Investigation of oxygen effects induced by carbon ion irradiation via Geant4-DNA simulations

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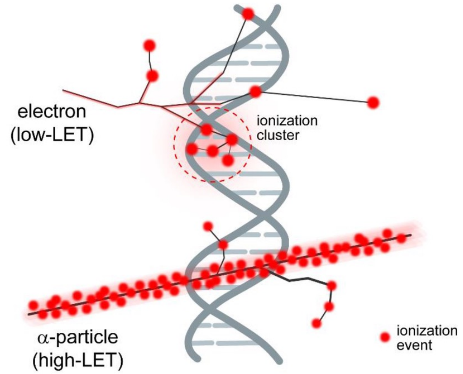
Context

- **Carbon ion radiotherapy (CIRT)**
  - Highly effective treatment due to its high linear energy transfer (LET) compared to classical photon radiotherapy and proton therapy
    - Leads to a higher relative biological effectiveness (RBE): 2-3 times more clustered DNA damage to cells than low-LET radiations[1, 2]
    - Mainly used for radio-resistant tumors
    - Japan is the leading country: 7 facilities in operation today[3], e.g. 43000 patients treated (1994-2023)
      - Therapeutic carbon beams in Caen, France, expected around 2030 ("ARCHADE" facility)
  - A key factor in radiation therapy is the oxygen enhancement effect
    - The presence of oxygen significantly increases DNA damages in tumor cells : **more oxidative stress**[4,5]
    - However, many solid tumors develop "hypoxic" regions
      - More resistant to standard photon or proton irradiation
      - On the contrary, CIRT is less dependent on cell oxygen level and is more efficient
        - **Physics & chemistry**: high-LET (more clustered damages), production of oxygen (from water radiolysis)
        - Specific **biological mechanisms** at play, e.g. influence of transcription factors (e.g. hypoxia-inducible transcription factor-1[4]) on radioresistance under hypoxic conditions, cell type dependence…



Cancers 11, 1671 (2019)

- **A possible "contribution" could arise from physics: the "multiple ionisation" process** (MI)
  - High-LET irradiation (like C) ions induces numerous ionisation events through MI
    - More (direct) clustered damage to DNA
    - Localized production of reactive molecular species from water radiolysis (e.g. **O(^{3}P)**, $O_2^{\bullet-}$, $HO_2^{\bullet}$, and H_2O_2 from MI)
      - Increasing oxygen production around C tracks
  - The quantitative impact of MI requires further investigation…

(1) Nature 508, 133-138 (2014)
(2) Advances in Radiation Oncology 9, 101317 (2024)
(3) PTCOG (link)
(4) Cancers 12, 2019 (2020)
(5) Cancers 11, 112 (2019)

Objectives of the project

- **Motivation**
  - **New project** to provide the scientific community with the possibility to simulate multiple ionisation from ion irradiation in liquid water in Geant4-DNA, and investigate its impact on physics, chemistry and radiobiology applications
- **Recent activities**
  - Relevant beta **physics classes** of Geant4 for the multiple ionisation processes in water have been implemented in version 11.3 (Dec. 2024), based on prior studies
    - Baba et al., J. Appl. Phys. 129, 244702 (2021)
    - For **proton, alpha particles and carbon ions**
    - **Double and triple ionisation cross sections** are calculated from single ionisation (Rudd semi-empirical model) and radiolysis data by Meesungnoen and Jay-Gerin[(1)]
      - Process classes: *G4DNADoubleIonisation* and *G4DNATripleIonisation*
      - Model classes: *G4DNADoubleIonisationModel* and *G4DNATripleIonisationModel*
  - Detailed verification & validation (physics, chemistry) have not yet been completed
- **Plan of the project (2 years…)**
  - We propose a verification & validation study following **three stages**:
    - Stage#1: verification of **physics** quantities ("physics stage")
    - Stage#2: validation of **water** radiolysis ("chemistry stage")
    - Stage#3: quantifying **biological impact such as DNA damage** ("biology stage") induced by multiple ionisation and comparison to experiments
  - Will be fully included in Geant4-DNA physics lists & examples

