

[FJPPN APP_01]

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

Shogo OKADA, Koichi MURAKAMI, Takashi SASAKI

KEK Computing Research Center, Japan

Sebastien INCERTI, Adrien PAILLET, Hoang TRAN

CNRS-IN2P3 & Bordeaux University, LP2i, France

Contents

■ Context

■ 2025 workplan

- Activity #1: addition of Multiple Ionisation (MI) physics to Geant4-DNA
- Activity #2: benchamrking of Geant4-DNA radiolysis against experimental data of the literature
- Activity #3: first investigation of Carbon MI effects on radiolysis

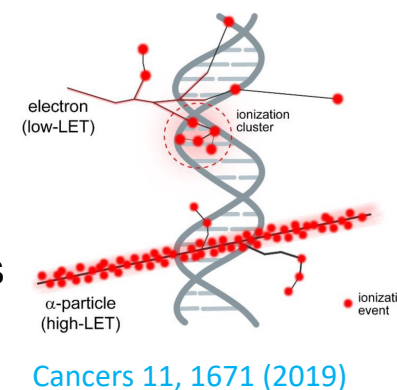
■ 2026 proposal

- Working items & budget request

Context

■ Carbon ion radiotherapy (CIRT)

- More effective treatment due to its **high linear energy transfer** (high-LET) compared to classical photon and proton radiotherapies
 - Leads to a **higher relative biological effectiveness** (high-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 today³, 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**



■ 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(³P)**, $O_2^{\cdot-}$, HO_2^{\cdot} , 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)

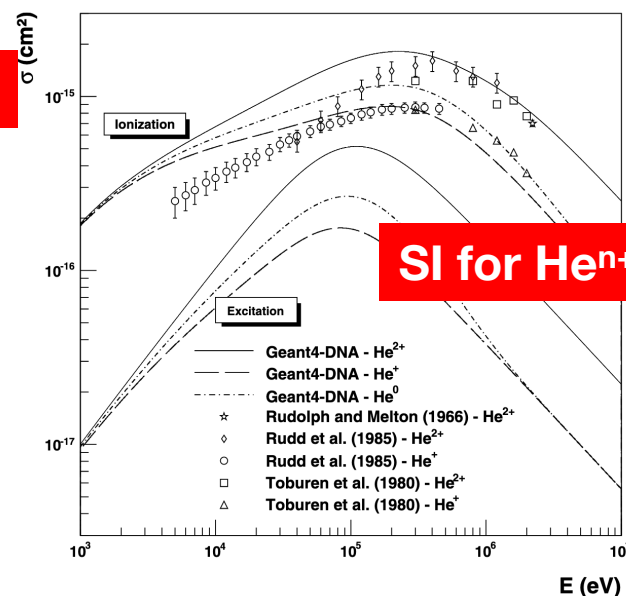
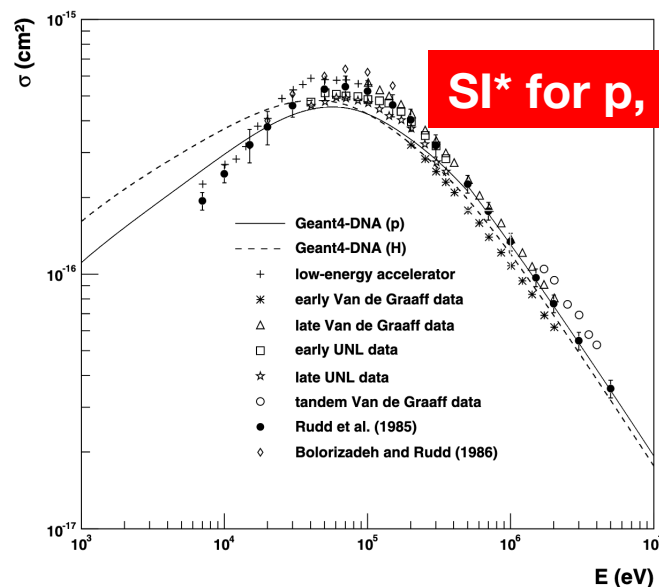
Activity #1: Multiple Ionisation (MI) now available in Geant4-DNA

■ Inclusion of double / triple / quadruple ionisation (DI/TI/QI) in Geant4-DNA Physics Constructors

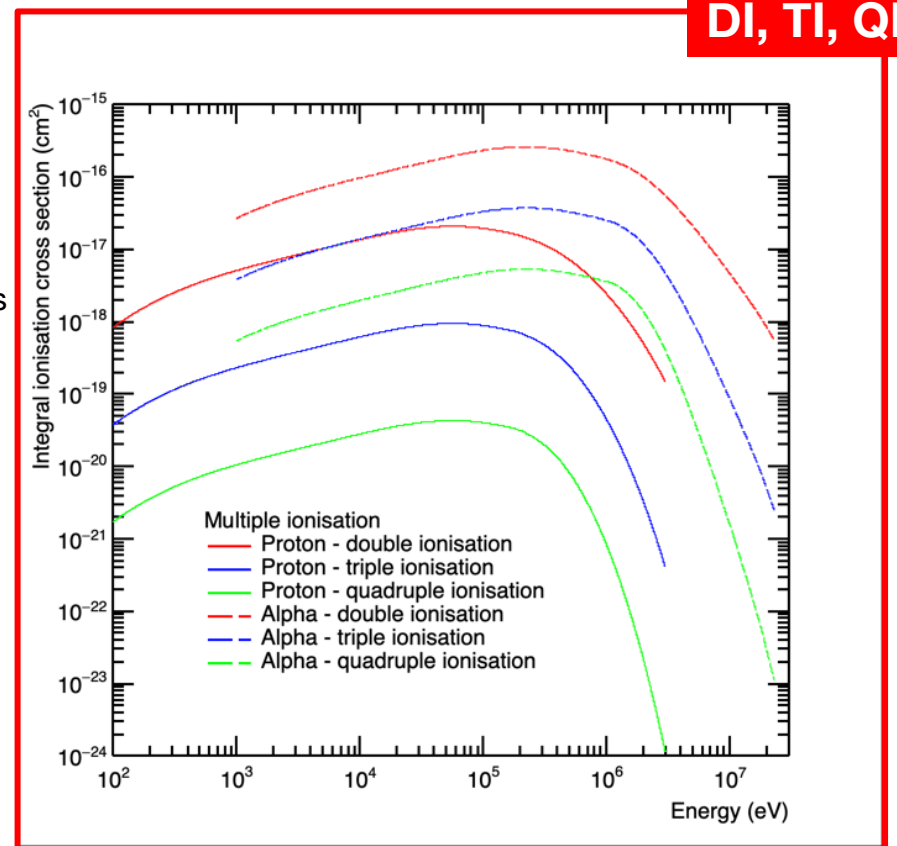
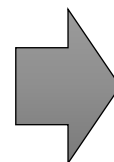
- ❑ Based on Meesungnoen, Jay-Gerin et al. (Sherbrooke U.) – [Baba et al., J. Appl. Phys. 129, 244702 \(2021\)](#)
- ❑ Applicable to protons, alpha particles, Carbon ions
- ❑ In all Geant4-DNA Physics constructors

