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INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

SIMULATION OF RADIO-INDUCED DNA DAMAGES AND THEIR REPAIR BY MEANS OF GEANT4-DNA MONTE CARLO TRACK STRUCTURE CODE

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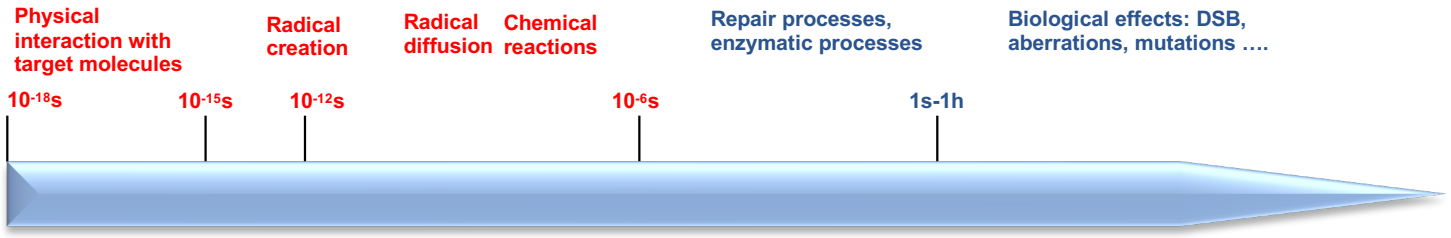
BioRadIII project
(ESA funding)