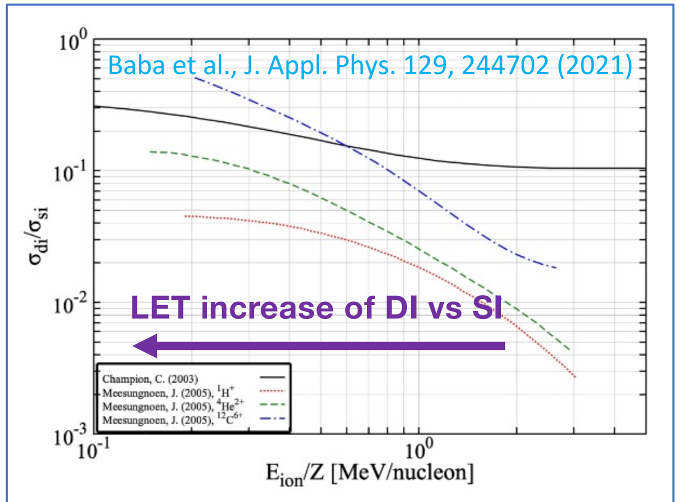
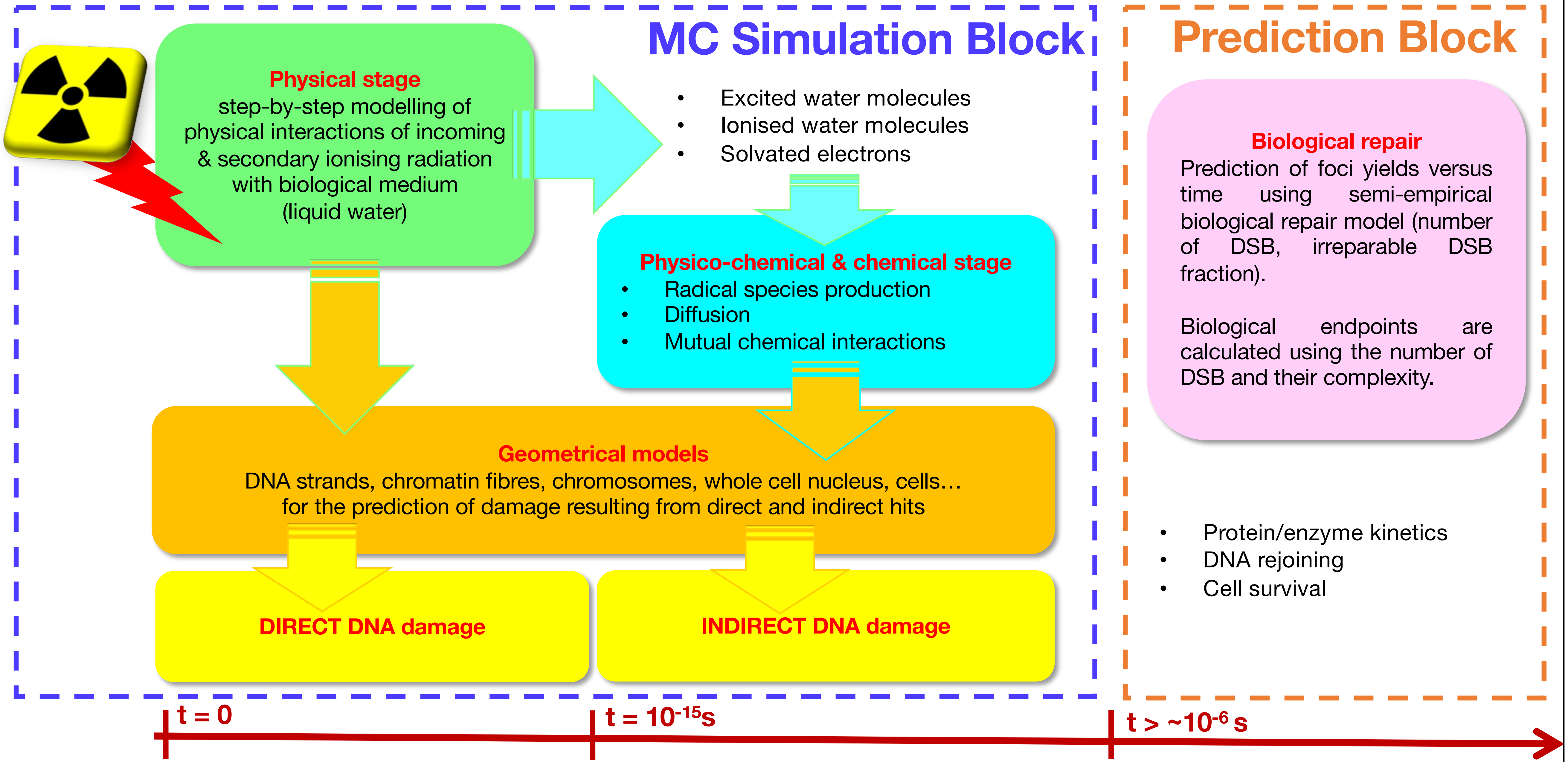


FIG. 1. The ratio of double-to-single ionization cross sections σ_{di}/σ_{si} for $^1H^+$ (dotted red line), $^4He^{2+}$ (dashed green line), and $^{12}C^{6+}$ (dashed-dotted blue line) ion beams reported by Meesungnoen and Jay-Gerin.[11] The values of σ_{di}/σ_{si} reported by Champion[25] for a variety of ions at intermediate velocities and gaseous water are also shown for the sake of comparison (solid black line).