■ New User Interface command available in Geant4

- ❑ `/process/dna/UseDNAMultipleIonisation true`



Derived MI cross sections

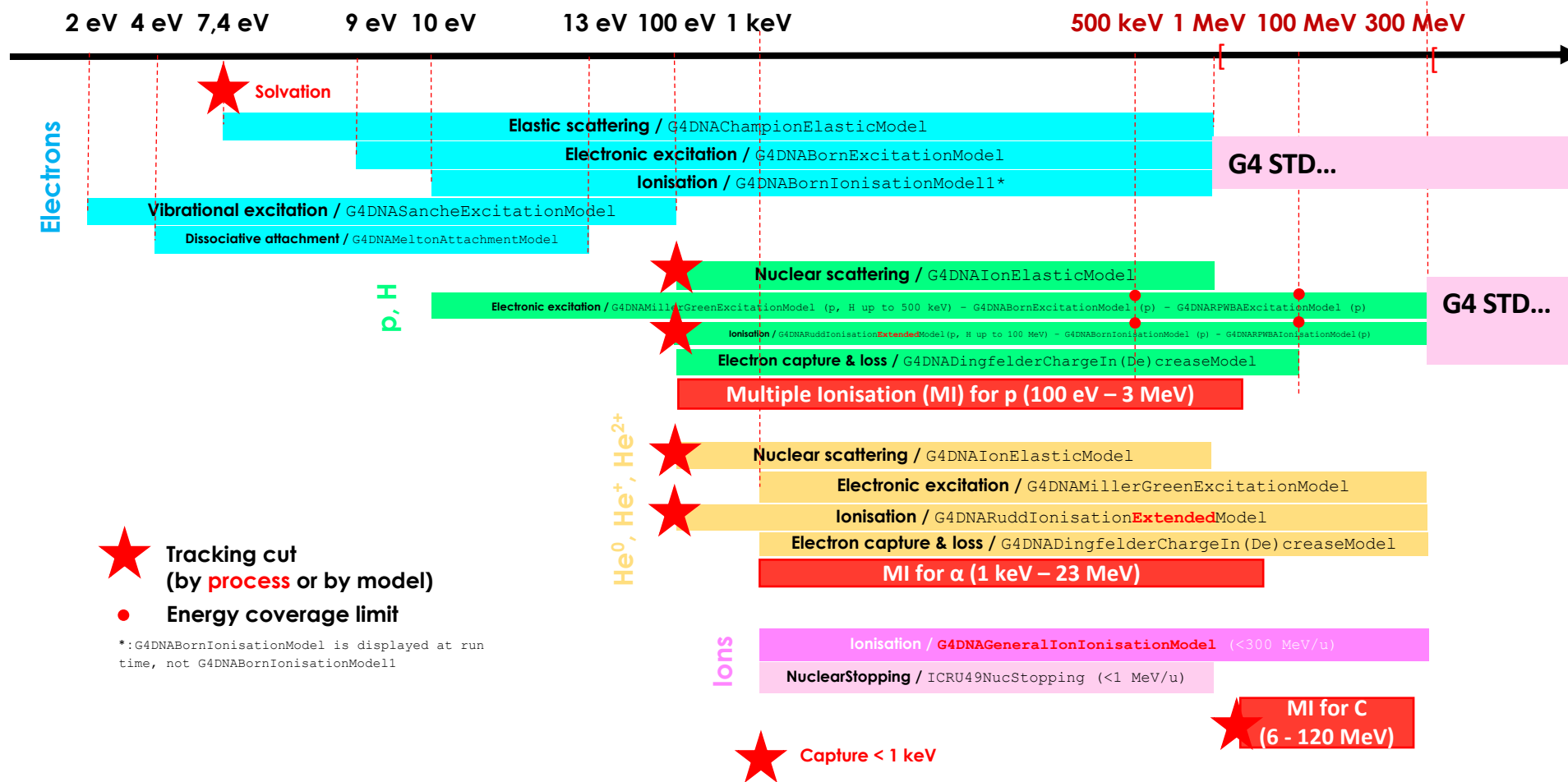


*SI: Single Ionisation

[Incerti et al., Med. Phys. 37 \(2010\) 4692-4708](#)

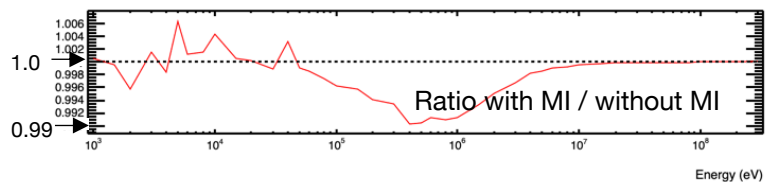
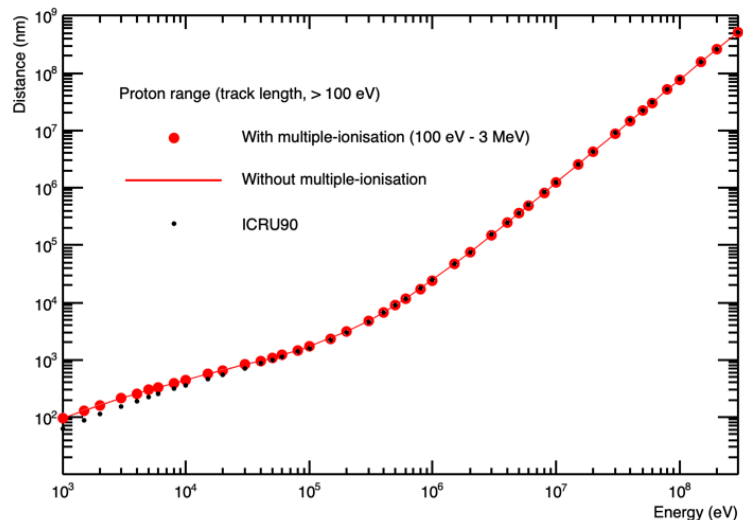
Energy Coverage of Geant4-DNA Physics

(e.g., Physics Constructor Option2)



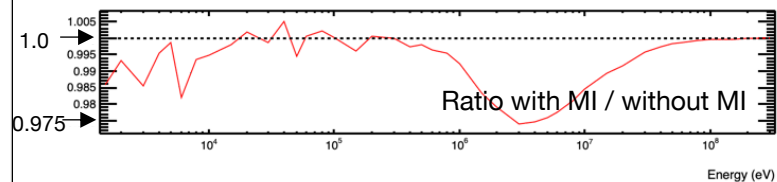
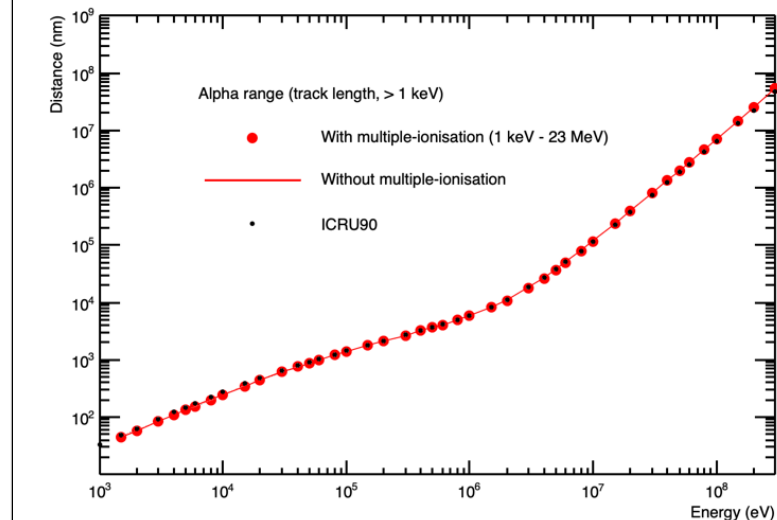
Impact of Multiple Ionisation on range

Proton



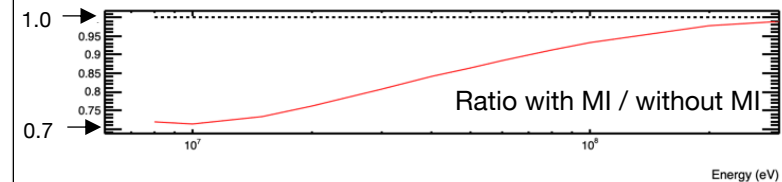
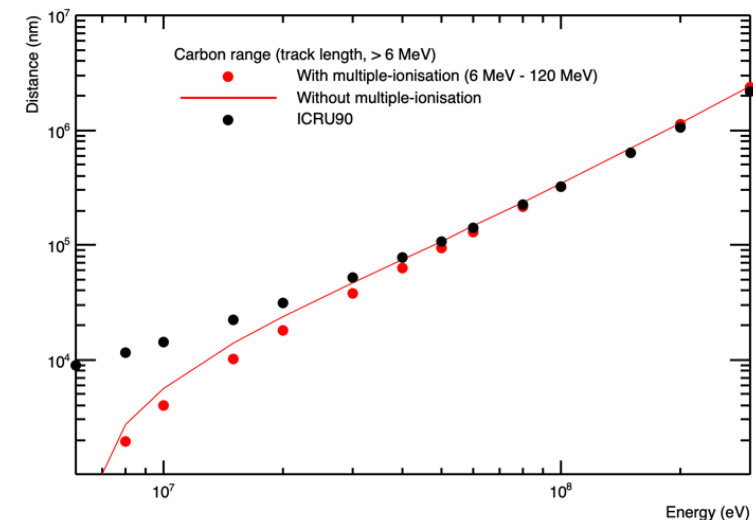
< 1%

Alpha



< 3%

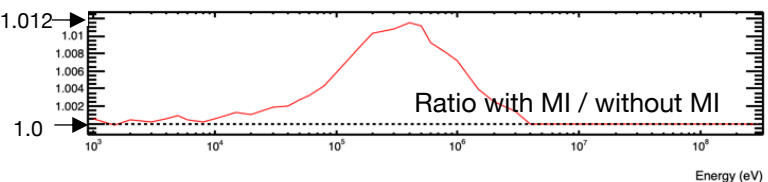
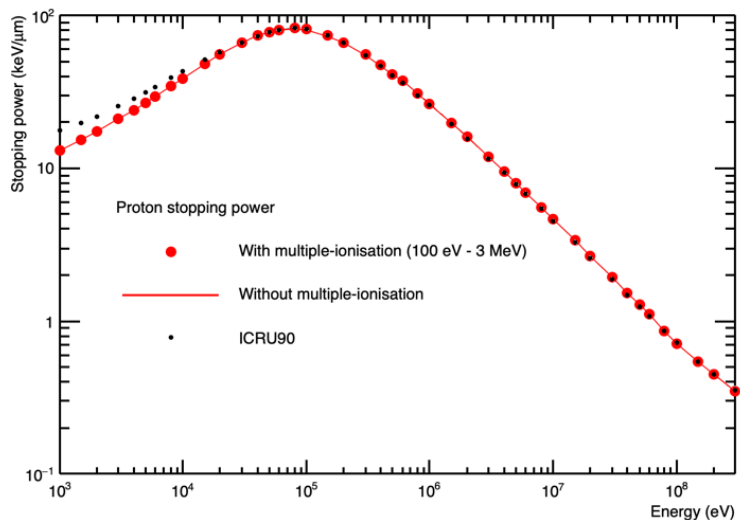
Carbon



