

Mechanistic simulation of early radio-induced DNA damage using TSMC codes

Example of the Geant4-DNA tool

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UNDERSTANDING RADIATION-INDUCED EFFECTS

[E.G. LATE EFFECTS OF RADIATION THERAPY ON HEALTHY TISSUES (ROSIRIS PROGRAM AT IRSN)



PARTICLE
ENERGY
DOSE
DOSE RATE
FRACTIONATION
ENVIRONMENT



WEIGHT
SURVIVAL

HISTOLOGY
ANATOMO PATHOLOGY
EARLY AND LATE INJURIES

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 **IRRADIATION**

 **LINK PHYSICS/
EARLY DAMAGE**

 **RISK**

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EARLY FOCI
LATE FOCI
MICRO AND
NANODOSIMETRIC
CHARACTERIZATION
DNA DAMAGE: NUMBER,
COMPLEXITY



WEIGHT
SURVIVAL
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UNDERSTANDING RADIATION-INDUCED EFFECTS

[E.G. LATE EFFECTS OF RADIATION THERAPY ON HEALTHY TISSUES (ROSIRIS PROGRAM AT IRSN)

 **IRRADIATION**

 **LINK PHYSICS/
EARLY DAMAGE**

 **MOLECULAR
MECHANISMS**

 **RISK**

PARTICLE
ENERGY
DOSE
DOSE RATE
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ENVIRONMENT

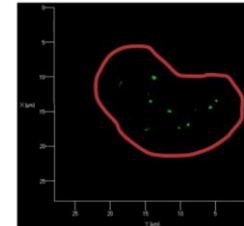
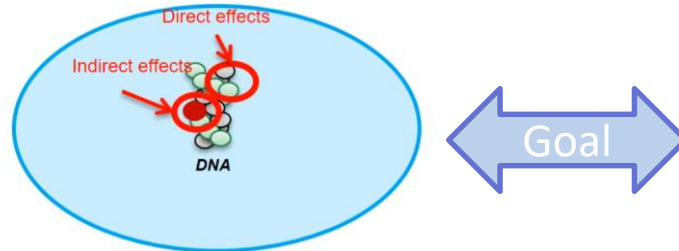
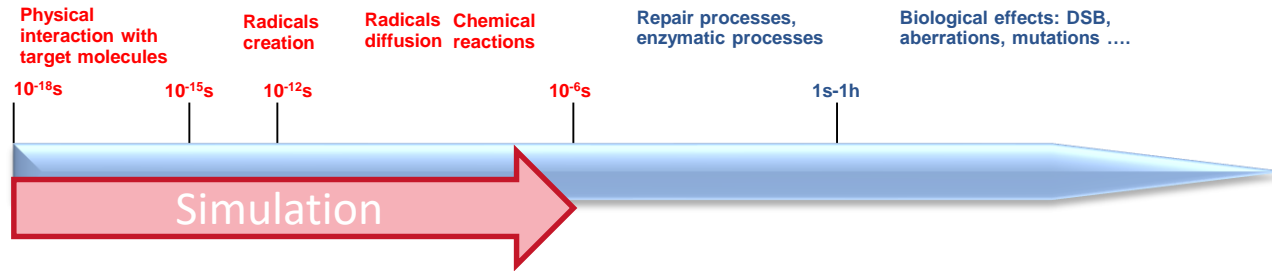
EARLY FOCI
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SURVIVAL CURVES
CELLULAR DEATH
SENESCENCE
OMICS

WEIGHT
SURVIVAL
HISTOLOGY
ANATOMO PATHOLOGY
EARLY AND LATE INJURIES

A MULTI-SCALE APPROACH



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



- Geant4-DNA is a project to extend the Geant4 general purpose MC simulation toolkit
- Open source, fully available inside Geant4 distribution
- Processes for the modeling of biological damage induced by ionising radiation at the DNA scale
- On-going developments include
 - Physics processes in liquid water and other materials
 - Physico-chemistry and chemistry processes for water radiolysis
 - Target geometries at the molecular level

Welcome to the web page of the geant4-dna project !

The Geant4 general purpose Monte Carlo simulation toolkit is being extended with processes for the modeling of biological damage induced by ionising radiation at the DNA scale. Such developments are ongoing in the framework of the Geant4-DNA project. This project was originally created by the European Space Agency (ESA). Developments are undertaken by an international consortium, established since 2008 by the National Centre of Nuclear and Particle Physics (INFN) of the National Centre for Scientific Research (CNRS) in France, in collaboration with the Geant4 MC toolkit authors.