Time line	Stage#1 (6 months)	Stage#2 (6 months)	Stage#3 (9 months)
2025/9			
2025/12			
2026/3			
2026/6			
2026/9			
2026/12			
2027/3			

(1) J. Phys. Chem. A 109, 6406-6419 (2005)

Reminder : damage to cells : the Geant4-DNA approach



Stage #1: Validation of physics quantities

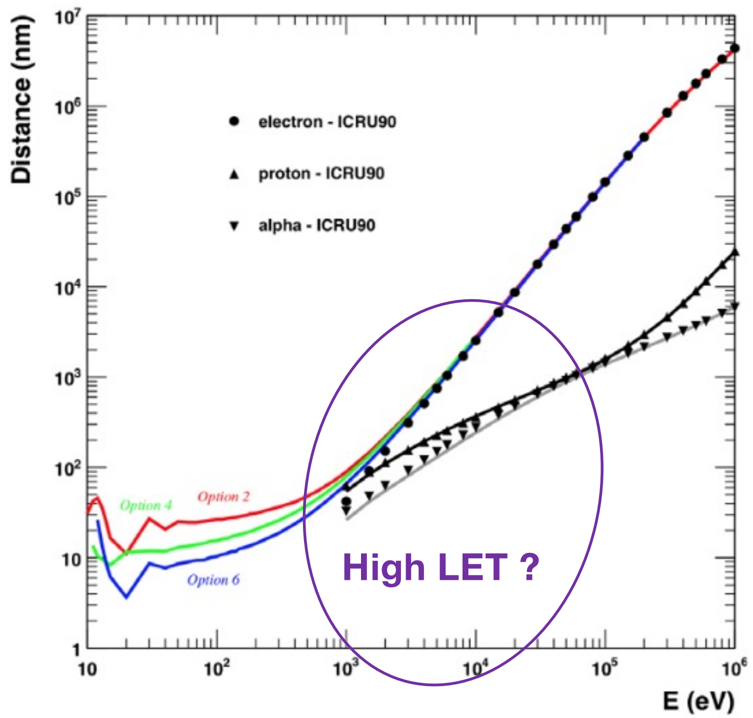
- **First stage tasks (2025)**
  1. Computing **fundamental physical quantities in liquid water** under irradiation of high-LET ions **(C, alphas, protons)** considering (or not) multiple ionisation and evaluate its impact on:
     - Secondary electron spectra (importance: responsible of most direct DNA damage)
     - Range
     - Stopping power
     - Radial doses
  2. Comparing with **published** (from other track-structure codes) and **reference** data / international recommendations (e.g. ICRU data)
  3. Including these new physics processes in **Geant4-DNA Physics constructors** and corresponding user Geant4-DNA **"extended" examples**
     - "range"
     - "spower"
     - "radial"

- **Outcome**
  - Geant4-DNA reference data and "ready to use" user examples showcasing the impact of MI