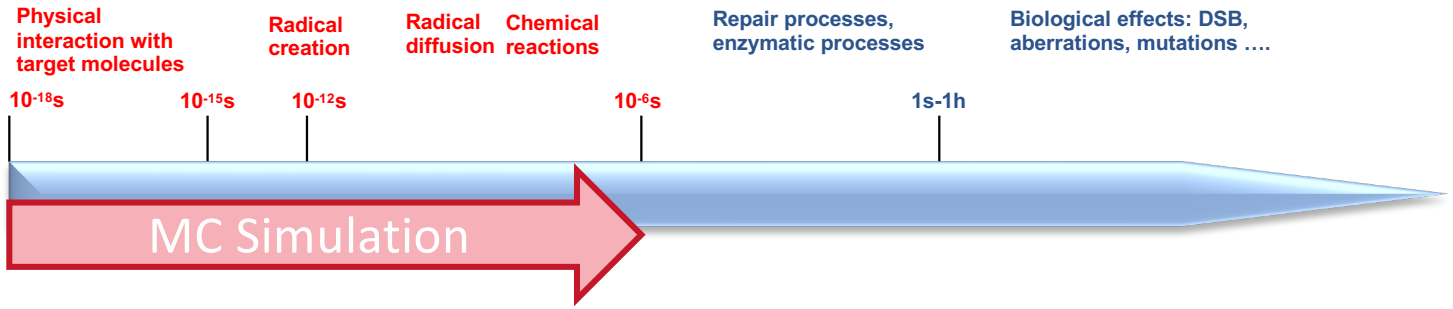
GEANT4-DNA
A SIMULATION TOOLKIT

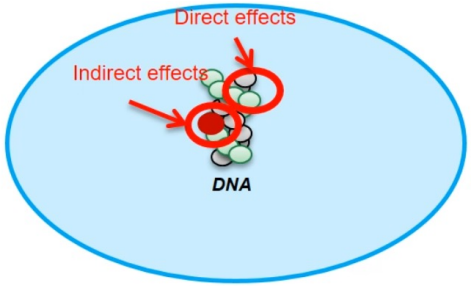
MEMBRE DE
ETSON

Modelling in Radiobiology: a Multi-Scale Approach

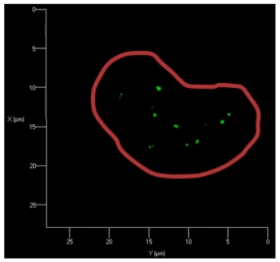


Modelling in Radiobiology: a Multi-Scale Approach



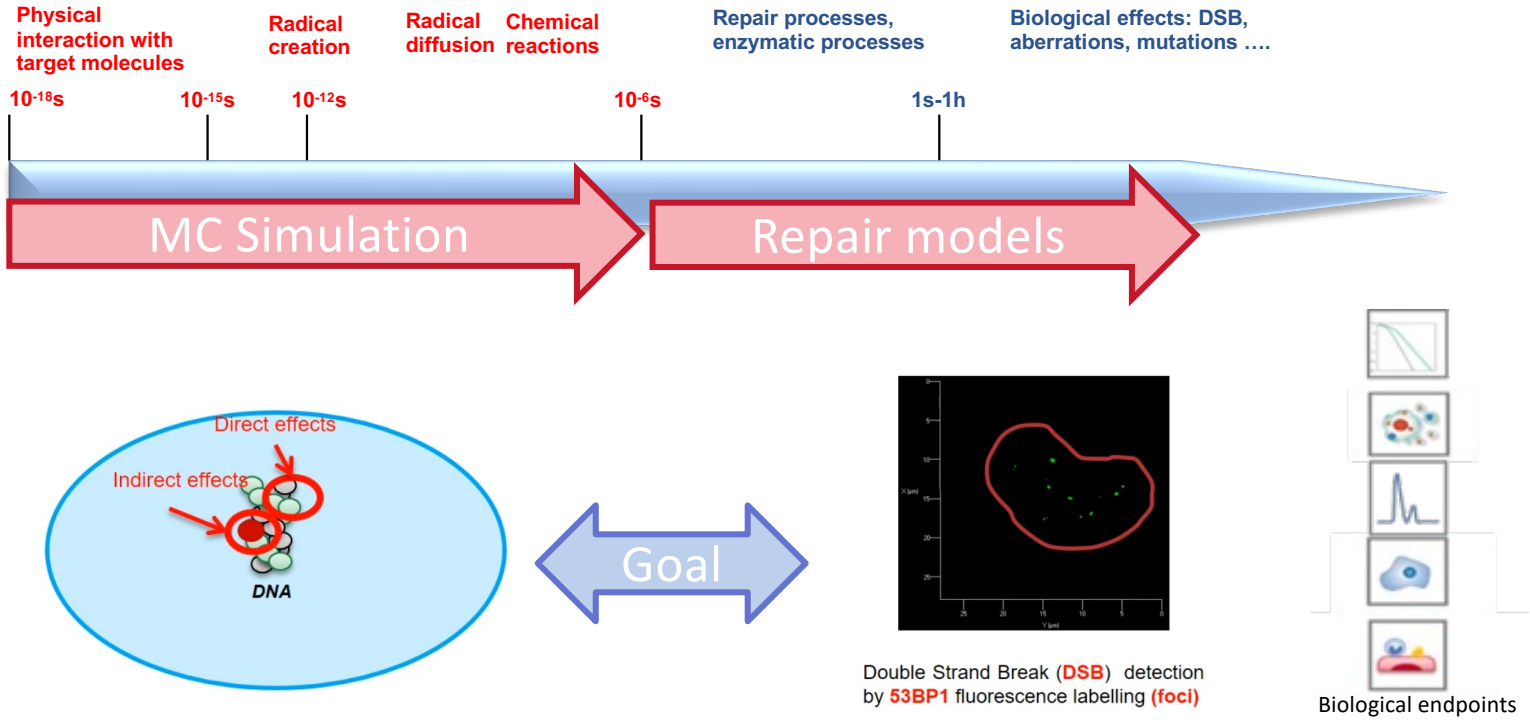


Goal



Double Strand Break (**DSB**) detection
by **53BP1** fluorescence labelling **(foci)**

Modelling in Radiobiology: a Multi-Scale Approach



NANODOSIMETRIC SIMULATION CHAIN

- Simulation chain at the origin of dnadamage1 user example and based on Geant4-DNA (Geant4 11.0)

- Includes physical, physico-chemical and chemical stages of the action of ionizing radiations

- **Validated for DSB induction** for a variety of particles and LETs:
  - Proton, alphas: *Meylan et al., Sci. Rep. 7 (2017)*
  - Kilovoltage and megavoltage X-Ray beams: *Tang et al., IJMS 20 (2019)*

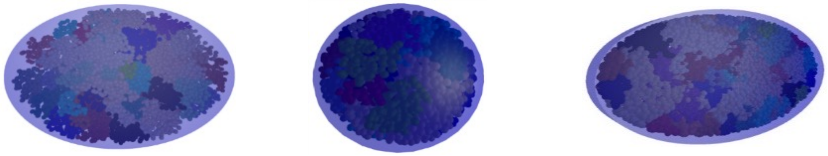
- New features include:
  - **New nuclei geometries** from the isochore theory: *Thibaut et al., IJMS 23 (2022*)
  - Possibility to use **Independent Reaction Time** of the chermical step: IRT-sync implementation of *Tran et al., Med. Phys. 48 (2021)*
  - Biological repair models