Once published, all developments are freely accessible in full open access through the [Geant4 toolkit](#) or through our [Public Accessible Geant4 Visualisation](#).

3D Monte Carlo simulation of a DNA molecule with alpha particles
-New courtesy of L. Barthe (CNRS)-

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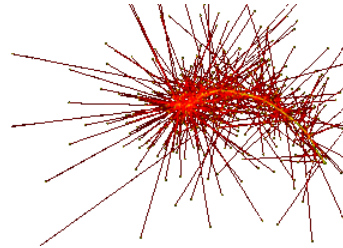
Original developments include:

- Physics processes in liquid water and other biological materials
- Physico-chemistry and chemistry processes for water radiolysis
- Molecular dynamics
- Simulation of DNA

Dedicated example applications are provided as well. Please refer to our [FAQ](#) for [publications](#) and [more](#) for more information.

Our current [job listing](#) is available here.

geant4-dna.org



- Liquid water, main medium of biological matter
 - electrons, protons, alphas, few ions
- Other materials
 - THF, TMP, PY, PU
 - Electrons (12 eV to 1 keV), protons (70 keV to 10 MeV)
 - See *examples/extended/dna/icsd*
 - Electrons: solid gold
- On-going developments
 - Electrons: N2, C3H8 (EURADOS WG6)
 - Discrete electrons models in liquid water up to 10 MeV
 - Discrete inelastic proton and hydrogen models from 100 MeV to 300 MeV

Processes and models for electrons and protons in liquid water, default physics list

Particle	Process	Model	Energy range
electron	Elastic scattering	Champion	7.4 eV – 1 MeV
	Electronic excitation	Born	9 eV – 1 MeV
	Ionisation	Born	11 eV – 1 MeV
	Vibrational excitation	Sanche	2 eV – 100 eV
	Attachment	Melton	4 eV – 13 eV
proton	Nuclear scattering		100 eV – 100 MeV
	Electronic excitation	Miller & Green	10 eV – 500 keV
		Born	500 keV – 100 MeV
	Ionisation	Rudd	0 keV – 500 keV
		Born	500 keV – 100 MeV
	Electron capture	Dingfelder	100 eV – 100 MeV

GEANT4-DNA - Chemistry

First developments: Step by Step method

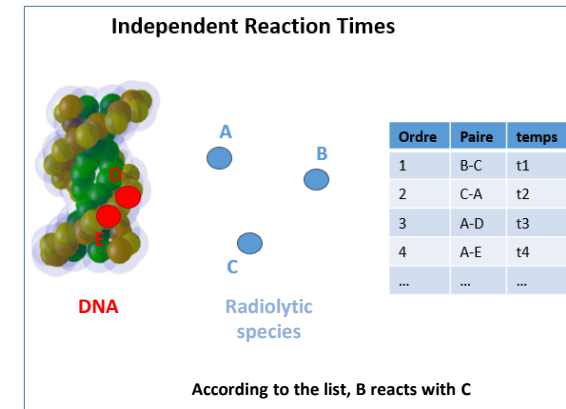
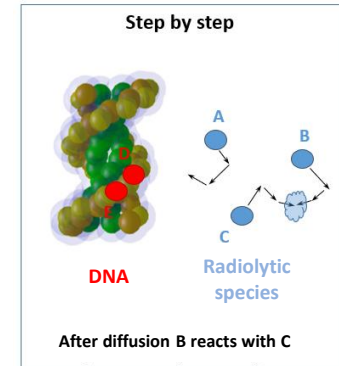
- Particle-continuum based, each individual molecule is simulated
- Simulation of diffusion controlled reactions based on full step-by-step Brownian dynamics

