp apart to form complex SSB and DSB

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COMPARISON WITH EXPERIMENTAL RESULTS

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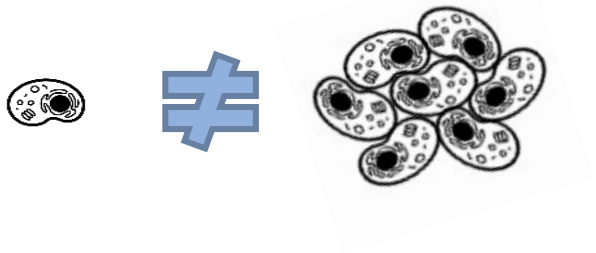

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  - Simulations performed for one single cell
  - Comparison in terms of **mean number** of DNA damages (DSB, SSB..)
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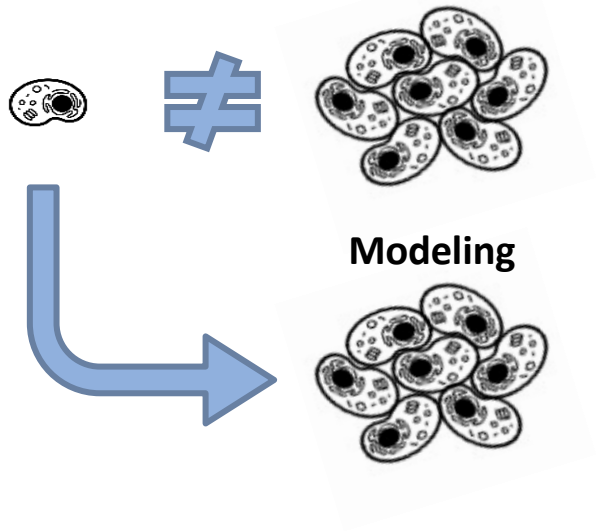

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  - Increase the scale of our simulation chain
  - Multiscale Monte Carlo simulation approach *

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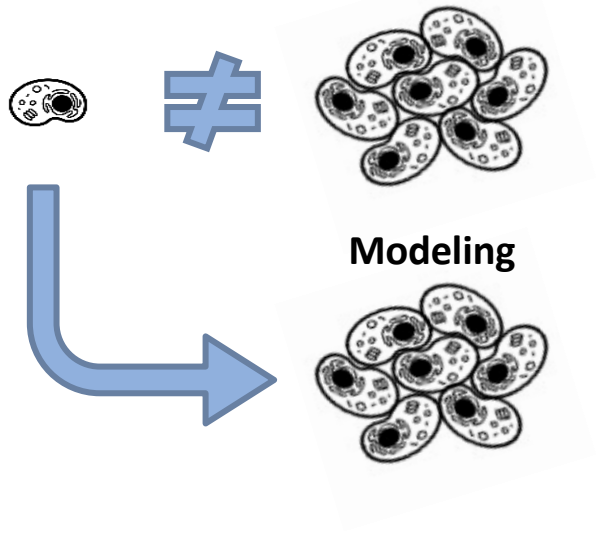

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- A new Geant4-DNA-based tool is proposed:

MINAS TIRITH

MIcrodosimetry and NAnodosimetry to Simulate The Initial Radiation-Induced damage Topology's Heterogeneity

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MINAS TIRITH TOOL CONCEPT

TRACK DISTRIBUTION IN THE CELL POPULATION

- Variability in the responses of cells from the same population, exposed to a given macroscopic absorbed dose, could be related to the variation in energy imparted to each cell.

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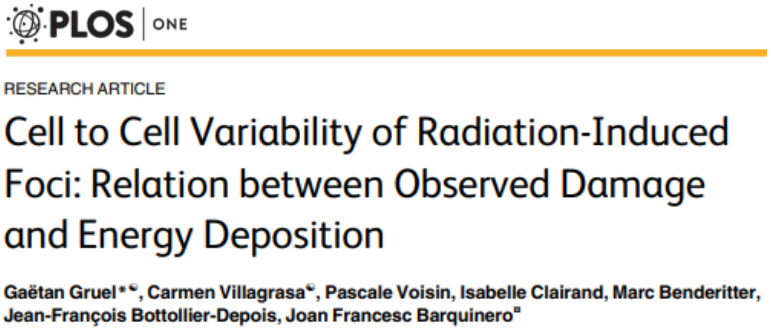
- Track distribution in the cell population must be done according to the **microdosimetry** formalism.