TARGET GEOMETRY

[DNA IS THE MAIN TARGET

- Creation of complete genome geometries (~6 Gbp) with DNAFabric software*

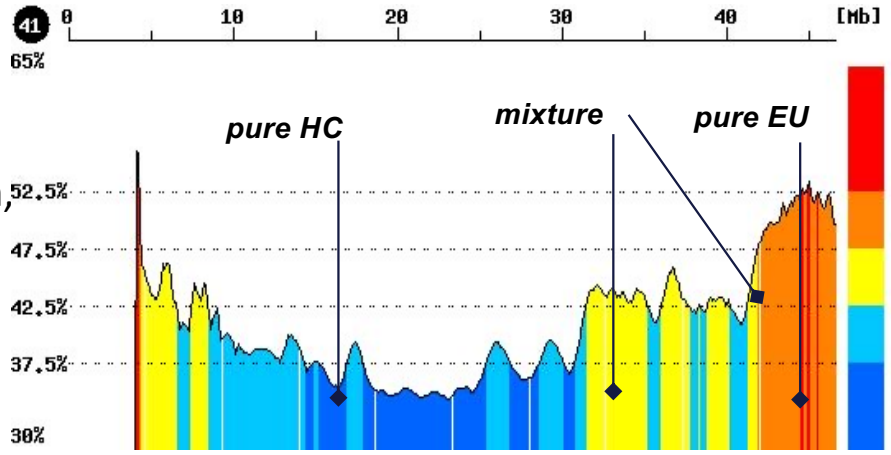
*Meylan S., Vimont U., Incerti S., Clairand I., Villagrasa C., Comput Phys Commun. 204:159 (2016)



Fibroblast *Lymphocyte* *Endothelial*

- Importance of chromatin fiber compactionDamage induction
  - Repair processes

- Hetero and euchromatin is not randomly distributed
  - Current developments consider a realistic distribution
  - isochore family theory: Genome contains 5 families compaction, each family is linked to a GC rate



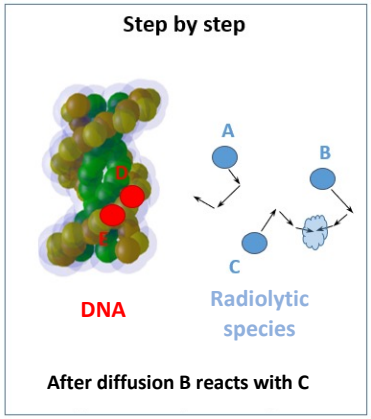
GC profile – chromosome 41

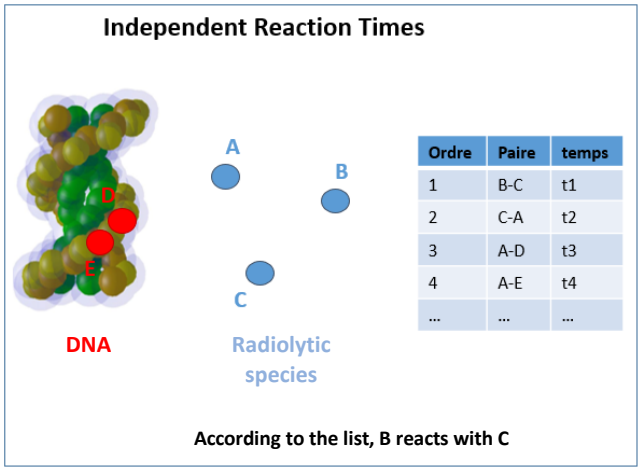
Chemistry

- First developments: Step by Step method
  - Particle-continuum based, each individual molecule is simulated
  - Simulation of diffusion controlled reactions based on full step-by-step Brownian dynamics