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

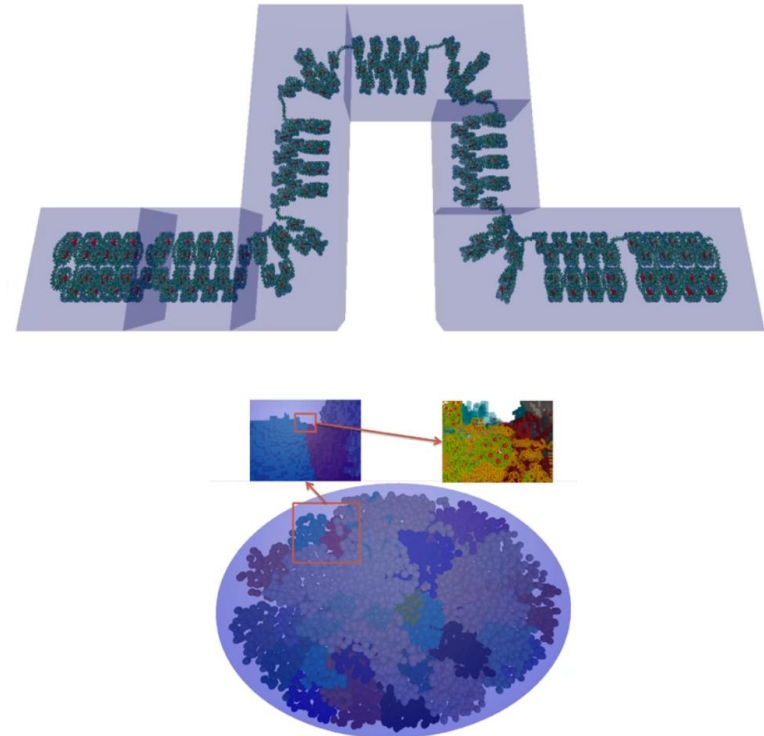
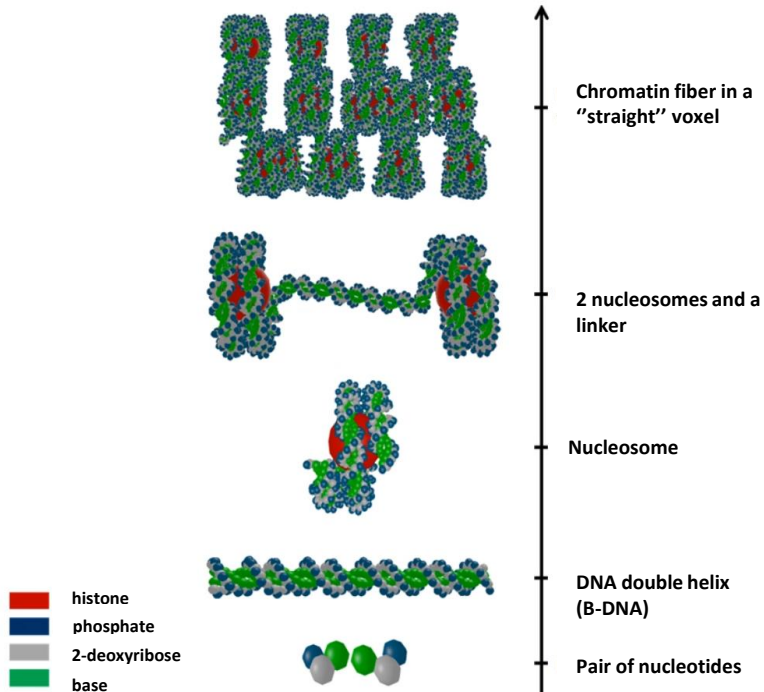
Reaction	Reaction rate ($10^9 M^{-1} s^{-1}$)
2-deoxyribose + OH^{\bullet}	1.8
Adenine + OH^{\bullet}	6.1
Guanine + OH^{\bullet}	9.2
Thymine + OH^{\bullet}	6.4
Cytosine + OH^{\bullet}	6.1
2-deoxyribose + e_{aq}^{-}	0.01
Adenine + e_{aq}^{-}	9.0
Guanine + e_{aq}^{-}	14.0
Thymine + e_{aq}^{-}	18.0
Cytosine + 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 \rightarrow Histone	-

Recent developments: Independent Reaction Times approach

- N-body \rightarrow 2-body
- Comparison of reaction times for all pairs of radicals independently of the system

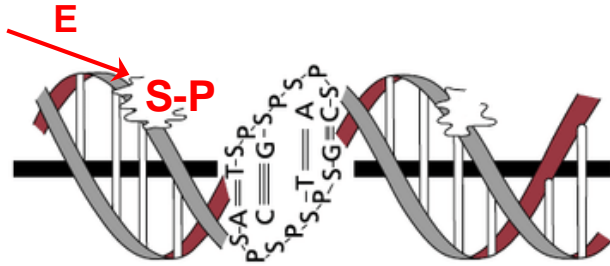


DNA geometry generation using DNAFabric*



DNA STRAND BREAK CALCULATION

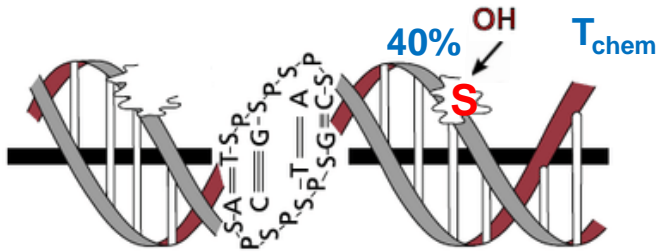
[DIRECT DAMAGE



- Limitations due to cross section uncertainties
 - Missing at low energy, for specific materials
 - Theoretical model for liquid water
- Mechanism at the origin of the strand break

