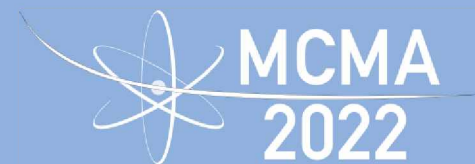


NANODOSIMETRIC CALCULATIONS OF RADIATION-INDUCED DNA DAMAGE IN A NEW NUCLEUS GEOMETRICAL MODEL BASED ON THE ISOCHORE THEORY

Thibaut Y.^{1*}, Villagrasa C.¹, Incerti S.², Perrot Y.¹

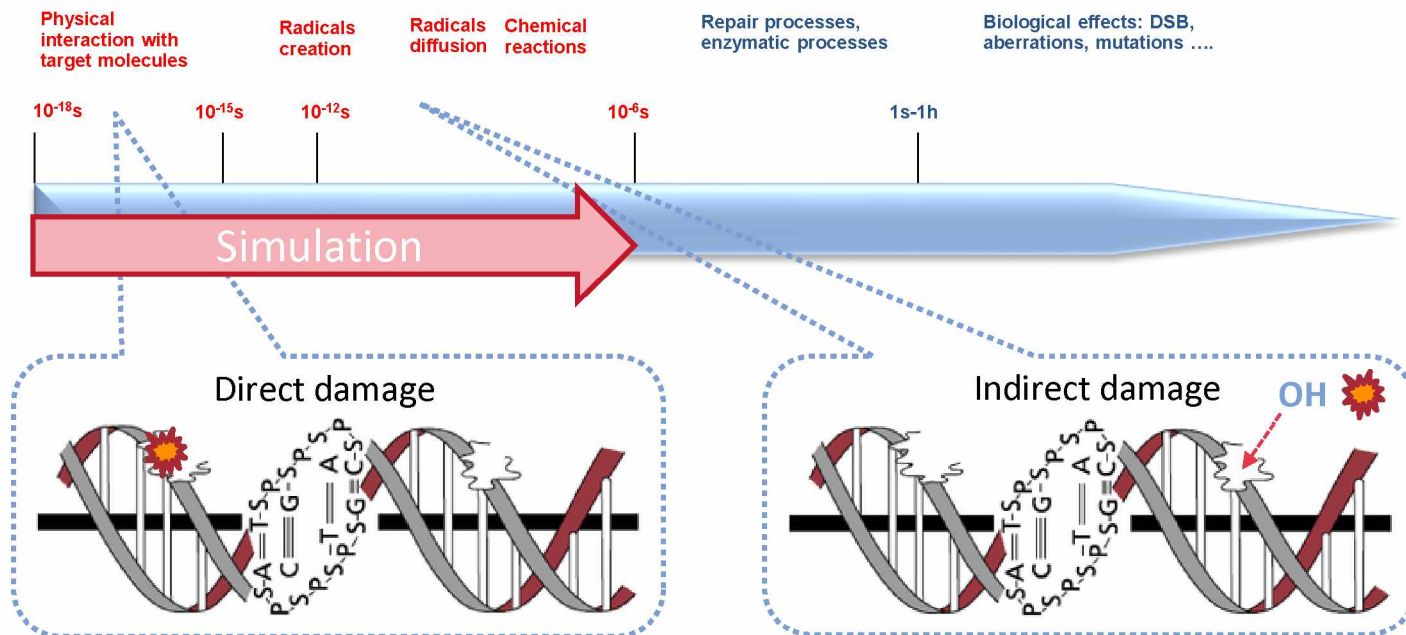
¹ IRSN/PSE-SANTE/SDOS/LDRI

² CNRS/IN2P3/LP2I



UNDERSTANDING RADIATION-INDUCED EFFECTS

MODELING THE EARLY TOPOLOGY OF RADIATION-INDUCED DAMAGE

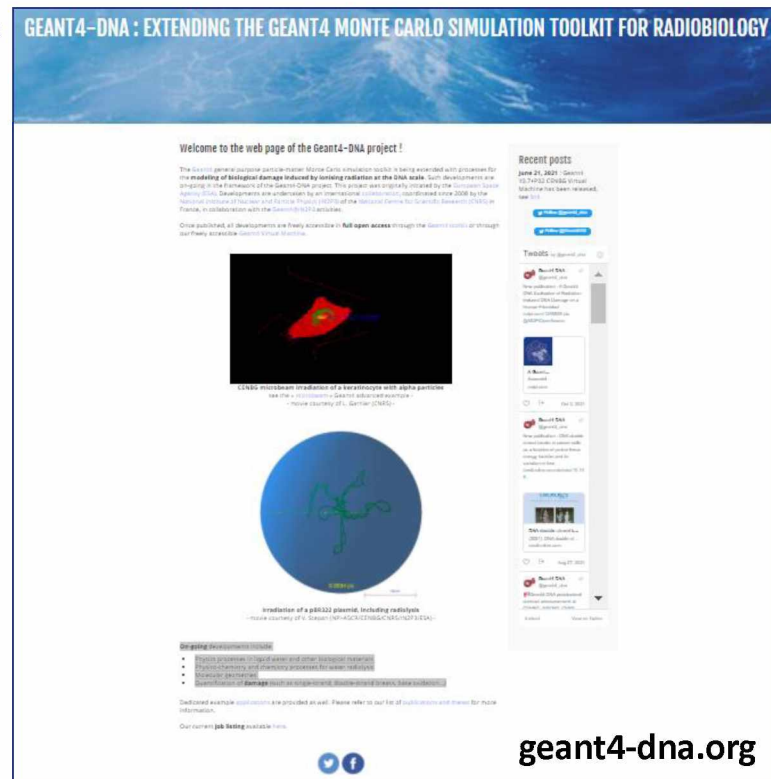


Modeling these effects is a major challenge in radiobiology.

TOOLS FOR MODELING THE TOPOLOGY OF EARLY RADIATION-INDUCED DAMAGE

MONTE CARLO TRACK STRUCTURE CODE: GEANT4-DNA*

- Geant4-DNA is a project aiming to extend the capabilities of Geant4 general purpose MC simulation toolkit.
- Open source, fully available within Geant4 distribution.
- Processes for the modeling of early biological damage induced by ionising radiation at the sub-cellular and DNA scale.