Reaction	reaction rate ($10^{10} M^{-1} \cdot s^{-1}$)
$H^\bullet + e^-_{aq} + H_2O \rightarrow OH^- + H_2$	2.65
$H^\bullet + OH^\bullet \rightarrow H_2O$	1.44
$H^\bullet + H^\bullet \rightarrow H_2$	1.20
$H_2 + OH^\bullet \rightarrow H^\bullet + H_2O$	$4.17 \cdot 10^{-3}$
$H_2O_2 + e^-_{aq} \rightarrow OH^- + OH^\bullet$	1.41
$H_3O^+ + e^-_{aq} \rightarrow H^\bullet + H_2O$	2.11
$H_3O^+ + OH^- \rightarrow 2H_2O$	14.3
$OH^\bullet + e^-_{aq} \rightarrow OH^\bullet$	2.95
$OH^\bullet + OH^\bullet \rightarrow H_2O_2$	0.44
$e^-_{aq} + e^-_{aq} + 2H_2O \rightarrow 2OH^- + H_2$	0.50

Reaction	Reaction rate (10^9 $M^{-1}s^{-1}$)
2-deoxyribose + $OH^\bullet$	1.8
Adenine + $OH^\bullet$	6.1
Guanine + $OH^\bullet$	9.2
Thymine + $OH^\bullet$	6.4
Cytosine + $OH^\bullet$	6.1
2-deoxyribose + e^-_{aq}	0.01
Adenine + e^-_{aq}	9.0
Guanine + e^-_{aq}	14.0
Thymine + e^-_{aq}	18.0
Cytosine + e^-_{aq}	13.0
2-deoxyribose + $H^\bullet$	0.029
Adenine + $H^\bullet$	0.10
Guanine + $H^\bullet$	-
Thymine + $H^\bullet$	0.57
Cytosine + $H^\bullet$	0.092
Histone + radical → Histone	-





- Recent developments: Independent Reaction Times approach
  - N-body → 2-body
  - Comparison of reaction times for all pairs of radicals independently of the system
  - Hybrid approach: *Tran et al., Med. Phys. 48 (2021)*

Repair Models

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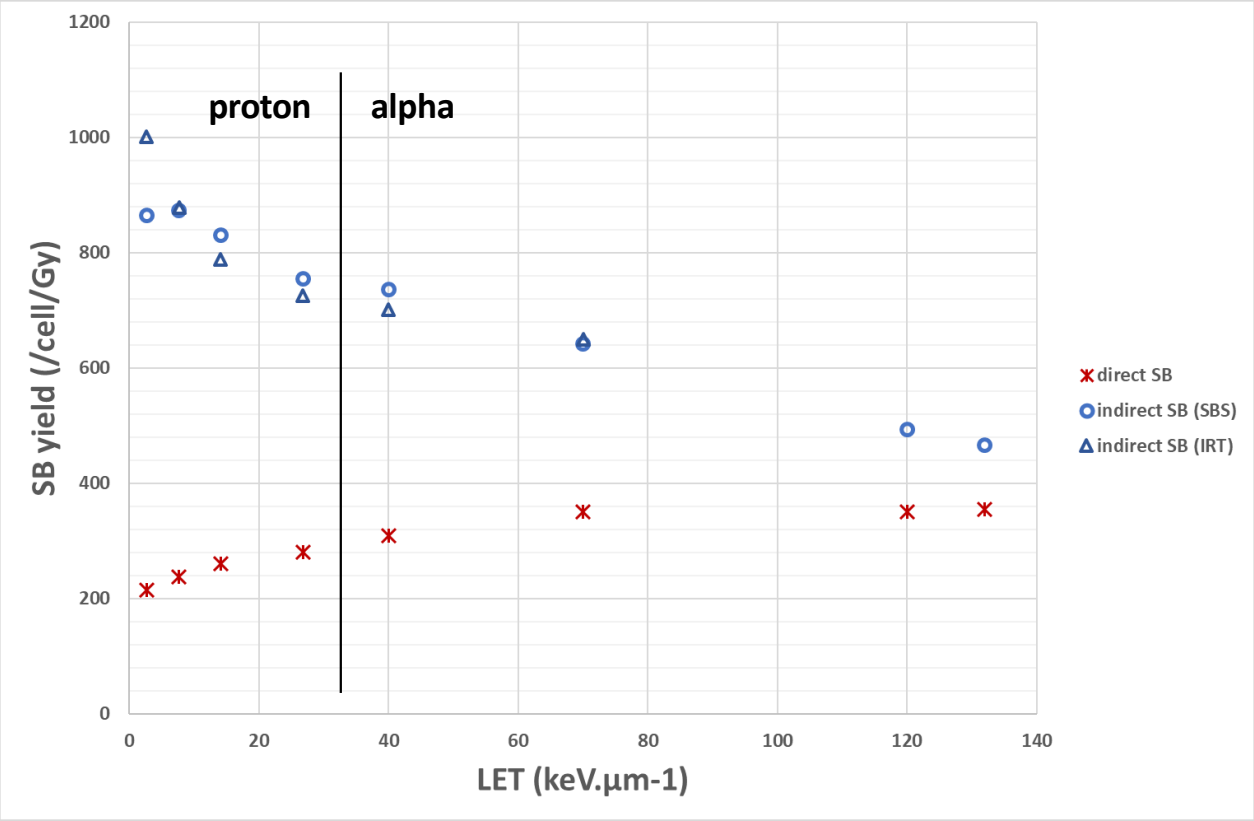
(ESA funding)