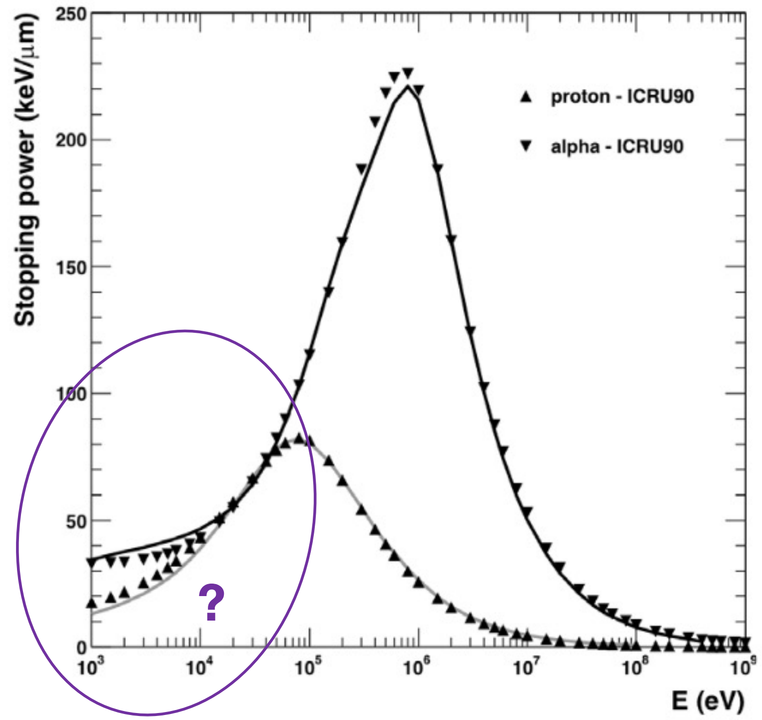
- **Expected duration**
  - 6 months

Example of physics verification

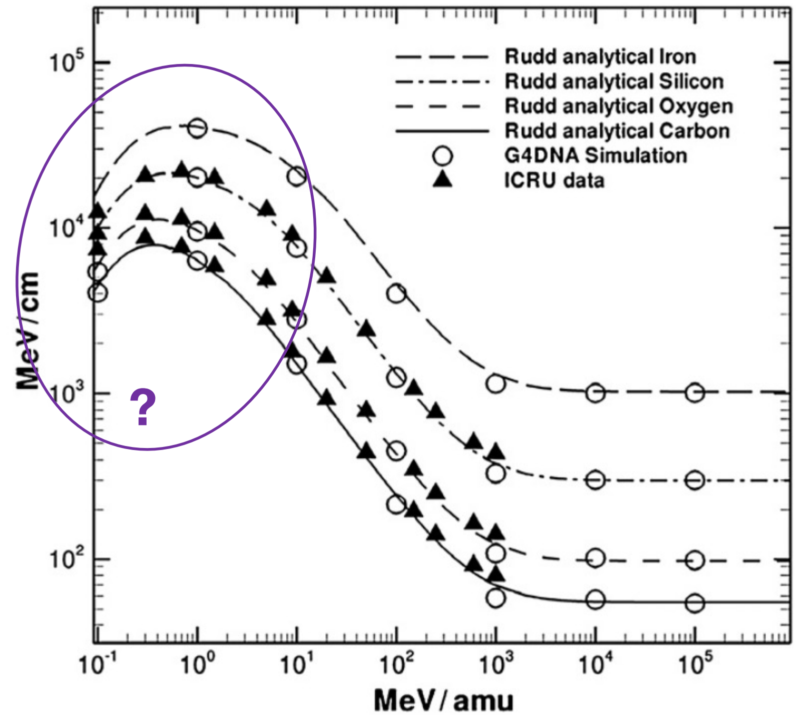
Range



Stopping power



Stopping power

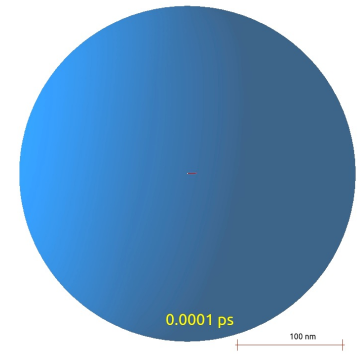


Francis et al., Phys. Med. Biol. 57, 209-224 (2012)
Incerti et al., Med. Phys. 45, e722-e739 (2018)

Stage #2: Validation of water radiolysis

- **Second stage tasks (2025 - 2026)**
  - Simulation of water radiolysis yields, known as “G-values” of water radiolysis by ions **(C, alphas, protons)**, considering (or not) multiple ionisation
    - A a function of **time**
    - As a function of **LET**
    - Using the **four Geant4-DNA chemistry models**
      - “step-by-step”, “IRT”, “IRT-sync”, “mesoscopic”
      - See recent review in Tran et al., Med. Phys. 51, 5873–5889 (2024)
  - Comparing with **experimental data** to evaluate the impact of multiple ionisation and Geant4-DNA simulation accuracy
  - In addition, we propose to investigate how high-density ionization affects the **local oxygen concentration**
    - **Do we observe an increase of oxygen production in CIRT around Carbon ion tracks ? What is the time evolution ?**
    - **And what about p, He irradiation ?**

1 keV electrons in Geant4-DNA



- **Outcome**
  - Reference Geant4-DNA data on time and LET evolution of G-values
  - Evaluation of impact of MI on local oxygen concentration
- **Expected duration**
  - 6 months

oxygen production

TABLE II. Dissociation channels related to multiple ionization events at the physicochemical stage. The distances between the fragments are given in

Double ionization state: H_2O^{2+}	$\rightarrow$	$H^+ + H^+ + O(^3P)$	$\rightarrow$	$2H_3O^+ + O(^3P)$	55%
	$\rightarrow$	$H^+ + OH^+$	$\rightarrow$	$2H_3O^+ + O(^3P)$	29%
	$\rightarrow$	$H^+ + H^\bullet + O^+$	$\rightarrow$	$2H_3O^+ + H^\bullet + \bullet OH + O(^3P)$	16%
Triple ionization state: H_2O^{3+}	$\rightarrow$	$H^+ + H^+ + O^+$	$\rightarrow$	$3H_3O^+ + \bullet OH + O(^3P)$	100%

$$\bullet OH + O(^3P) \rightarrow HO_2^\bullet \quad 2.02 \times 10^{10}\ (dm^3\ mol^{-1}\ s^{-1}),$$

$$O(^3P) + O(^3P) \rightarrow O_2 \quad 2.2 \times 10^{10}\ (dm^3\ mol^{-1}\ s^{-1}),$$

$$HO_2^\bullet + O(^3P) \rightarrow O_2 + \bullet OH \quad 2.02 \times 10^{10}\ (dm^3\ mol^{-1}\ s^{-1}).$$