- On-going developments include:
 - Physical processes in liquid water and other materials.
 - Physico-chemical and chemical processes for water radiolysis.
 - Target geometries at the molecular level.

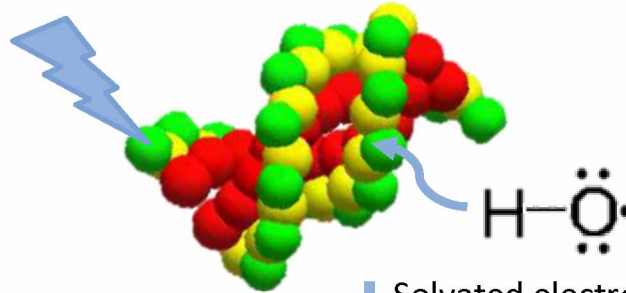


* Incerti *et al.*, Int. J. Model. Simul. Sci. Comput. (1) **2010** / Incerti *et al.*, Med. Phys. (35) **2010** / Bernal *et al.*, Phys. Med. (31) **2015** / Incerti *et al.*, Med. Phys. (45) **2018**

TOOLS FOR MODELING THE TOPOLOGY OF EARLY RADIATION-INDUCED DAMAGE

DAMAGE CALCULATION WITH GEANT4-DNA*

Physics



Chemistry

- Particle transportation in a liquid water medium.
- Track structure modeling: location of energy deposits inside nucleus geometry.
- Induction of direct damage from an energy deposition above **17.5 eV** in a phosphate deoxyribose group of the DNA backbone.