< 30%

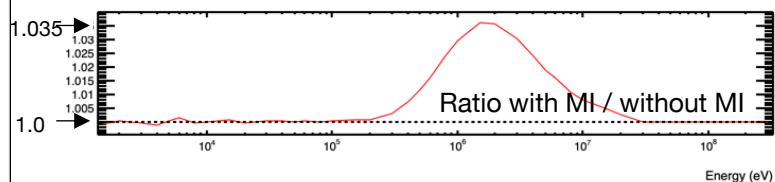
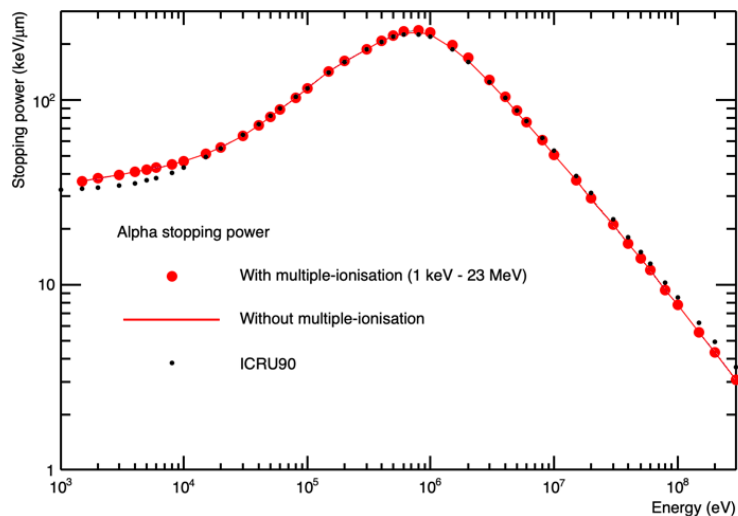
Impact of Multiple Ionisation on **stopping power**

Proton



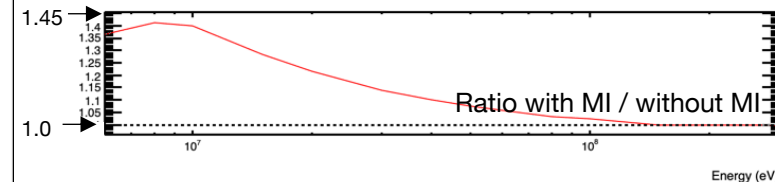
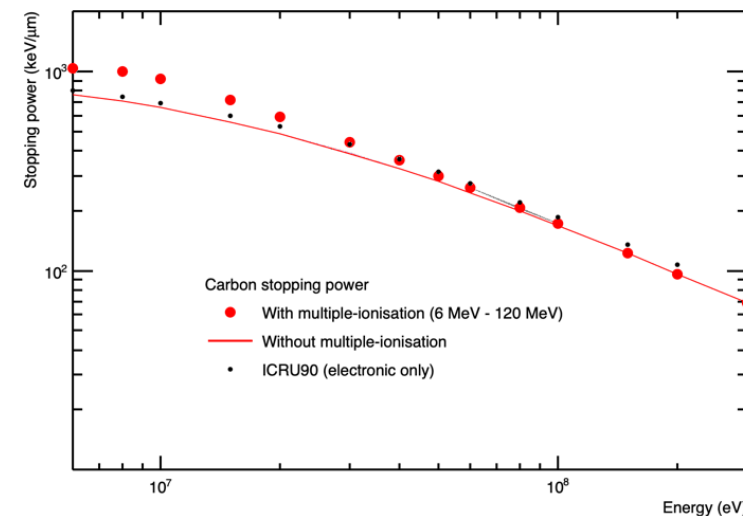
< 2%

Alpha



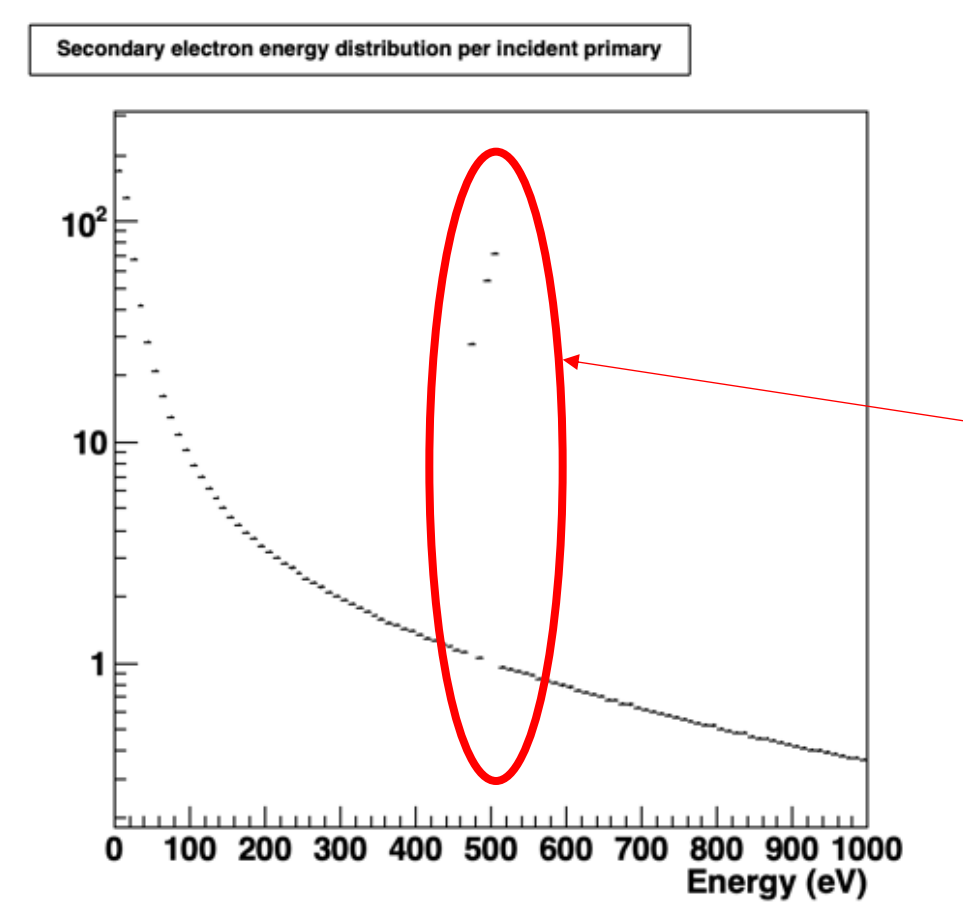
< 4%

Carbon



< 45%

Auger electron production



■ Secondary electron spectrum

- from 10^5 incident Carbon of 100 MeV
- **Auger electrons** are visible
 - Atomic rearrangement following deexcitation of ionised oxygen in water

Activity #2: benchmark of radiolysis

- **Develop a full benchmark of Geant4-DNA radiolysis simulations against experimental data from the literature**
 - For incident electrons, protons and alpha beams
 - Differential radiochemical yields: “G-values” = $N_{\text{molecules}} / (\Delta E / 100 \text{ eV})$
 - As a function of **time** for incident electrons
 - As a function of **LET** and **MZ²/E** for protons, alphas and Carbon ions
- **Motivation: identify the most plausible Geant4-DNA**
 - Physics constructor
 - can Chemistry help better constrain Physics ?
 - (At this stage, Multiple Ionisation is NOT considered)
 - Chemistry constructor
 - Time step model

Geant4-DNA Physics and Chemistry Settings

- **Geant4-DNA (recommended) Physics constructors: physics processes and models**
 - Mainly differ by their electron elastic & inelastic models (identical for ions)
 - **Option2** (historical): dielectric formalism for liquid water for inelastic & partial wave analysis for elastic
 - **Option4** (most recent): improved DRF with correlation & exchange corrections; SR for elastic
 - **Option6** (ex. of software re-engineering): CPA track-structure code (BEB and DRF for inelastic; IAM for elastic)
 - Review in [Incerti et al., Med. Phys. 45, e722-e739 \(2018\)](#)

- **Geant4-DNA Chemistry constructors: dissociation scheme, chemical actions, and models involved in water radiolysis**
 - **Default** : first constructor implemented with parameter values from PARTRAC software
 - **Option1** : revisited set of chemistry parameters from TRACs + Burns et al. (1981) + Rowe et al. (1988)
 - **Option2** : includes chemistry parameters for reactions with DNA components from Buxton et al. (1988)
 - **Option3** : implements the IRT approach from Ramos-Mendez et al. (2020), from RITRACKS & Elliot et al. (1994)
 - Review in [Tran et al., Med. Phys. 51, 5873-5889 \(2024\)](#)

- **Geant4-DNA Chemistry time step models**
 - **SBS (Step-by-step)** : fixed time step molecular transport method
 - **IRT (Independent Reaction Times)** : calculates the reaction times between all possible pairs. Reactions occur one by one, starting with the pair with the shortest reaction time.
 - **IRT-syn (Synchronized IRT)** : a mixed approach to benefit from speed of IRT and tracking of SBS
 - (*mesoscopic*: a compartment-based representation that describes the evolution of species through their concentrations in different compartments.)
 - Review in [Tran et al., Med. Phys. 51, 5873-5889 \(2024\)](#)