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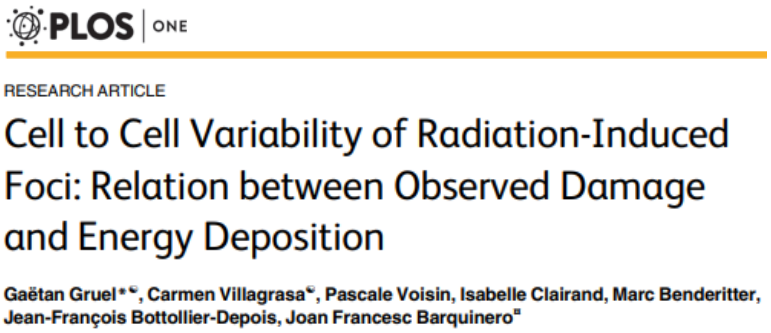
PLOS ONE

RESEARCH ARTICLE

Cell to Cell Variability of Radiation-Induced Foci: Relation between Observed Damage and Energy Deposition

Gaëtan Gruel*, Carmen Villagrasa, Pascale Voisin, Isabelle Clairand, Marc Benderitter, Jean-François Bottollier-Depois, Joan Francesc Barquinero

  - Construction of a database of $f_1(y)$ and $f(CL)$ microdosimetric spectra by Monte Carlo simulations over a large range of energies (1 keV to 20 MeV) for different types of particles (e-, p+, α) in a volume representing an endothelial cell nucleus.

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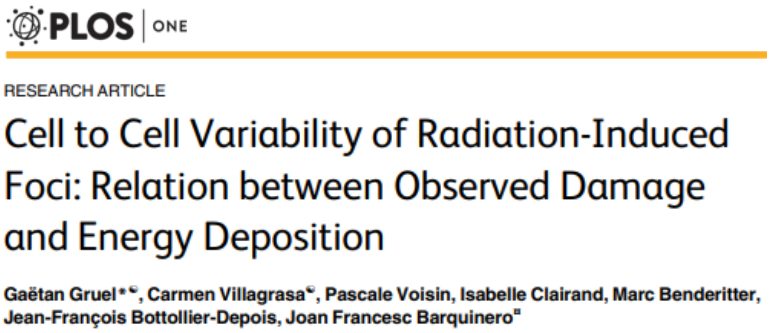
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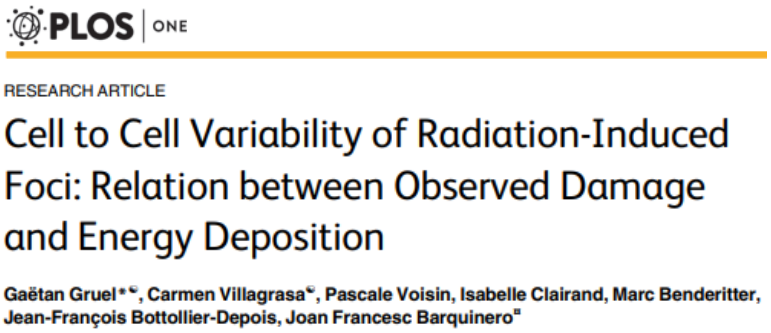
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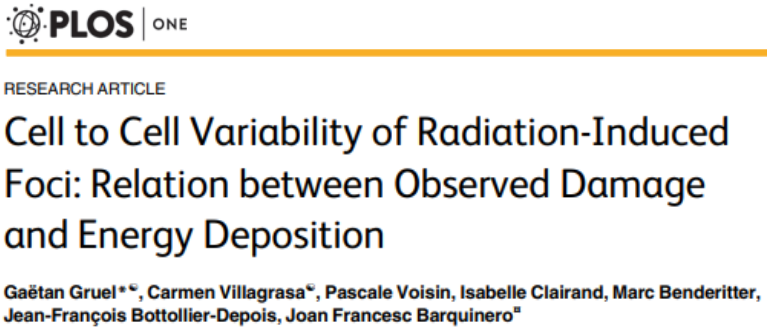