DNA STRAND BREAK CALCULATION

[INDIRECT DAMAGE

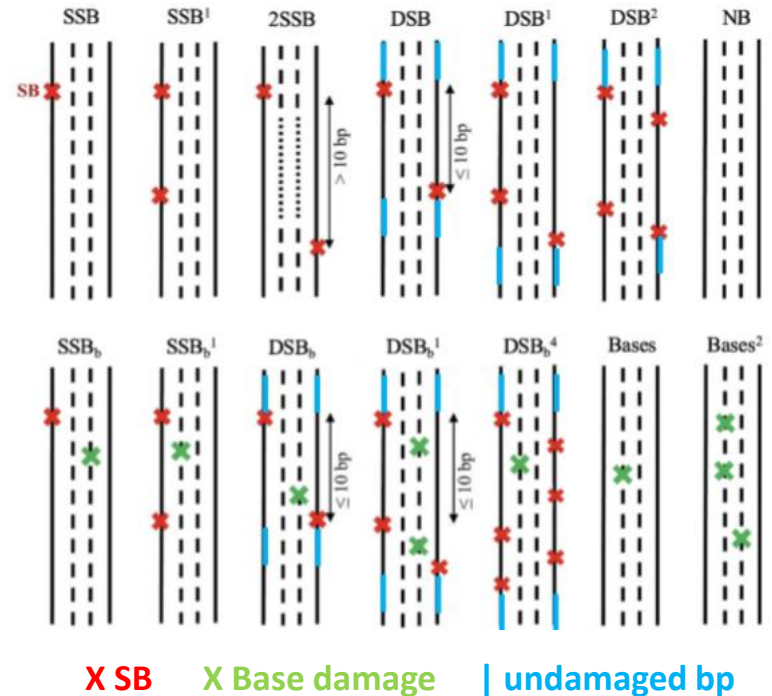


- Experimental data based on the evolution of the number of radiolytic species in liquid water
- No data on the biological target
- Benchmarking efforts: different simulation approaches
 - Step By Step: more natural but too long
 - Independent Reaction Times: efficiency improved but approximations could not be adapted to all applications

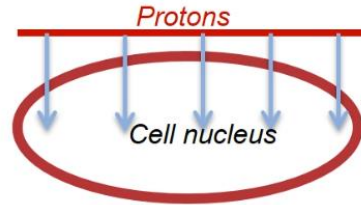
DNA DAMAGE CALCULATION

[CONVERT STRAND BREAKS TO DAMAGE

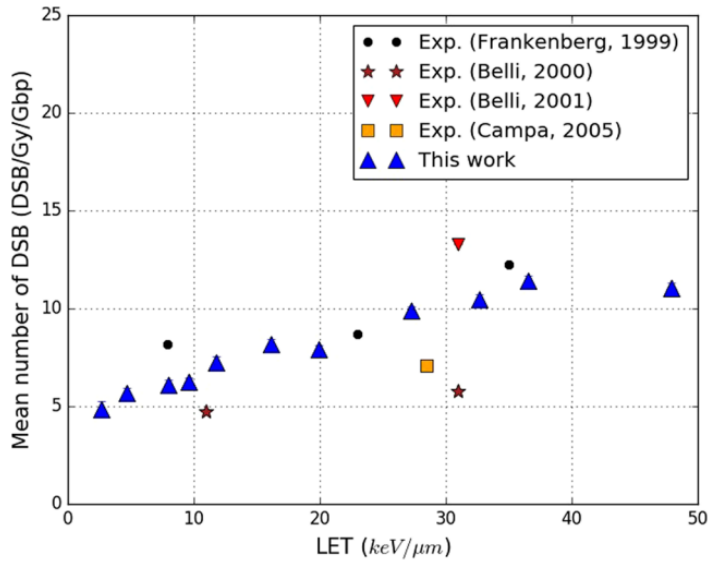
- Analysis of the configuration of the damaged elements on each strand
- Classification of such configuration = damage definition
- Benchmarking DSB calculation is not obvious
 - Experimental data give foci induction few minutes after irradiation
 - lack of standardization of irradiation and measurement protocols
 - Difficulty to compare damage between different codes: Standard DNA Damage (SDD) data format initiative