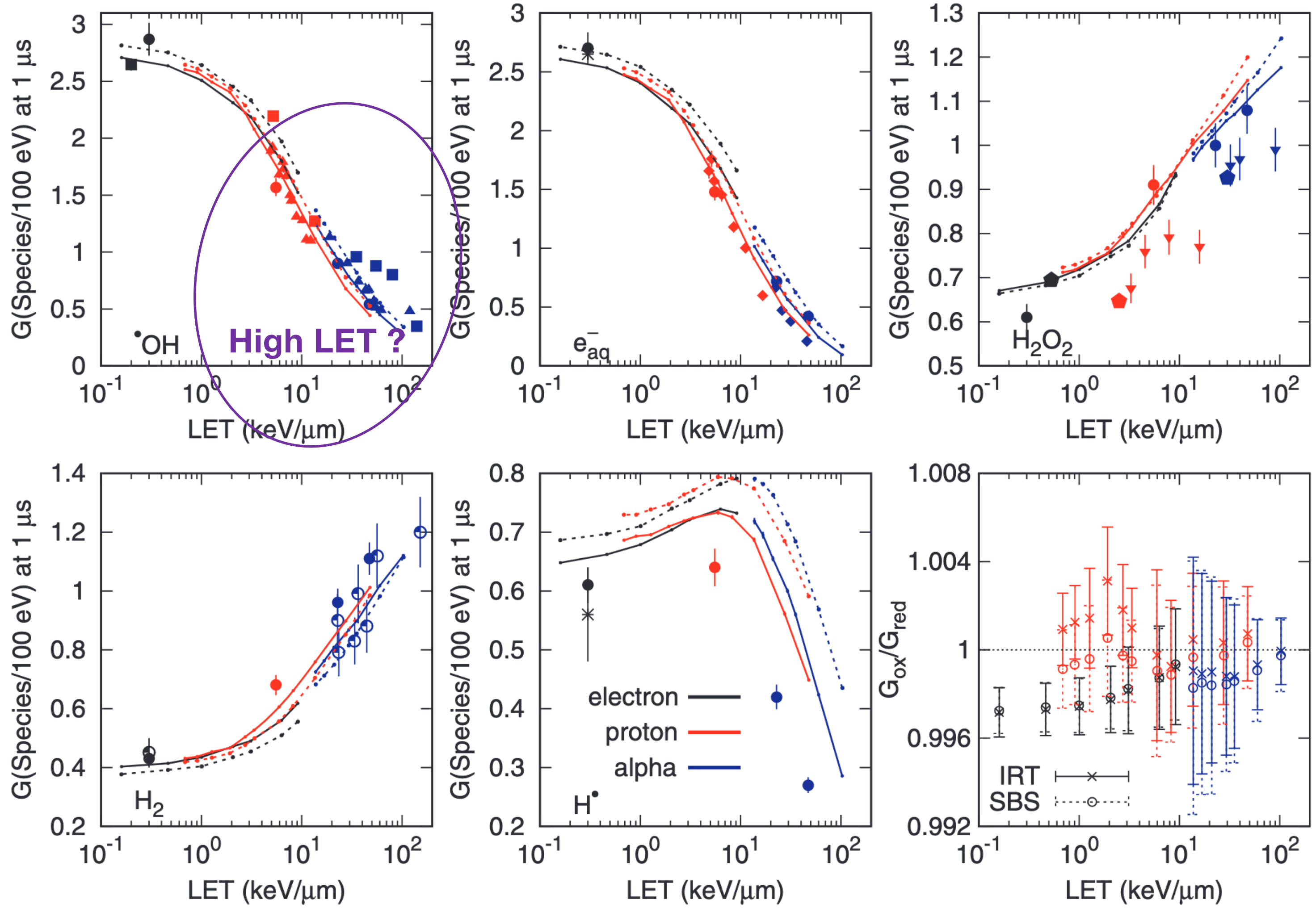
- OH production

Baba et al., J. Appl. Phys. 129, 244702 (2021)