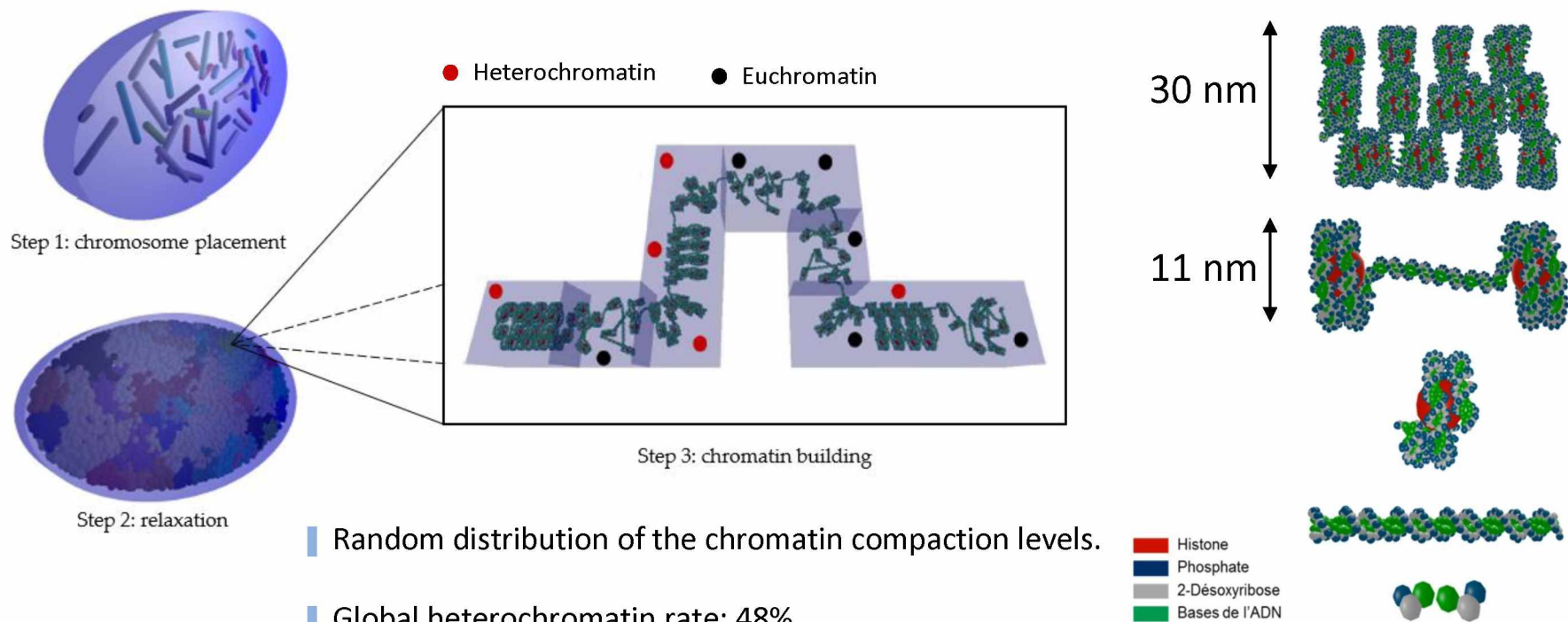
- Solvated electrons and radicals creation from ionized or excited water molecules.
- Radical diffusion and interaction with DNA components using a step-by-step approach.
- Induction of indirect damage for **42%** of interactions between a hydroxyl radical and a deoxyribose.

➡ Geometry samples reactions leading to strand breaks, a realistic description is required.

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

TOOLS FOR MODELING THE TOPOLOGY OF EARLY RADIATION-INDUCED DAMAGE

REALISTIC NUCLEAR MODELS COMPATIBLE WITH G4-DNA CALCULATION – DNAFABRIC*



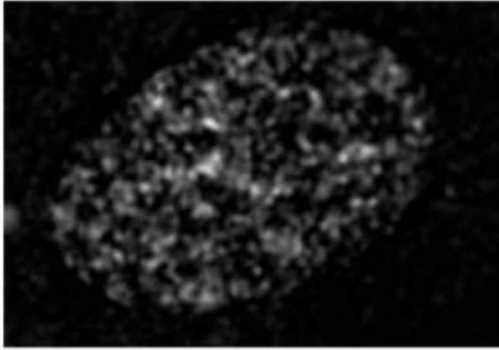
Random distribution of the chromatin compaction levels.

Global heterochromatin rate: 48%.