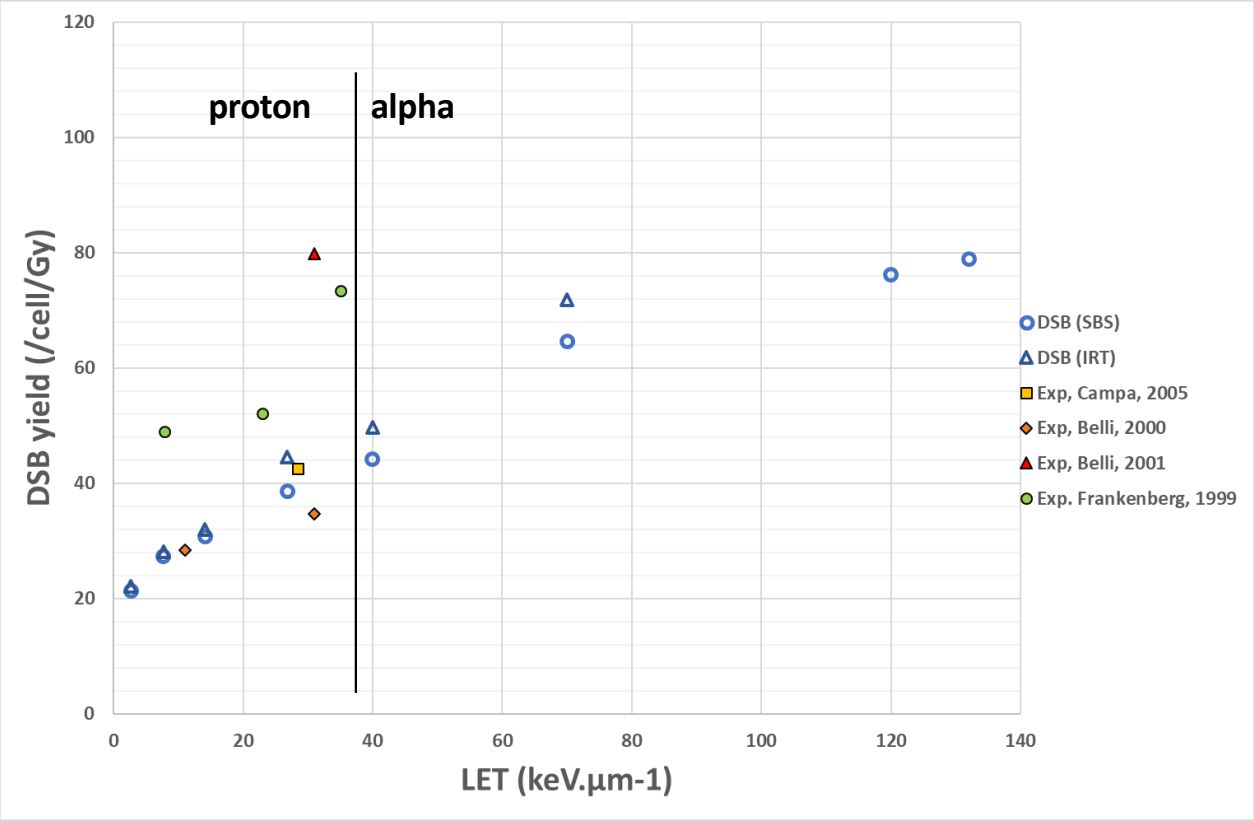
Model	Endpoint	Reference	Input Data	Validation Experimental Data from Literature
Local Effect Model	Non rejoined DSB	Tommasino et al (2013) *Rad. Res. 180, 524-538*	Simple and complex DSBs in 1 Mbp chromatin loops	- Stenerlow (2000): Fibroblast, α 40 keV/µm
Two Lesion Kinetic Model	Surviving fraction	Stewart (2001) *Rad. Res. 156, 365-378*	Simple and complex DSBs	- Belli (2000): Fibroblast, p 7.7 keV/µm - Netti (2004): Fibroblast, α 132 keV/µm
Belov model	DSB repair	*Belov et al. (2015)* *J. Theo. Biol. 366, 115-130*	Simple and complex DSBs	- Antonelli (2015): Fibroblast, p 28.5 keV/µm