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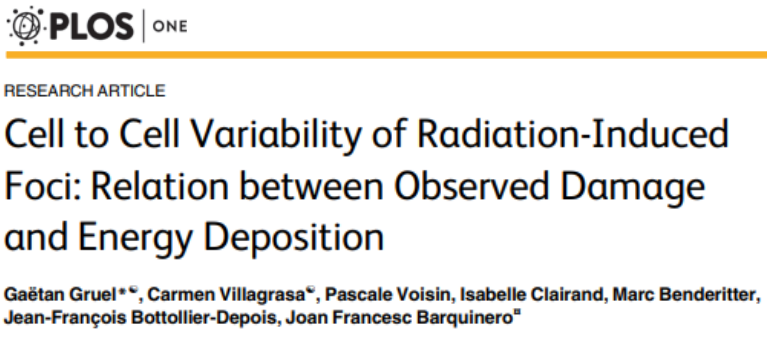
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- Calculation of the mean value $\overline{z_f}$ of the $f_1(z)$ spectrum.
- Distribution of the number of tracks per cell in the population from a Poisson law with parameter $\frac{\overline{z_f}}{D_{abs}}$ with D_{abs} the value of the macroscopic absorbed dose delivered to the population.

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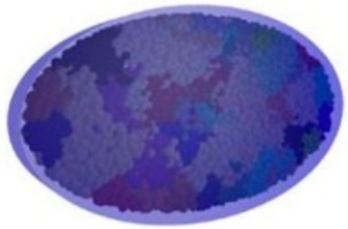

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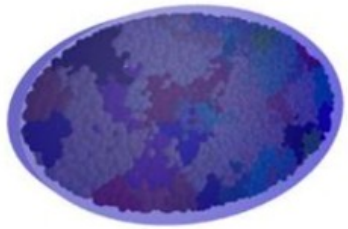

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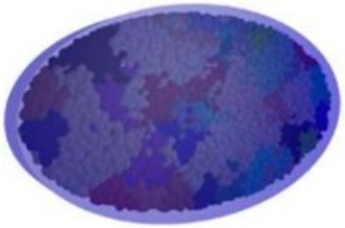

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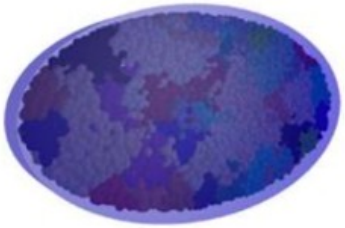

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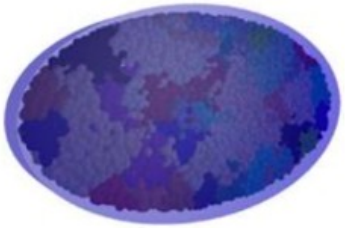

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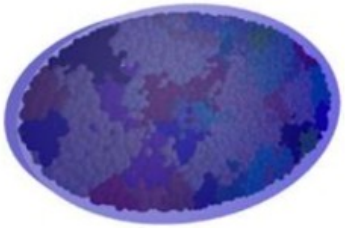

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  - Determination of the number of DSB and SSB by sampling in the damage spectra as a function of z.

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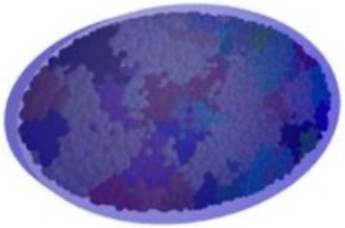

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  - Calculation of the z value based on the CL and the interpolated $f_1(y)$ spectrum.
  - Determination of the number of DSB and SSB by sampling in the damage spectra as a function of z.
  - Localization of each DSB and SSB by sampling in the damage spectra based on the geometric characteristics of the track (entrance point, direction, particle type).
  - Determination of the complexity and type (direct, indirect or hybrid) of damage by sampling.

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- The method cannot be validated by direct comparison with a simulation performed using the Monte-Carlo method with Geant4 because the scale is too important.

- A step-by-step validation is therefore required:

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MATHEMATICAL EVALUATION OF THE SPECTRUM RECONSTRUCTION BY INTERPOLATION

Performed using the **M**ean **A**bsolute **P**ercentage **E**rror (MAPE) statistical indicator.

- Less than 4% for microdosimetric spectra.
- Less than 8% for ion damage spectra.
- Less than 15% for electron damage spectra.