* Meylan *et al.*, Comput. Phys. Commun. (204) **2016** / Tang *et al.*, Med. Phys. (46) **2019**

TOOLS FOR MODELING THE TOPOLOGY OF EARLY RADIATION-INDUCED DAMAGE

IMPROVEMENT ON GEOMETRIC CELL NUCLEUS MODELS



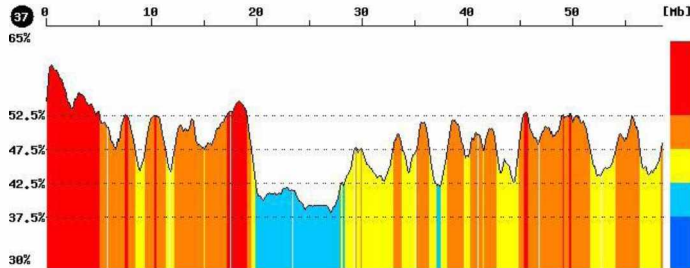
- Chromatin compaction levels are not uniformly distributed in the nucleus.
- How to model a realistic distribution of compaction levels?

Isochore Theory*

The coding parts of the genome contain a high GC rate.

Family	GC Rate	Heterochromatin Content
L ₁	<37.5%	100%
L ₂	37.5–42.5%	70%
H ₁	42.5–47.5%	50%
H ₂	47.5–52.5%	20%
H ₃	>52.5%	0%

GC rates and compaction levels of the five isochore families



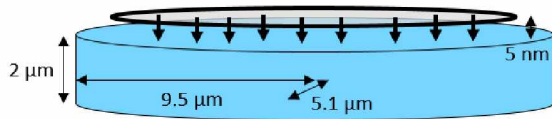
GC profile for chromosome 37

* Pačes *et al.*, Gene (333) **2004** / Costantini *et al.*, Genome Res. (16) **2006** / Costantini & Musto, J. Mol. Evol. (84) **2017**

IMPACT OF GEOMETRIC MODELS ON DAMAGE CALCULATIONS

SIMULATION CONFIGURATION

- Differences between the old geometric model and the new isochore model:
 - Overall heterochromatin rate (48% vs 62%).
 - Distributions of chromatin compaction levels (Random vs Isochore).
- A third test geometry is developed to quantify the impact of these two changes:
 - Overall heterochromatin rate : 62%.
 - Chromatin compaction levels randomly distributed.
- Simulation parameters:



Endothelial nucleus

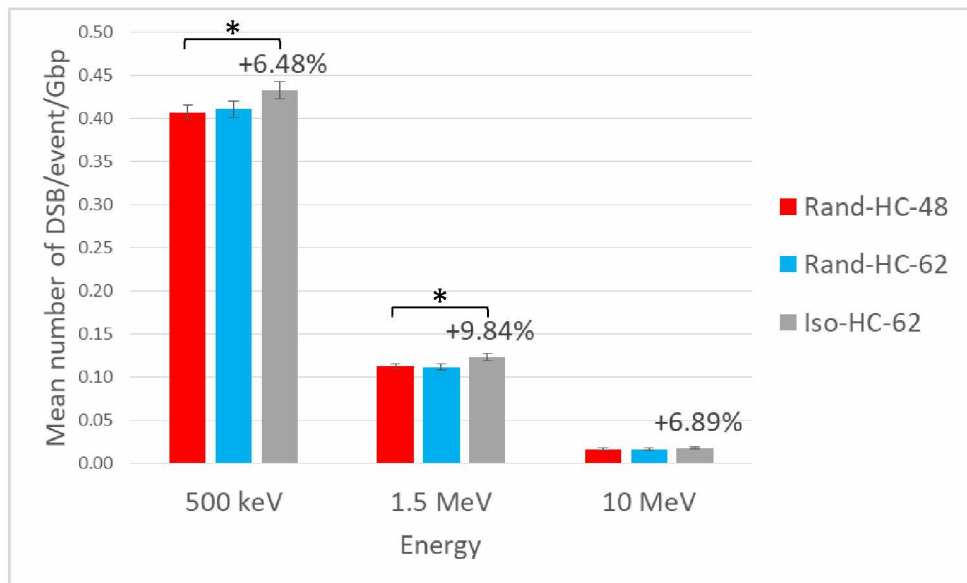
Irradiation geometry

Energy	Rand-HC-48	Rand-HC-62	Iso-HC-62
500 keV	1000 protons	1000 protons	1500 protons
1.5 MeV	1500 protons	1500 protons	2000 protons
10 MeV	2000 protons	2000 protons	3000 protons

Number of events for each simulation.