Radiolysis Benchmarking Summary

- **Comparison with comprehensive set of experimental data**
 - Distributions of relative differences between simulations and experiments for given time (electrons) or MZ^2/E values (protons, alphas)
 - Evaluation of median values
- **Scarcity of exp. data : evaluation of « plausability » only**
 - Impact of **Physics constructor**
 - **Option4** (most recent, DRF of liquid water)
 - Impact of **Chemistry constructor**
 - **Option3** (most recent set of chemistry parameters)
 - Impact of **Chemistry time-step model**
 - Depends on the **user simulation requirements** (e.g., tracking of molecules : IRT-syn)
- **Paper submitted to EJMP, under review**

Physics constructor impact on G-values

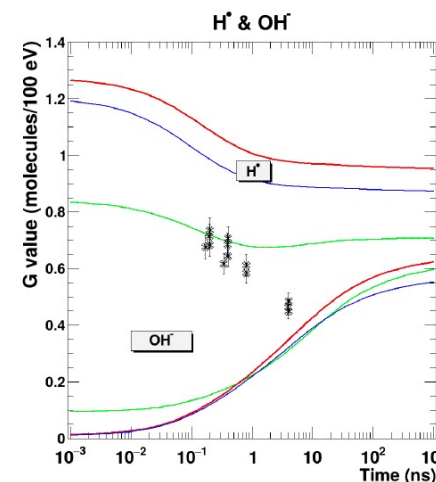
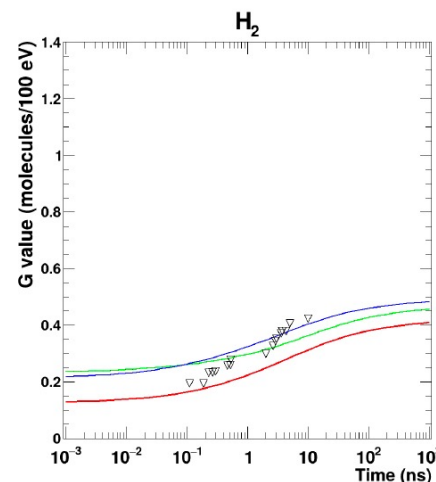
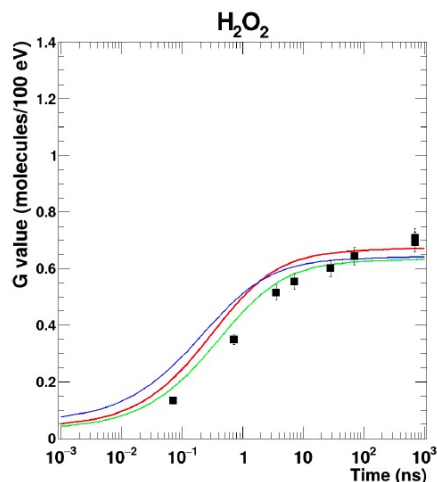
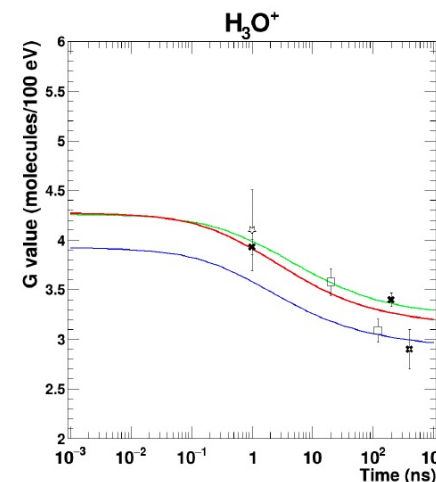
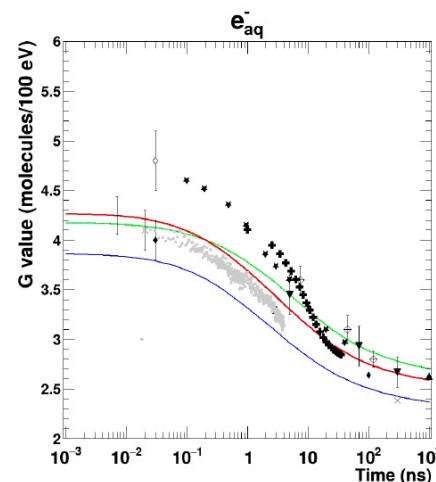
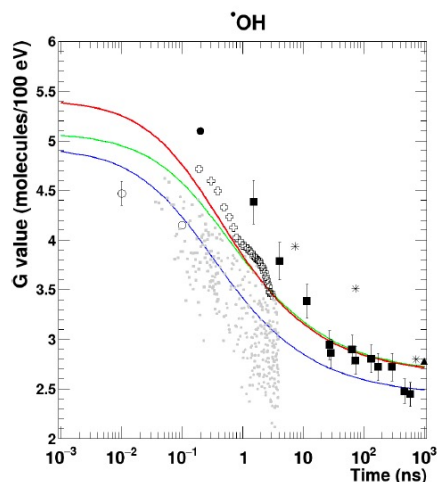
G = radiochemical
yield for a given
species

$$G = N / 100 \text{ eV}$$

Electrons
G versus time

Physics
constructors

Option2
★ Option4
Option6



Geant4-DNA - IRT - UI

— G4EmDNAPhysics_option2
— G4EmDNAPhysics_option4
— G4EmDNAPhysics_option6

Experimental values for incident electrons

- Wang et al. (2018) - 7.5 MeV
- Pachnerova et al. (2015) - PROTONS 30 MeV
- Ma LTD et al. (2015) - 7 MeV
- Ma STD et al. (2015) - 7 MeV
- El Omar et al. (2011) - 7 MeV
- Muroya et al. (2005) - 20 MeV
- Bartels et al. (2000) - 20 MeV
- LaVerne (2000) - source ⁶⁰Co
- Elliot et al. (1993) - 2.25 MeV
- Shiraishi et al. (1988) - 35 MeV
- Anderson et al. (1985) - 3.5 MeV
- Belloni et al. (1983) - 0.6 MeV
- Sumiyoshi and Katayama (1982) - 45 MeV
- (× 0.8) Jonah et al. (1977) - 20-22 MeV
- Jonah et al. (1976) - 20-22 MeV
- Pikaev et al. (1976) - 5 MeV
- Draganic and Draganic (1975) - source ⁶⁰Co
- Wolff et al. (1973) - 41 MeV
- Jonah et al. (1973) - 19 MeV
- Buxton (1972) - 2.9 MeV
- Draganic and Draganic (1972) - source ⁶⁰Co
- Cercek and Kongshaug (1969) - source ⁶⁰Co & 8 MeV
- Schmidt and Ander (1969) - 15 MeV

Chemistry constructor impact on G-values

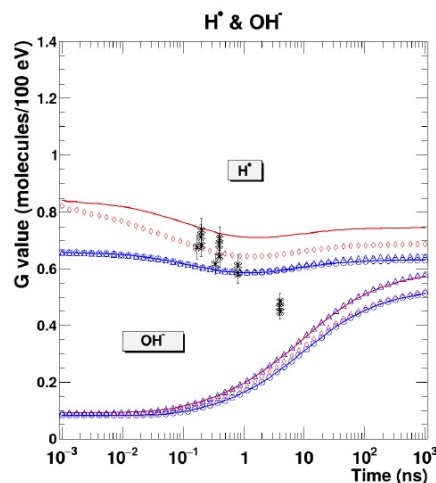
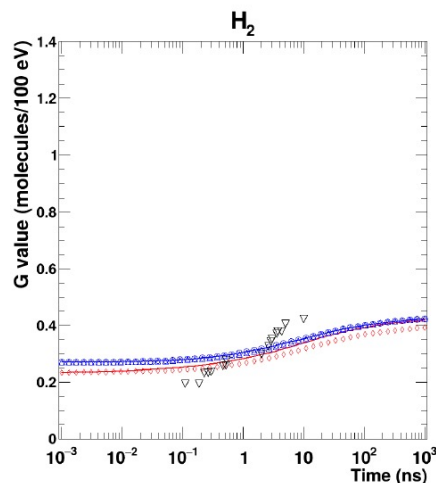
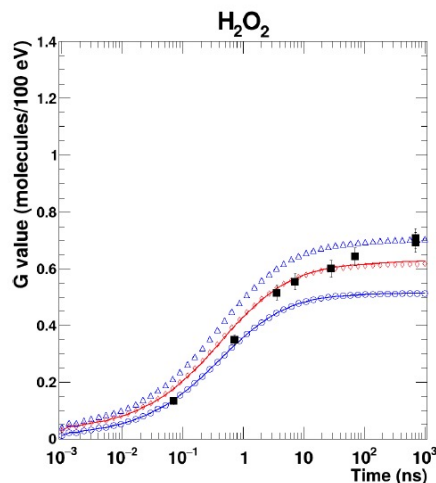
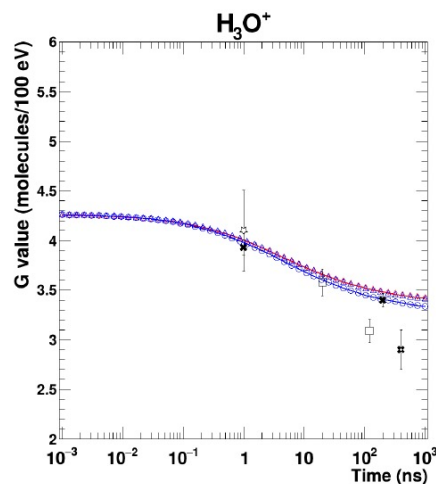
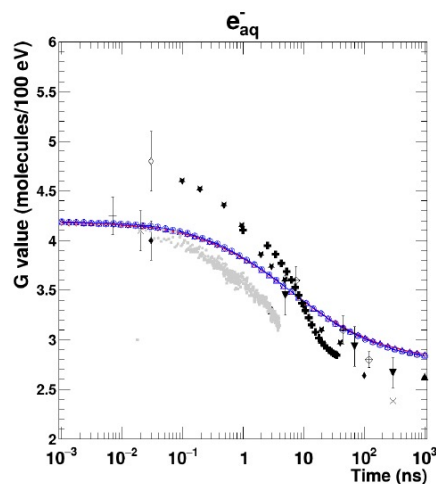
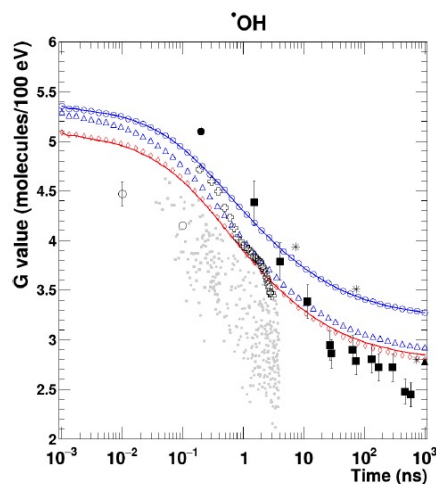
G = radiochemical
yield for a given
species