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DOSE DISTRIBUTION EVALUATION IN A CELL POPULATION BY COMPARISON WITH MC-MODELING

Performed by making a comparison between the microdosimetric spectra obtained by MINAS TIRITH and by Monte-Carlo simulation for the same irradiation.

The number of tracks attributed to each nucleus of the cell population in MINAS TIRITH is directly correlated to the dose distributed to each cell.

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- A step-by-step validation is therefore required:

MATHEMATICAL EVALUATION OF THE SPECTRUM RECONSTRUCTION BY INTERPOLATION

Performed using the **M**ean **A**bsolute **P**ercentage **E**rror (MAPE) statistical indicator.

- Less than 4% for microdosimetric spectra.
- Less than 8% for ion damage spectra.
- Less than 15% for electron damage spectra.

DOSE DISTRIBUTION EVALUATION IN A CELL POPULATION BY COMPARISON WITH MC-MODELING

Performed by making a comparison between the microdosimetric spectra obtained by MINAS TIRITH and by Monte-Carlo simulation for the same irradiation.

The number of tracks attributed to each nucleus of the cell population in MINAS TIRITH is directly correlated to the dose distributed to each cell.

EVALUATION OF THE DAMAGE ASSOCIATED PER TRACK BY COMPARISON WITH MC-MODELING

If the tracks are well distributed in the cell population, it remains to evaluate that each track is assigned the correct damage topology, according to its characteristics.

To validate this point, we compare the mean number of damages computed by MINAS TIRITH for different track types, compared to the one obtained with the simulation chain based on Geant4-DNA.

MINAS TIRITH TOOL VALIDATION

DOSE DISTRIBUTION EVALUATION IN A CELL POPULATION BY COMPARISON WITH MC-MODELING

In order to evaluate the method over the whole energy range and for each particle type, the phase space chosen for this validation is the one of a **monoenergetic neutron** irradiation of **15.1 MeV**.

- Containing alphas, electrons and protons.
- Covers the **whole energy range** of the tool.
- Provides a wide range of particle incidence (angle).