IMPACT OF GEOMETRIC MODELS ON DAMAGE CALCULATIONS

INCREASE IN THE MEAN NUMBER OF DSB/EVENT/GBP



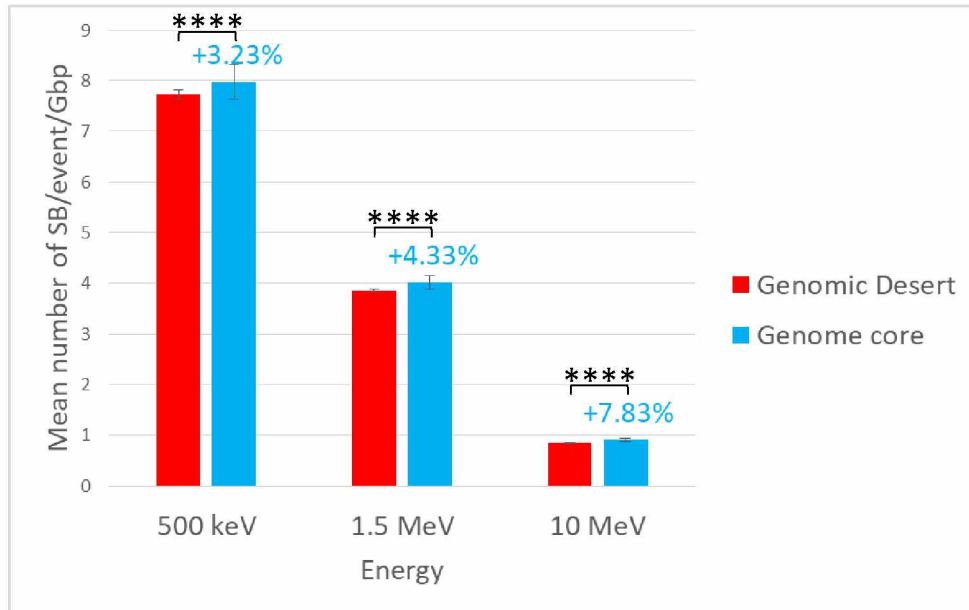
Mean number of DSB/event/Gbp obtained for three proton energies on different geometrical models.

- Changing the overall heterochromatin rate by 14% does not have a significant impact on the mean number of calculated DSBs.
- The creation of long segments composed exclusively of euchromatin and heterochromatin induces a significant increase in the number of calculated DSBs.
- The number of DSB/event/Gbp remains in agreement with the literature* (protons under 50keV/ μm).

* Frankenberg *et al.*, Rad. Res. (151) **1999** / Friedland *et al.*, Rad. Res. (159) **2003**

IMPACT OF GEOMETRIC MODELS ON DAMAGE CALCULATIONS

THE NEW GEOMETRIC MODEL'S POTENTIAL



Location of strand breaks in the new geometric isochore model

- The new model allows to know the level of compaction of the fiber at the location of the damage
- There is a significant increase of the mean number of SB in the genome core compared to the genomic desert.
- The increased radiosensitivity of the decondensed fiber compared to the condensed fiber is clearly reproduced here.

IMPACT OF GEOMETRIC MODELS ON DAMAGE CALCULATIONS

CONCLUSIONS AND PERSPECTIVES

- We have developed a new nuclear model taking into account the distribution of chromatin compaction levels in the genome compatible with Geant4-DNA.
- With this geometrical model used in our Geant4-DNA calculation chain we obtain a significant increase (6-10%) in the mean number of DSBs in agreement with experimental results.
- Finally, the knowledge of the compaction region in which the damage occurred will allow us to feed repair models sensitive to this kind of parameter*.
- For more details on the results:

Thibaut et al., *IJMS* (23) 2022



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Article

Nanodosimetric Calculations of Radiation-Induced DNA Damage in a New Nucleus Geometrical Model Based on the Isochore Theory

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* Taleei & Nikjoo, *Mutat. Res.* (756) **2013** / Belov *et al.*, *J. Theor. Biol.* (366) **2015**

Thank you for your attention

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