$$G = N / 100 \text{ eV}$$

Electrons
G versus time

Chemistry
constructors

Default
Option1
Option2
★ Option3



Geant4-DNA - SBS - G4EmDNAPhysics_option2

- UI
- G4EmDNAChemistry_option3
- G4EmDNAChemistry
- △ G4EmDNAChemistry_option1
- G4EmDNAChemistry_option2

Experimental values for incident electrons

- Wang et al. (2018) - 7.5 MeV
- × Pachnerova et al. (2015) - PROTONS 30 MeV
- Ma LTD et al. (2015) - 7 MeV
- Ma STD et al. (2015) - 7 MeV
- El Omar et al. (2011) - 7 MeV
- × Muroya et al. (2005) - 20 MeV
- Bartels et al. (2000) - 20 MeV
- LaVerne (2000) - source ⁶⁰Co
- ▲ Elliot et al. (1993) - 2.25 MeV
- ▼ Shiraishi et al. (1988) - 35 MeV
- Anderson et al. (1985) - 3.5 MeV
- △ Belloni et al. (1983) - 0.6 MeV
- ◇ Sumiyoshi and Katayama (1982) - 45 MeV
- ⊗ (× 0.8) Jonah et al. (1977) - 20-22 MeV
- ★ Jonah et al. (1976) - 20-22 MeV
- Pikaev et al. (1976) - 5 MeV
- ▽ Draganic and Draganic (1975) - source ⁶⁰Co
- ◆ Wolff et al. (1973) - 41 MeV
- Jonah et al. (1973) - 19 MeV
- ◇ Buxton (1972) - 2.9 MeV
- ★ Draganic and Draganic (1972) - source ⁶⁰Co
- ★ Cercek and Kongshaug (1969) - source ⁶⁰Co & 8 MeV
- Schmidt and Ander (1969) - 15 MeV

Chemistry time-step model impact on G-values

G = radiochemical
yield for a given
species

$$G = N / 100 \text{ eV}$$

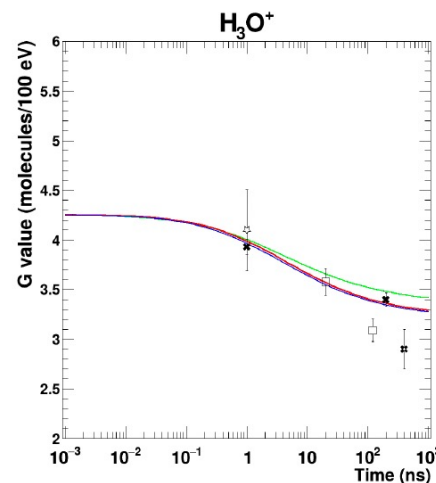
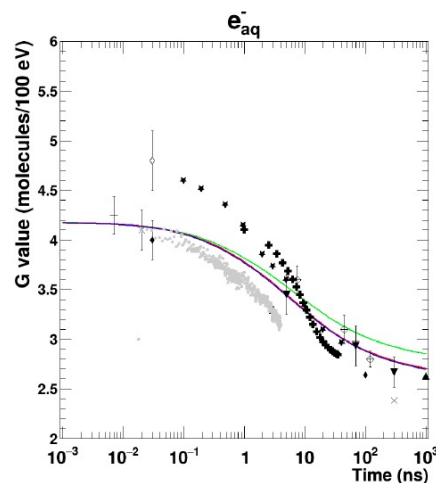
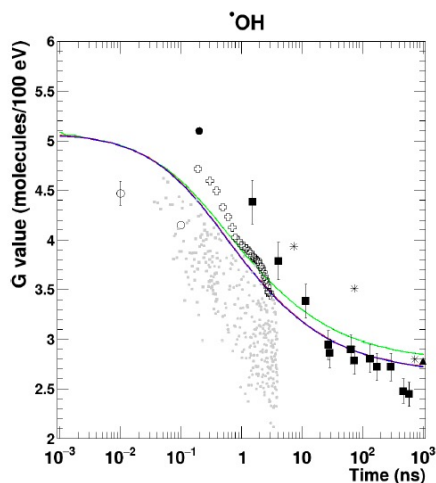
Electrons
G versus time

Chemistry
Time-step
model

SBS

IRT

★ IRT-syn

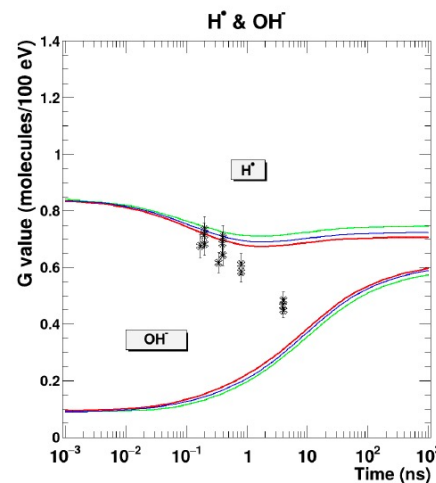
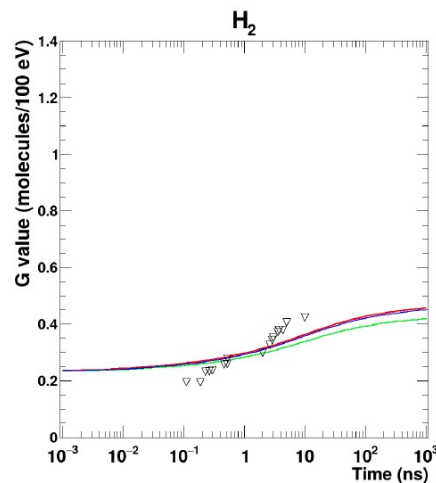
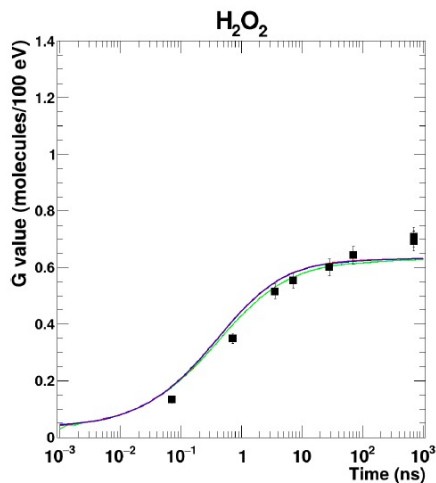


Geant4-DNA - G4EmDNAPhysics_option2 - UI

— SBS

— IRT

— IRT-syn



Experimental values for incident electrons

- Wang et al. (2018) - 7.5 MeV
- Pachnerova et al. (2015) - PROTONS 30 MeV
- Ma LTD et al. (2015) - 7 MeV
- Ma STD et al. (2015) - 7 MeV
- El Omar et al. (2011) - 7 MeV
- Muroya et al. (2005) - 20 MeV
- Bartels et al. (2000) - 20 MeV
- LaVerne (2000) - source ⁶⁰Co
- Elliot et al. (1993) - 2.25 MeV
- Shiraishi et al. (1988) - 35 MeV
- Anderson et al. (1985) - 3.5 MeV
- Belloni et al. (1983) - 0.6 MeV
- Sumiyoshi and Katayama (1982) - 45 MeV
- (× 0.8) Jonah et al. (1977) - 20-22 MeV
- Jonah et al. (1976) - 20-22 MeV
- Pikaev et al. (1976) - 5 MeV
- Draganic and Draganic (1975) - source ⁶⁰Co
- Wolff et al. (1973) - 41 MeV
- Jonah et al. (1973) - 19 MeV
- Buxton (1972) - 2.9 MeV
- Draganic and Draganic (1972) - source ⁶⁰Co
- Cercek and Kongshaug (1969) - source ⁶⁰Co & 8 MeV
- Schmidt and Ander (1969) - 15 MeV

Activity #3: impact of Multiple Ionisation on radiolysis

■ Can we observe increased oxygen production around (high-LET) carbon tracks?