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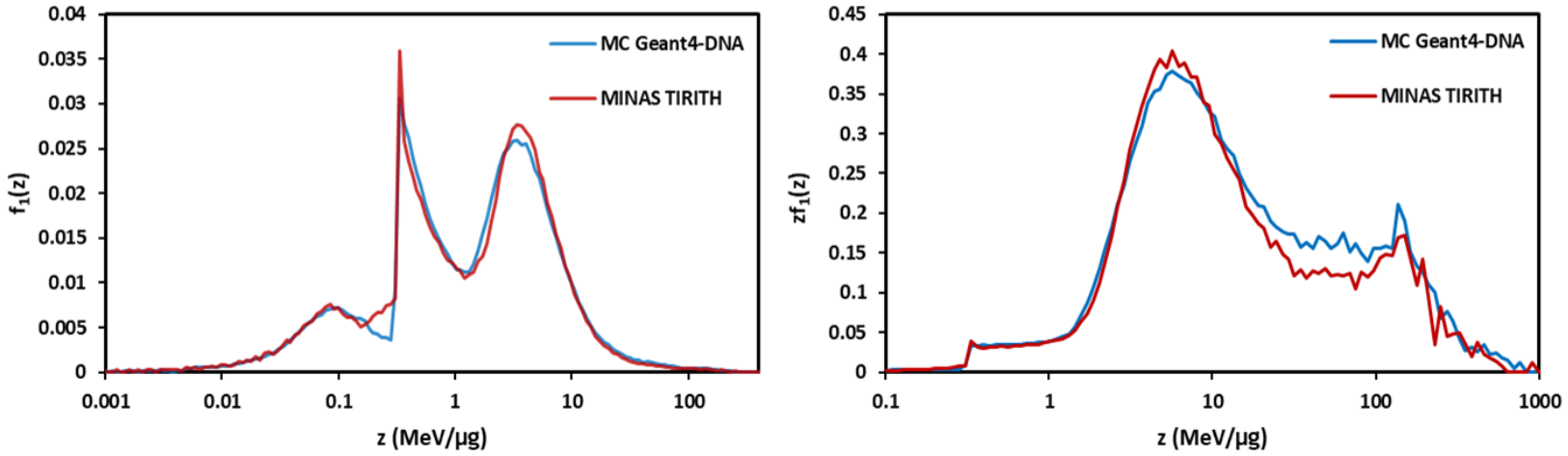
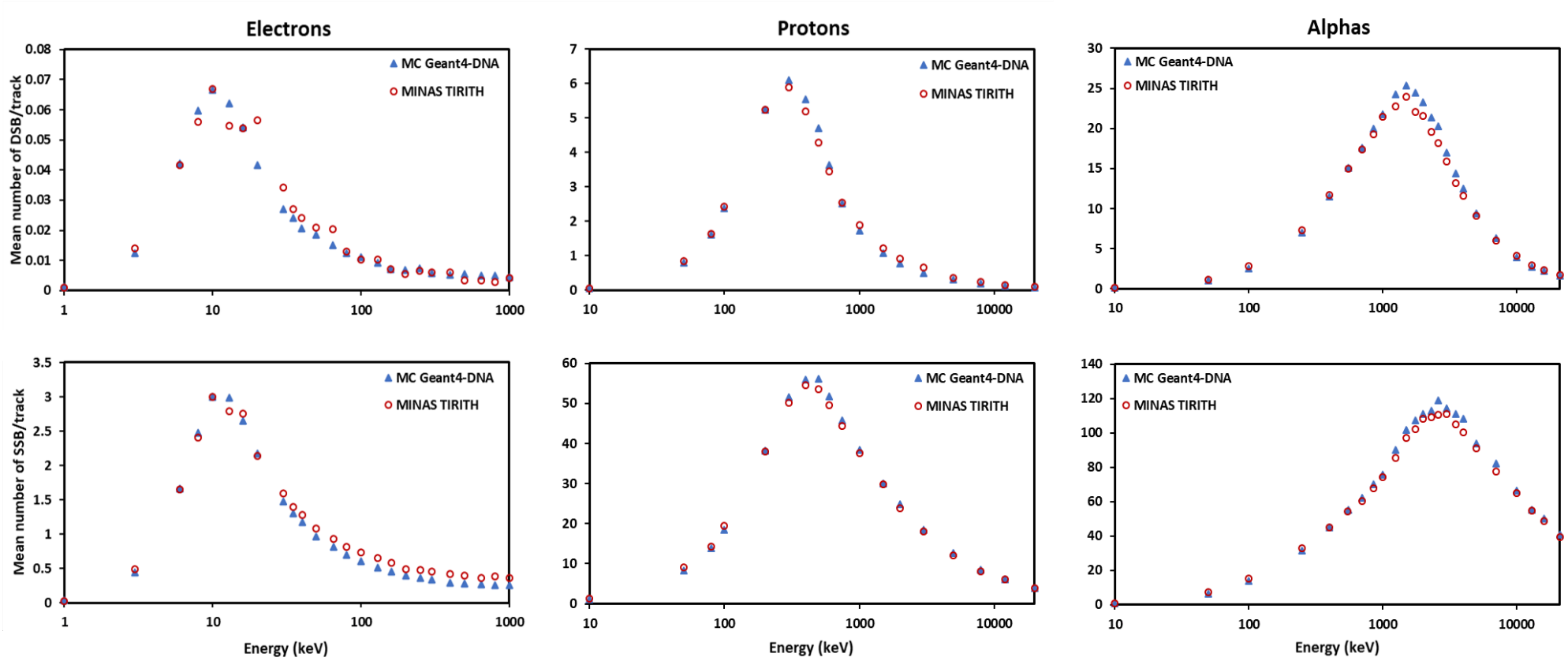


Comparison of $f_1(z)$ (left) and $zf_1(z)$ (right) spectra obtained using the MINAS TIRITH tool (red) and by Monte Carlo simulation with the Geant4 and Geant4-DNA simulation codes (blue)