Example of radiolysis validation

Radiochemical yields of molecular species w/o MI, **as a function of LET**

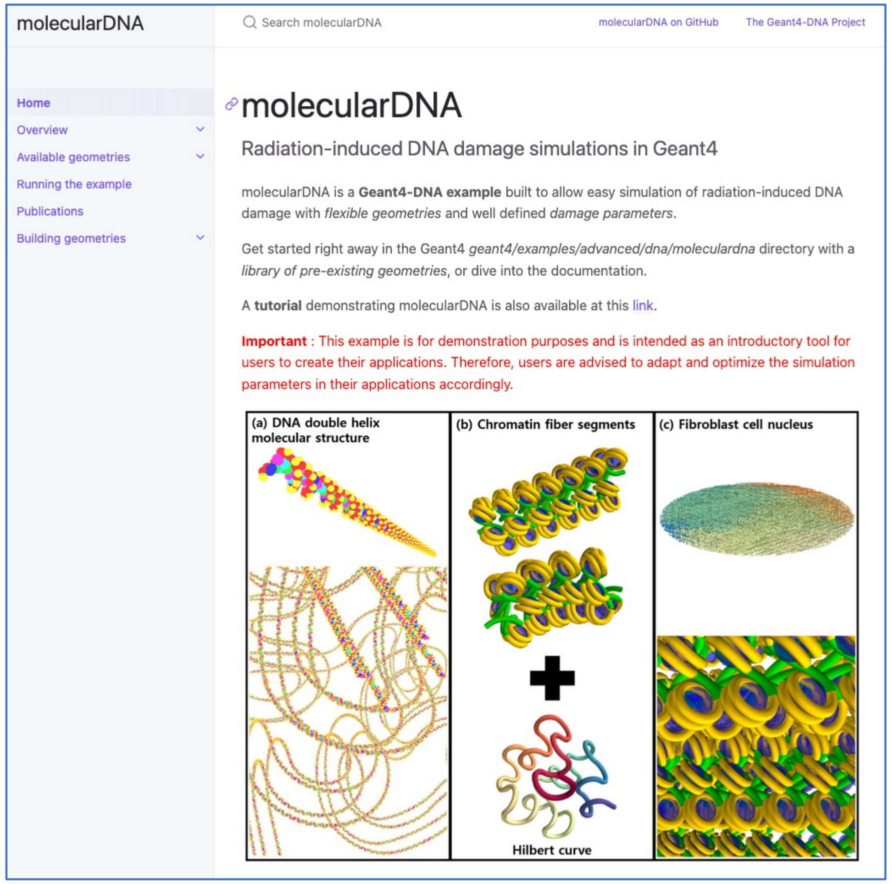
Ramos-Mendez et al., Med. Phys. 47 (2019)



Stage #3: quantifying biological impact

- **Third stage tasks (2026)**
  - Combining Geant4-DNA physics & radiolysis simulation with geometries of biological cells in order to estimate early DNA damage
    - At different **LET**
    - For **C**, but also **p and He ions**
    - Using the "**molecularDNA**" Geant4-DNA example
      - Human cell geometries (6.4 Gbp of DNA)
      - Example development is coordinated by LP2i
    - Direct and non-direct DNA early breaks (before repair)
      - **Simple & complex DNA breaks**
  - Comparison with **experimental measurements** on DNA damage
    - From the literature and in collaboration with QST
    - Towards future **multi-ion therapy studies @ QST (C, He, O…)** (link)