Strand Breaks Yield



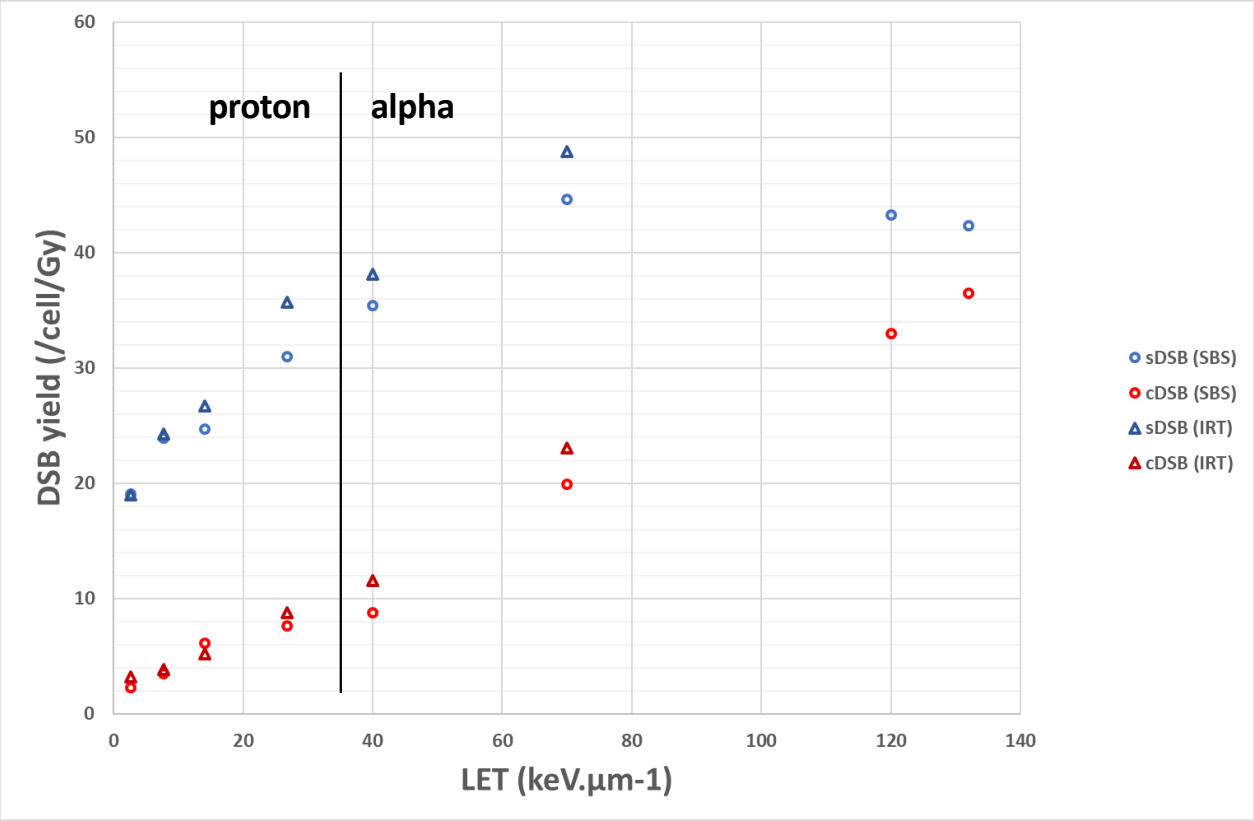
- Fibroblast cell nucleus
- Protons and alphas: 2.7-132 keV/µm
- Direct SB:
  - 17.5 eV in Sugar-Phosphat
  - Saturation with increasing LET
- Indirect SB
  - Tchem = 5 ns
  - 42% hydroxyl-Sugar reactions
  - Decrease of indirect SBs with increasing LET
- **Good agreement IRT-sync / SBS**