- Simulations of G-values versus time and LET with and w/o MI
- 2×10^4 C ions, from 0.67 MeV/u to 160 MeV/u

■ Results for G (at 1 us) vs LET

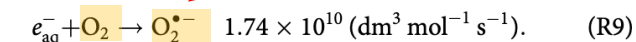
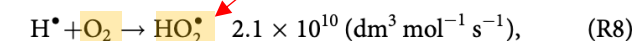
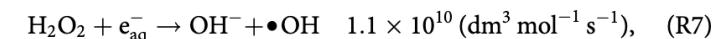
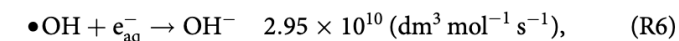
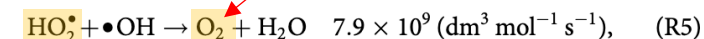
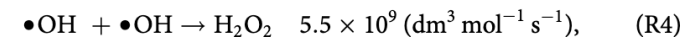
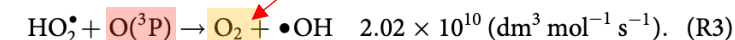
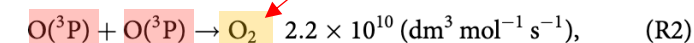
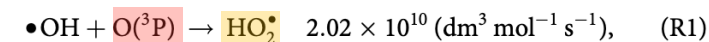
- **Increase with MI: HO_2^\bullet , O_2 , $\text{O}_2^{\bullet-}$, HO_2^- , O_3^- , O_3**
 - As expected from MI
- Decrease with MI: H_2 , H_2O_2
- No impact on other species (e.g., $^\bullet\text{OH}$: indirect DNA damage)

oxygen production

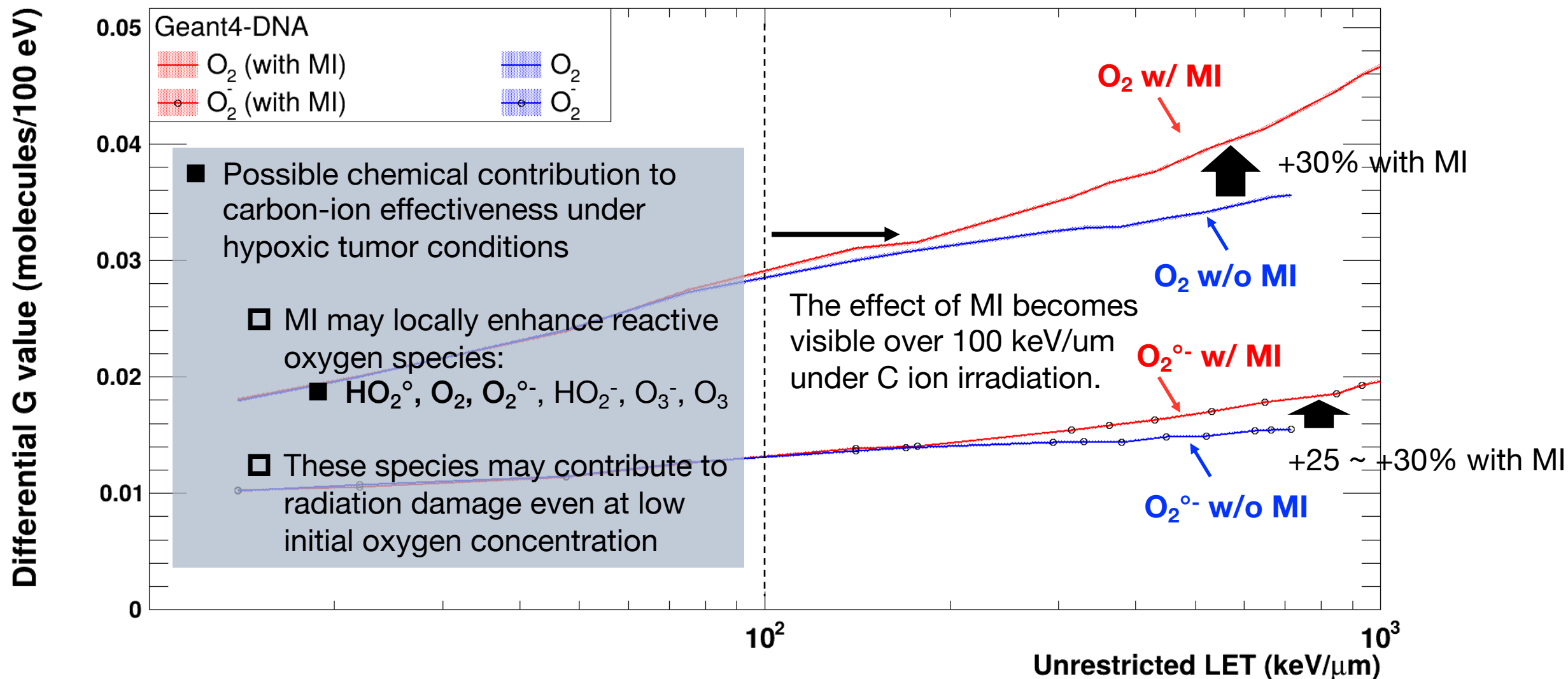
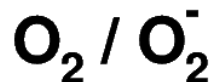
TABLE II. Dissociation channels related to multiple ionization events at the physicochemical stage. The distances between the fragments are given in

| | | | | | |
|--|---------------|--|---------------|--|------|
| Double ionization state: H_2O^{2+} | \rightarrow | $\text{H}^+ + \text{H}^+ + \text{O}(^3\text{P})$ | \rightarrow | $2\text{H}_3\text{O}^+ + \text{O}(^3\text{P})$ | 55% |
| | \rightarrow | $\text{H}^+ + \text{OH}^+$ | \rightarrow | $2\text{H}_3\text{O}^+ + \text{O}(^3\text{P})$ | 29% |
| | \rightarrow | $\text{H}^+ + \text{H}^+ + \text{O}^+$ | \rightarrow | $2\text{H}_3\text{O}^+ + \text{H}^+ + \bullet\text{OH} + \text{O}(^3\text{P})$ | 16% |
| Triple ionization state: H_2O^{3+} | \rightarrow | $\text{H}^+ + \text{H}^+ + \text{O}^+$ | \rightarrow | $3\text{H}_3\text{O}^+ + \bullet\text{OH} + \text{O}(^3\text{P})$ | 100% |

Increased with MI



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



Proposal for 2026

■ Activity #1

- Impact of the multiple ionisation on **radiochemical yields as a function of LET and MZ^2/E for incident protons, alphas, and carbons.**
- Influence of oxygen concentration in water (normoxic vs hypoxic)

■ Activity #2

- Quantify the impact of MI on the **induction of DNA damage in cells**, using the “molecularDNA” Geant4-DNA simulation chain
 - <https://moleculardna.org>
 - First in E. coli bacteria (containing 4.6×10^6 base pairs of DNA), then in human cells (6.4 Gbp of DNA).
 - How much direct damage & indirect damage, considering normoxic or hypoxic conditions
- CNRS Nuclear & Particles Computing Center, where the “Geant4” group was reactivated in 2025 specifically for this FJPPN project.

■ Activity #3

- Organize a **Geant4-DNA School for the first time in Tsukuba** in 2026 or 2027, as we did in Osaka in 2024 (see <https://indico.rcnp.osaka-u.ac.jp/event/2100/#>)
- Progress and findings of this project will be presented during the school.

molecularDNA

Home

Overview

Available geometries

Running the example

Publications

Building geometries

molecularDNA

Radiation-induced DNA damage simulations in Geant4

molecularDNA is a **Geant4-DNA example** built to allow easy simulation of radiation-induced DNA damage with *flexible geometries* and well defined *damage parameters*.

Get started right away in the Geant4 `geant4/examples/advanced/dna/moleculardna` directory with a *library of pre-existing geometries*, or dive into the documentation.

A **tutorial** demonstrating molecularDNA is also available at this [link](#).

Important : This example is for demonstration purposes and is intended as an introductory tool for users to create their applications. Therefore, users are advised to adapt and optimize the simulation parameters in their applications accordingly.

| | | |
|--|------------------------------|-----------------------------|
| (a) DNA double helix molecular structure | (b) Chromatin fiber segments | (c) Fibroblast cell nucleus |
|--|------------------------------|-----------------------------|

human cell example

[Get started from example](#) [See publications](#) [Available geometries](#)

This site uses Just the Docs, a documentation theme for Jekyll.