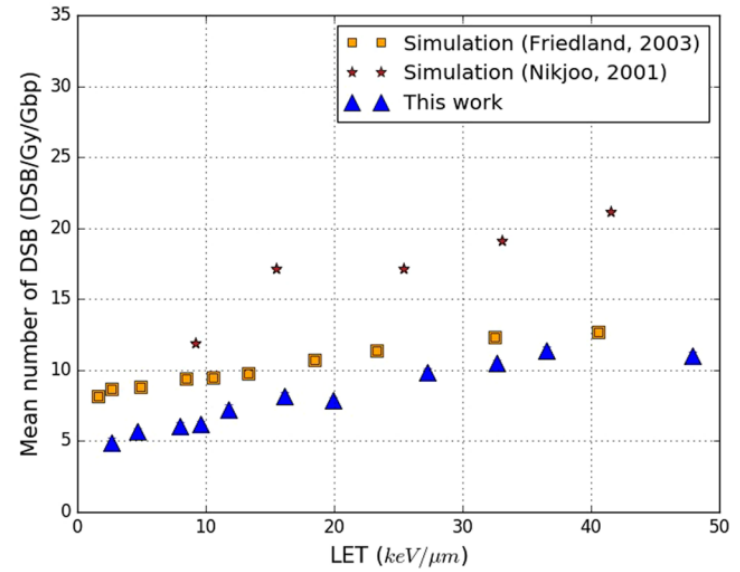
BENCHMARKING



[VS LITERATURE

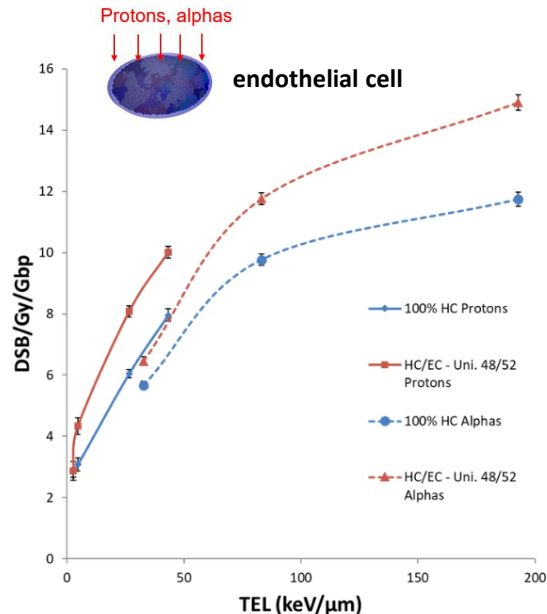
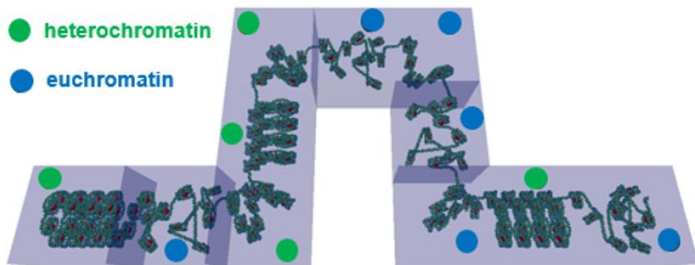
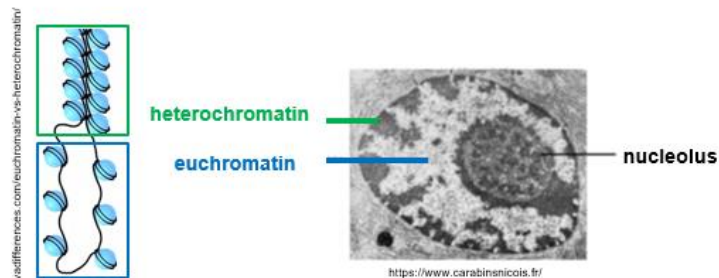


[VS OTHER CODES



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

IMPACT OF GEOMETRY



- More DSB/Gy/Gbp induced in HC/EC than in HC alone
- Euchromatin more exposed to the effects of molecular species: more hydrated, fewer histones

Tang et al., Med. Phys. 7 (2019)

CONCLUSION

- Simulations of radiation induced DNA damage based on TSMC codes are being used in a mechanistic or AOP approach in order to improve risk assessment for the use of ionizing radiation in medical applications or low dose exposure
- Important progress have been achieved during the last decade in the development of this kind of simulation tools including physical, physico-chemical and chemical stages
- Geant4-DNA is an open access source code in continuous development in order to increase the knowledge and possibilities of the scientific community