Double Strand Breaks Yield



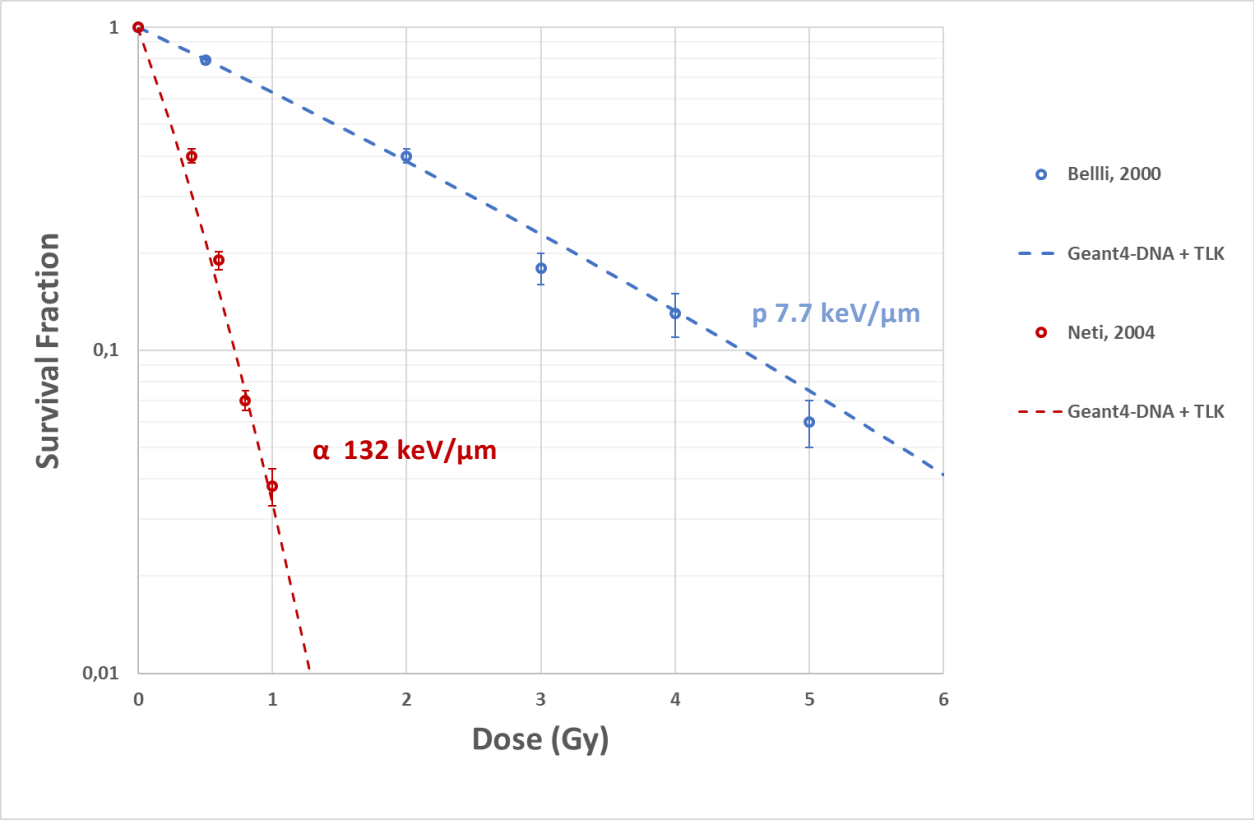
- Fibroblast cell nucleus
- Protons and alphas: 2.7-132 keV/µm
- Sparse experimental data
- **Both methods SBS and IRT are in agreement with experimental data**

Simple and Complex Double Strand Breaks Yield



- Fibroblast cell nucleus
- Protons and alphas: 2.7-132 keV/µm
- Saturation of simple DSB yield with increasing LET
- Linear evolution of complex DSB yield with LET on this range
- sDSB and cDSB calculation method provided as a deliverable of BioRadIII project