Budget request for 2026

■ From Japan side

- A support to organize a Geant4-DNA tutorial in Tsukuba (e.g., at KEK or other location)
 - 400 kJPY asked to KEK
- Previously organised in Japan
 - 2024: Osaka U.
 - 2015: Hiroshima U.
 - Progress and findings of this project will be shown during the tutorial

■ From France side

- 1 trip to KEK, Tsukuba
 - 3000 € asked to IN2P3

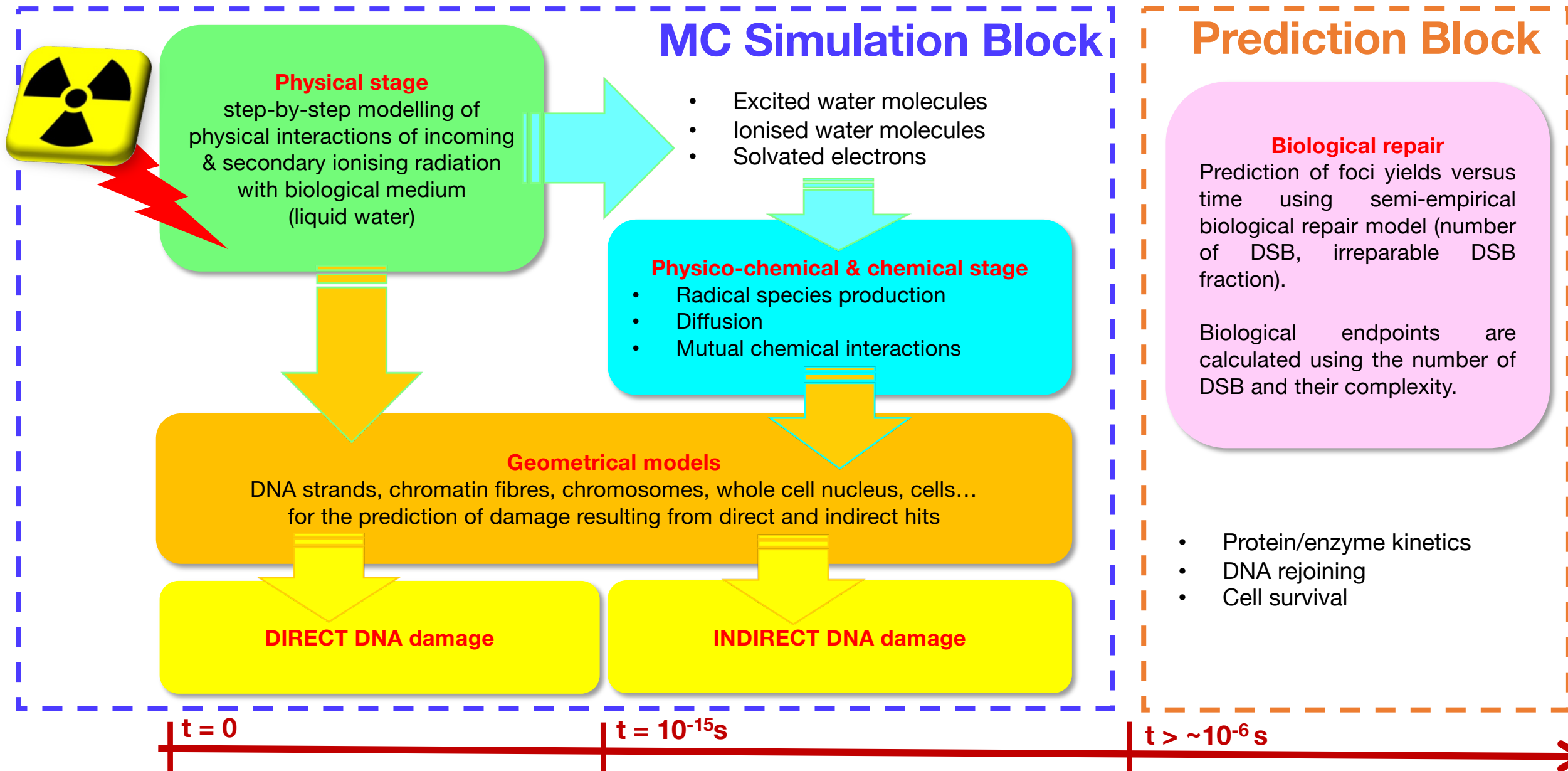
■ Additional support (confirmed)

- Postdoctoral fellow @ LP2i: recruited on Sep. 2025 for 24 months

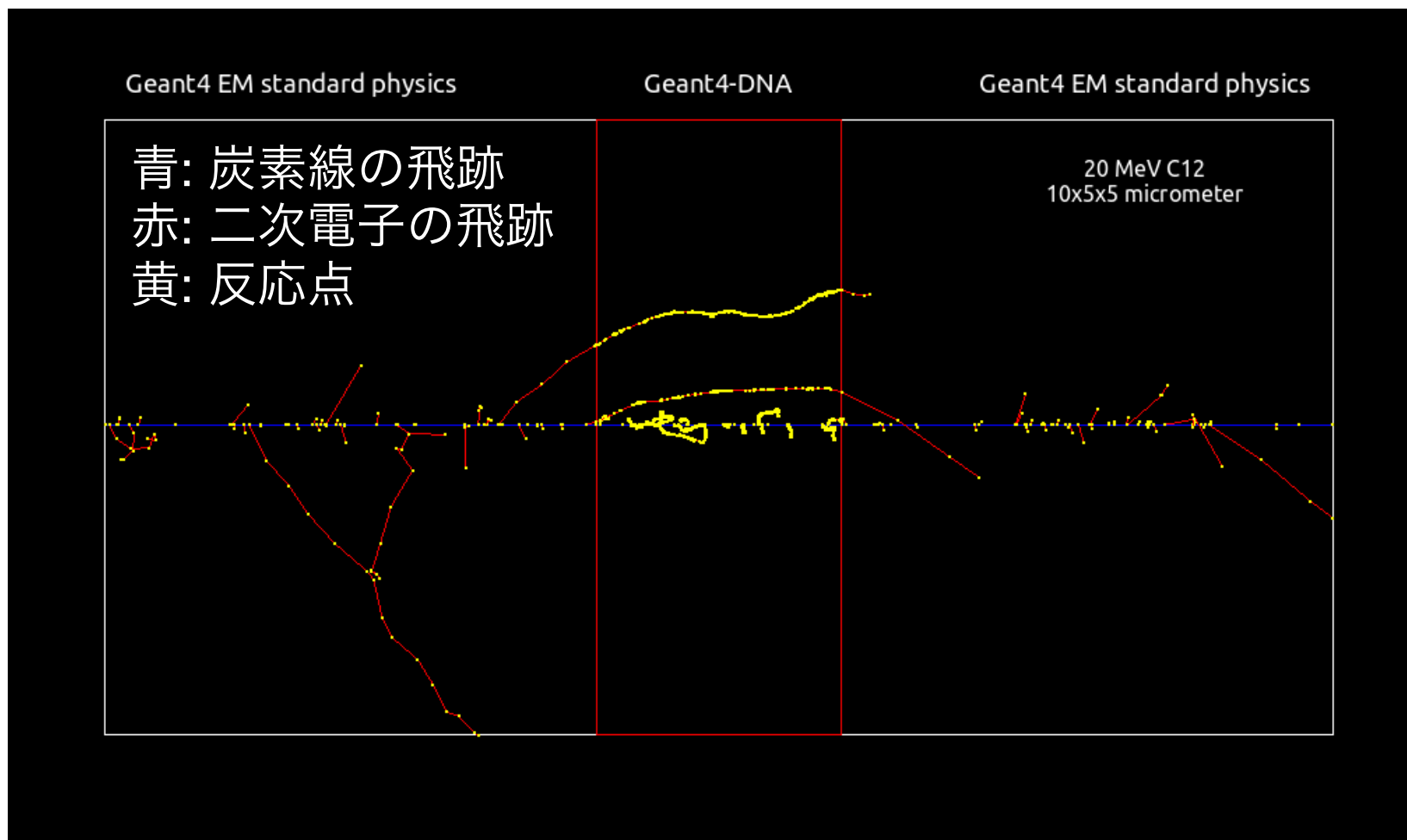
Thank you very much !

Backup

Reminder : damage to cells : the **Geant4-DNA** approach



Geant4 vs Geant4-DNA



Physics constructor impact on G (2)