MINAS TIRITH TOOL VALIDATION

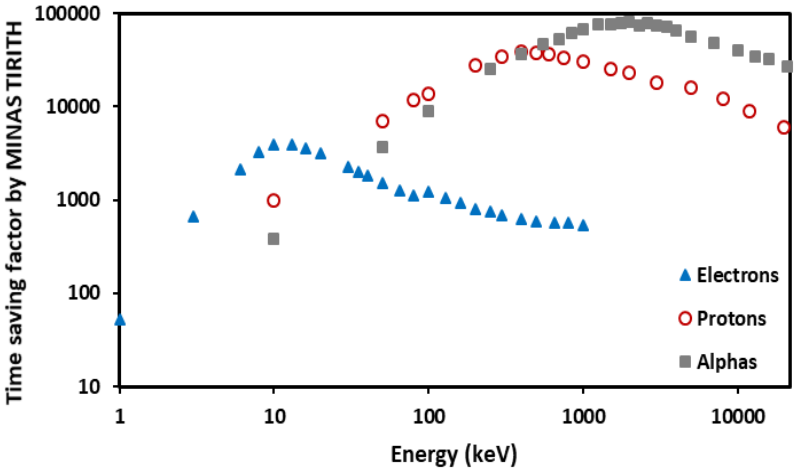
EVALUATION OF THE DAMAGE ASSOCIATED PER TRACK BY COMPARISON WITH MC-MODELING



Comparison of the mean number of $DSB/track$ (top) and $SSB/track$ (bottom)

CONCLUSION ET PERSPECTIVES

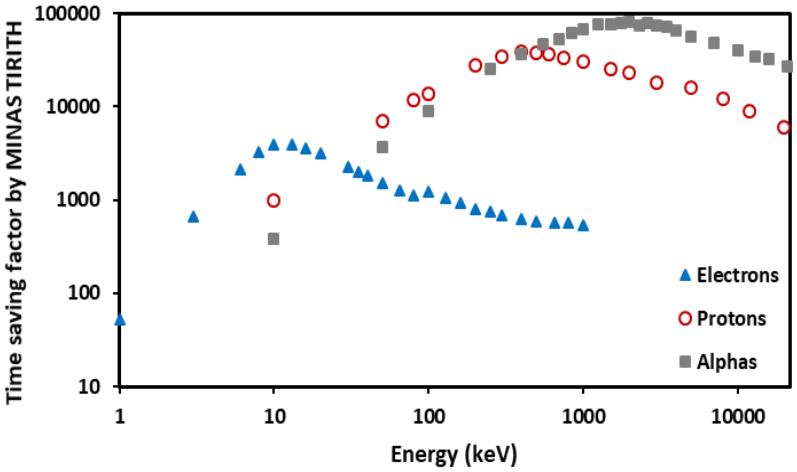
CONCLUSION



Time saving by MINAS TIRITH compared to the Geant4-DNA based simulation chain over the whole energy range and for each particle type without damage location

CONCLUSION ET PERSPECTIVES

CONCLUSION

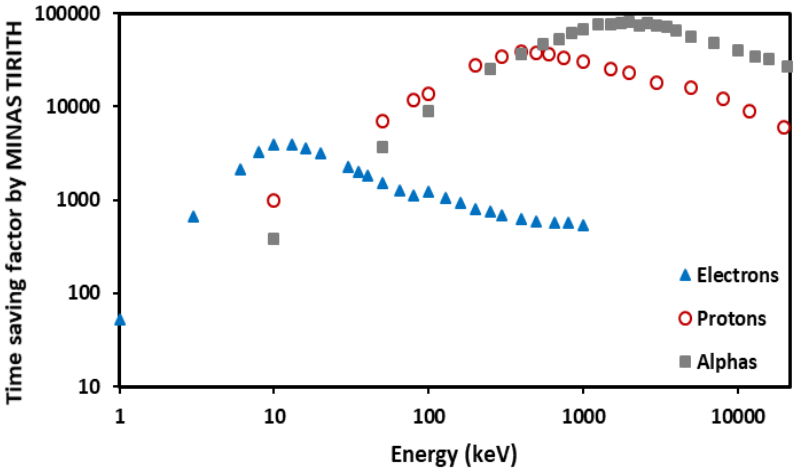


Time saving by MINAS TIRITH compared to the Geant4-DNA based simulation chain over the whole energy range and for each particle type without damage location

- MINAS TIRITH has been **validated** by comparison:
  - Well distributed dose in the population
  - Successful calculation of the mean number of damages per track
- Time saving allows to scale-up the simulation to the cell population level.

CONCLUSION ET PERSPECTIVES

CONCLUSION



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PERSPECTIVES

- Some observables that can influence the repair are, like damage location, not validated yet
- An experimental validation is planned by comparison with IRSN biological experiments.

Thank you for your attention!

More questions?  yann.thibaut@irsn.fr