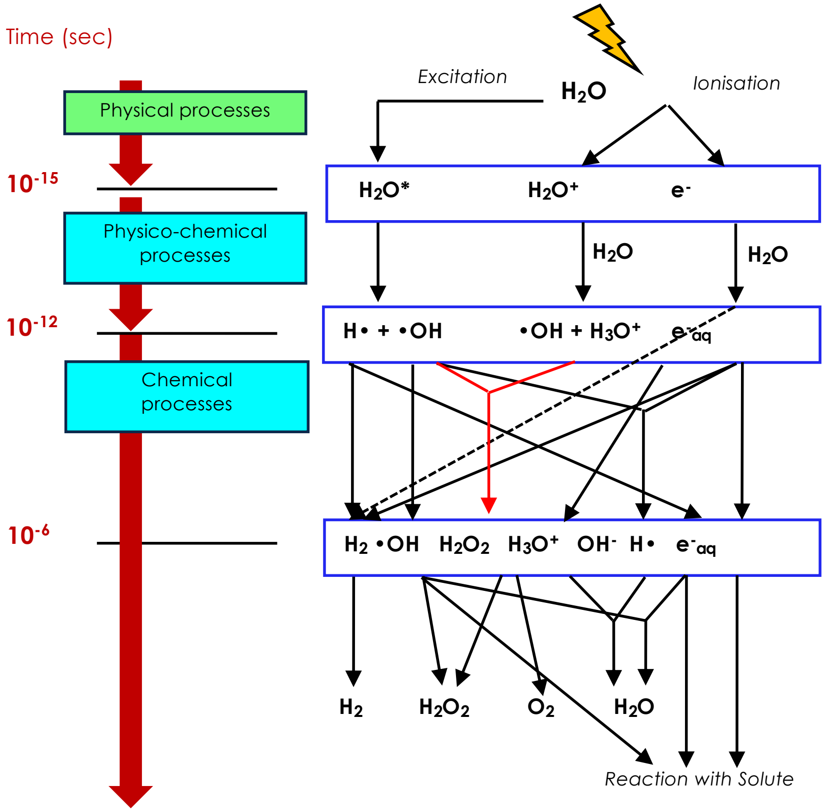
https://moleculardna.org

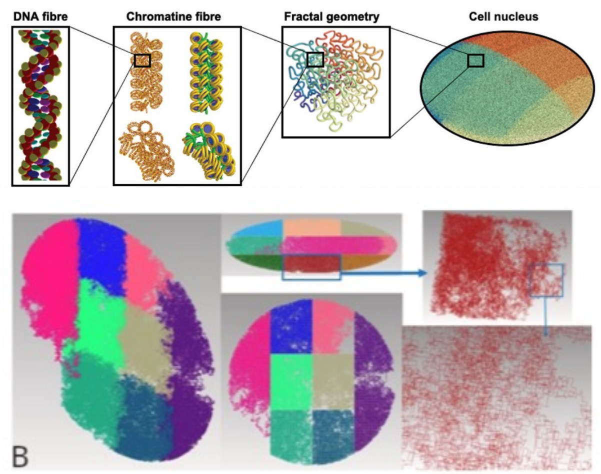


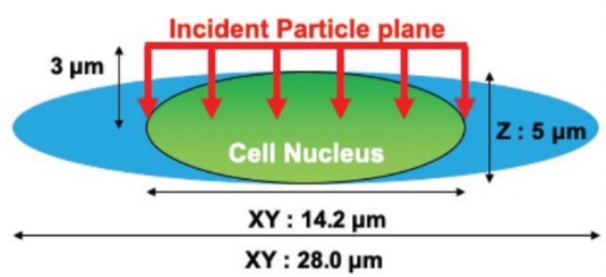
- **Outcome**
  - Possibility for users to take into account multiple ionisations in the "molecularDNA" example
  - Reference data on early direct and indirect DNA damages in biological cells
    - First time in Geant4
- **Expected duration**
  - 9 months
  - May require CC-IN2P3 dedicated hours (already requested)