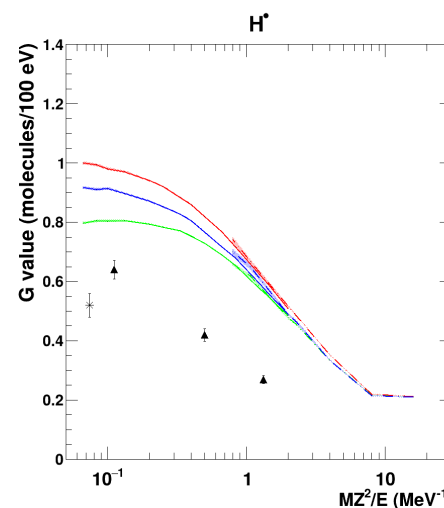
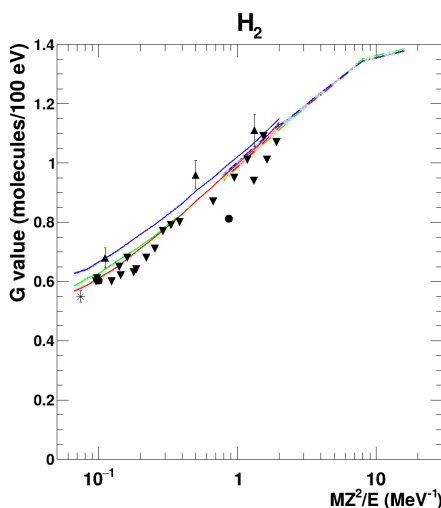
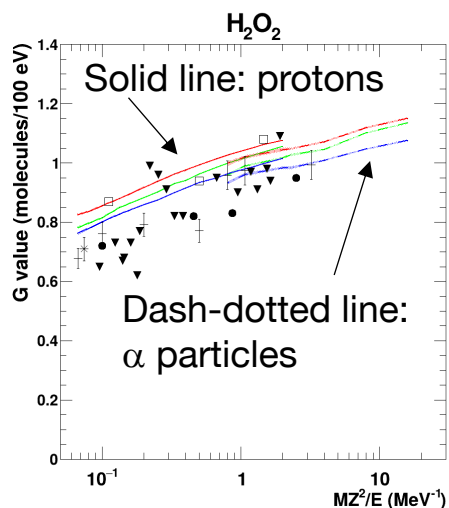
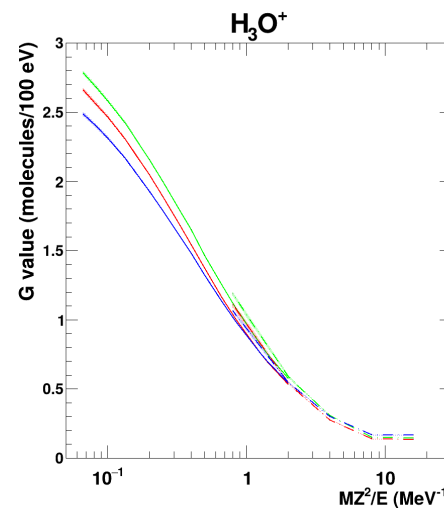
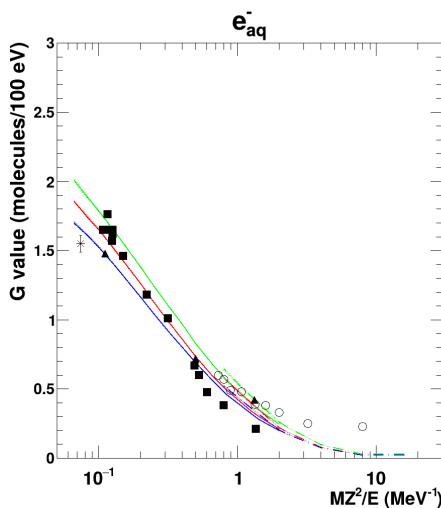
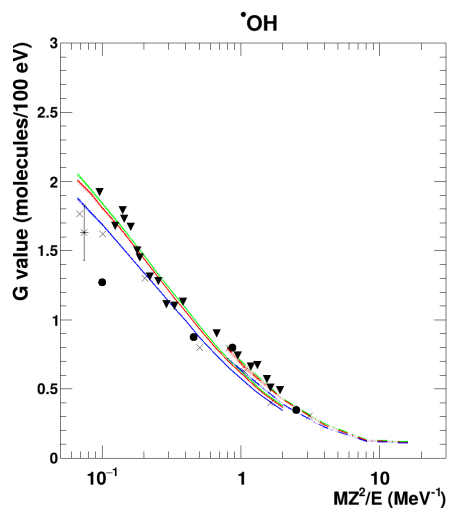
G = radiochemical
yield for a given
species

$$G = N / 100 \text{ eV}$$

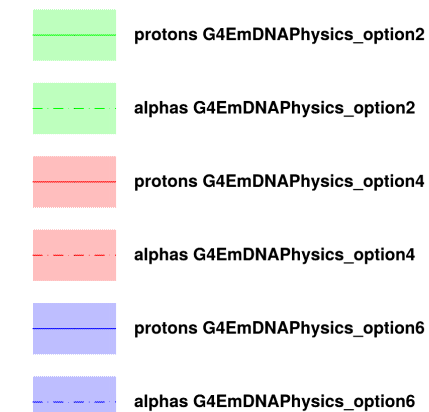
Proton, He
G versus MZ^2/E

Physics
constructors

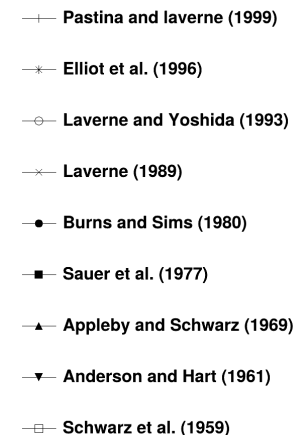
Option2
Option4
Option6



Geant4-DNA - IRT - UI



Experimental values



Chemistry time-step model impact on G (2)

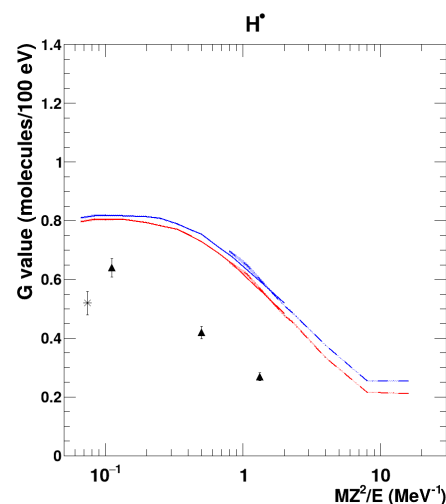
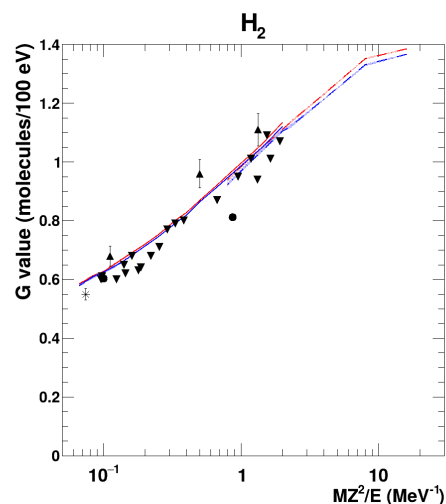
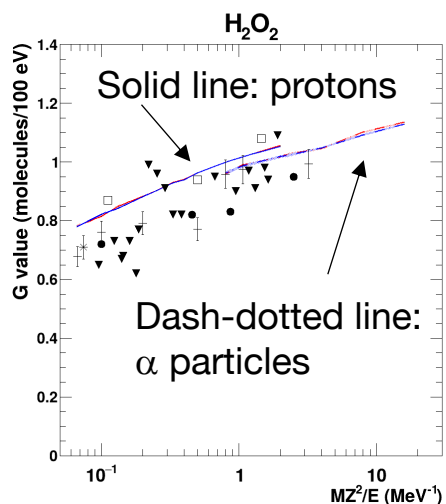
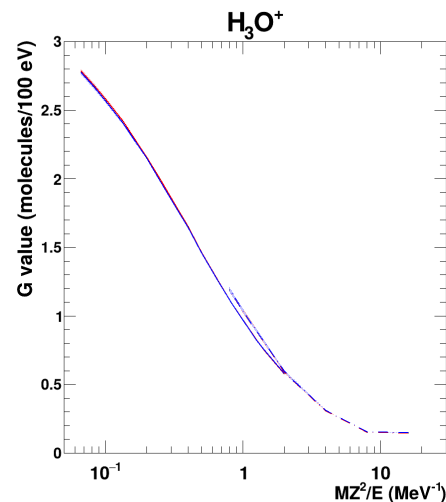
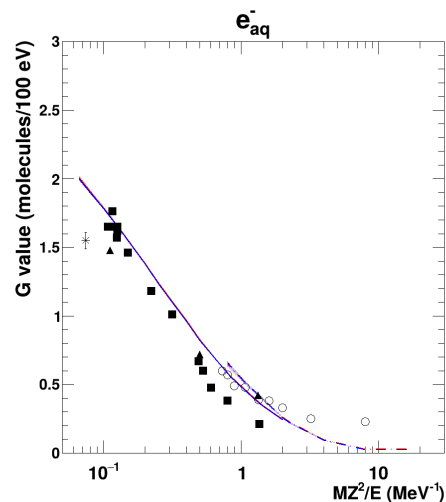
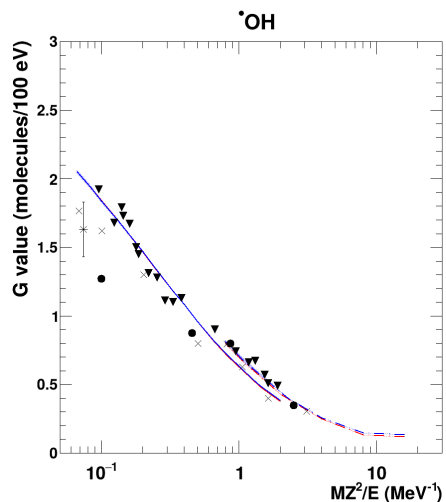
G = radiochemical
yield for a given
species

$$G = N / 100 \text{ eV}$$

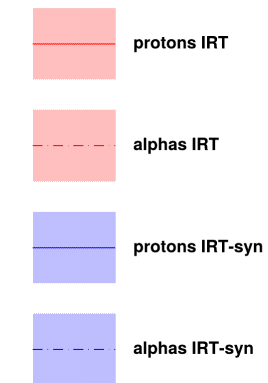
Proton, He
G versus MZ^2/E

Chemistry
Time-step
model

IRT
IRT-syn



Geant4-DNA - G4EmDNAPhysics_option2 - UI



Experimental values

- + Pastina and Laverne (1999)
- * Elliot et al. (1996)
- Laverne and Yoshida (1993)
- x Laverne (1989)
- Burns and Sims (1980)
- Sauer et al. (1977)
- ▲ Appleby and Schwarz (1969)
- ▼ Anderson and Hart (1961)
- Schwarz et al. (1959)

HO₂[•] / HO₂⁻