Survival Fraction (TLK Model)



- Fibroblast cell nucleus
- Protons 7.7 kev/µm and alphas 132 keV/µm
- Geant4-DNA+TLK: good agreement with experimental data

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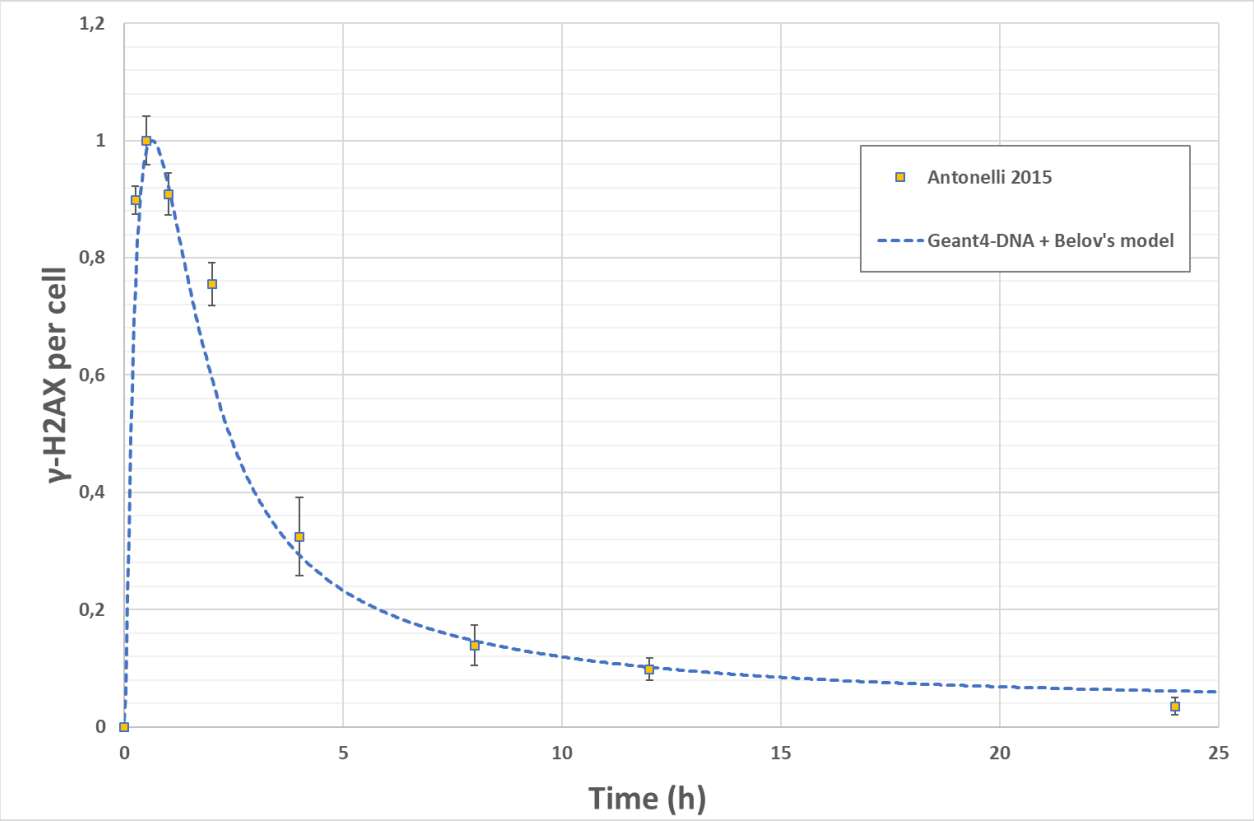
Time Evolution of γ-H2AX (Belov's model)



- Fibroblast cell nucleus
- Protons 26.8 keV/µm
- Satisfactory results in comparison with experimental data

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CONCLUSIONS

- A simulation chain based on Geant4-DNA MC tool was tested for fibroblast cells **from the generation of the initial DNA damage to its repair**
- DSB yields and biological endpoints that have been implemented are **in agreement with experimental data**
- BioRadIII project:
  - The **simulation chain will be publicly released** next year
  - DNAFabric **geometries of cell nuclei** (endothelial, lymphocyte, fibroblast) with random distribution of hetero and euchromatin **will be released** next year

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