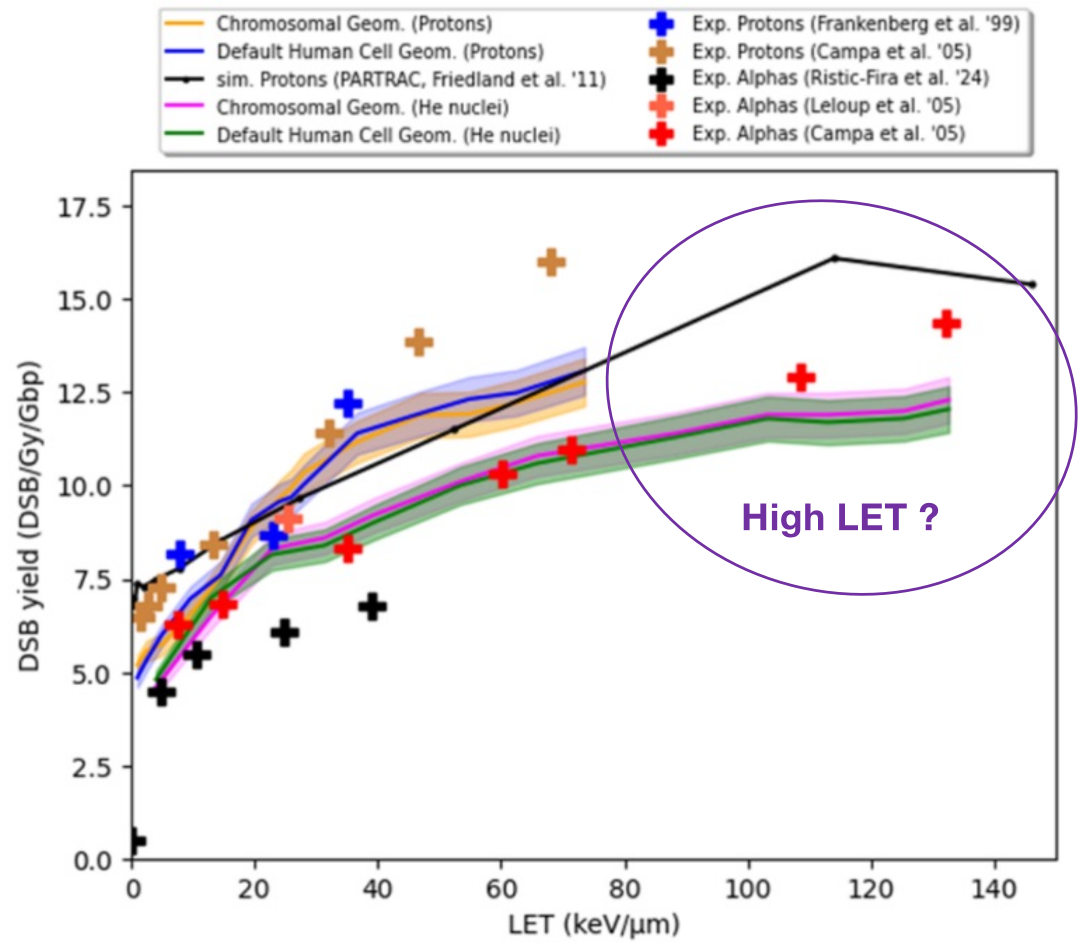
Example of radiobiology **validation**

molecularDNA





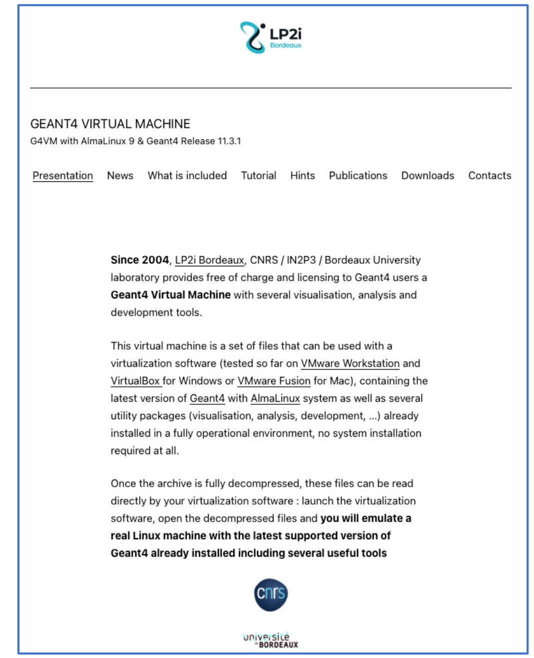




Sakata et al., Sci. Rep. 10, 20788 (2020)
Chatzipapas et al., Phys. Med. 127, 104839 (2024)

Open science & outreach

- **Visibility**
  - All software will be available freely in Geant4 (after publication)
  - Part of the **on-going workplan of Geant4-DNA** on the **improvement of accuracy of ion models**
    - In coll. with Geant4@CERN, ASNR, Wollongong U., …
- **Outreach**
  - A **Geant4-DNA tutorial** will be organised in Japan in 2026 or 2027
    - Series of past tutorials organised in Japan
      - 2024: Osaka
      - 2015: Hiroshima
    - Progress and findings of this project will be shown during the tutorial
      - Including live demonstration using the free **Geant4 Virtual Machine** (LP2i)



https://extra.lp2ib.in2p3.fr/G4/

LP2i Laboratoire de Physique des 2 infinis Bordeaux
KEK High Energy Accelerator Research Organization
GEANT4 A SIMULATION TOOLKIT

An interdisciplinary project & team

- **Consisting of experts in Geant4 and Geant4-DNA development, radiation chemistry and radiobiology**
  - **Geant4 & Geant4-DNA core development**
    - **Long-collaboration & fruitful collaboration between KEK & IN2P3 on Geant4 & Geant4-DNA developments (e.g. FJPPL 2007-2017)**
      - S. OKADA (KEK)
      - K. MURAKAMI (KEK)
      - T. SASAKI (KEK)
      - H. TRAN (IN2P3)
      - S. INCERTI (IN2P3)
  - **Radiation chemistry & biology data**
    - T. KUSUMOTO (QST Hospital)
      - Radiochemical yields (p, C)
      - Early DNA damage (p, C)

Collaborator	Stage #1 (6 months)	Stage #2 (6 months)	Stage #3 (9 months)
S. OKADA	x	x	x
K. MURAKAMI	x	x	x
T. SASAKI	x	x	x
H. TRAN	x	x	x
S. INCERTI	x	x	x
T. KUSUMOTO		x	x

Budget request for 2025

- **From Japan side**
  - A 10-day trip to LP2i, Bordeaux
    - 800 kJPY asked to KEK (S. OKADA)
- **From France side**
  - 2 trips of 6 days to KEK, Tsukuba
    - 4960 € asked to IN2P3 (H. TRAN and S. INCERTI)
      - (at least one trip if two trips are too expensive)
- **Additional support (confirmed)**
  - Postdoctoral fellow @ LP2i: to be recruited during autumn 2025 for 24 months
    - Candidates are very welcome to apply at these links:
    - https://emploi.cnrs.fr/Offres/CDD/UMR5797-JERBAU-077/Default.aspx?lang=EN
    - http://geant4.in2p3.fr

Thank you very much !