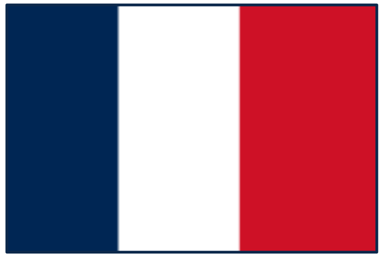
The SPARADA Project



« SPAce RAdiation DAmage »

« 우주 방사선 피해 »

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and **colleagues** (Seoul National University & National Cancer Center, CNRS-IN2P3, Jefferson Lab. / US)

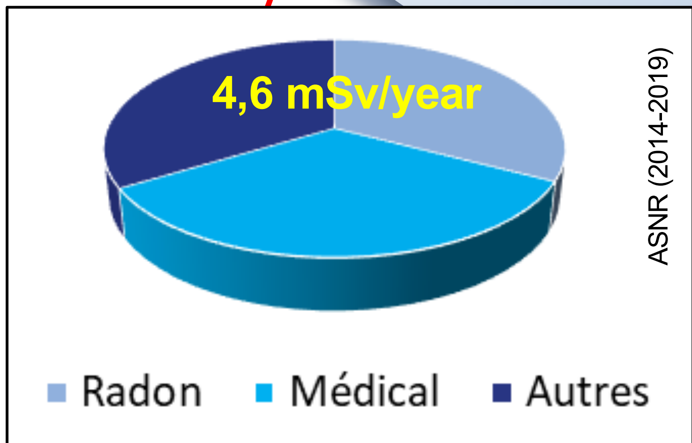
Context

- Understanding **mechanistically** the impact of ionising radiation at the DNA scale remains a major **challenge of today's biophysics and radiobiology**.
- Such a requirement arises from different **domains**
  - In **medical physics**, there is a need to develop novel or optimize existing **radiotherapy approaches**
    - Ultra-high dose rate, very high energy electrons, new radionuclides such as alpha emitters (Favaudon et al., 2014)
    - Hadrontherapy with p, C and other lighter ion beams such as alpha particles
  - For the future manned **space exploration** missions, the **health risks** due to exposure to ionising radiation is the strongest limiting factor to long-duration stays or trips (Mars)
    - e.g. Artemis by NASA, Gateway by ESA
    - No **consensus** among SA on cancer risks (Papadopoulos et al., 2023)
  - On the **environmental side**, fundamental questions exist on the impact of natural ionising radiation on the **development of organisms** and how they adapted to such harsh conditions, notably in underground environments (e.g. radiothrophic fungi, Tibolla et al., 2025)

Context: orders of magnitude

Increasing absorbed dose

Chronic exposure

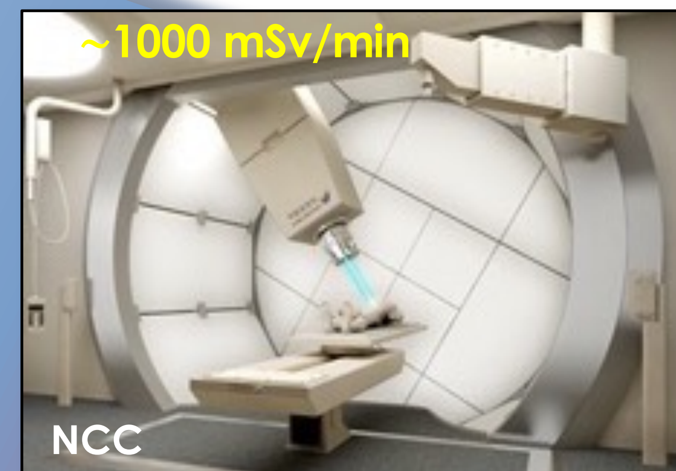


1 mSv/year
Public

>100 mSv
Long term effects

Space missions

Radiotherapy



Major questions in radiation protection

What are the biological effects of low doses?

What are the risks associated with high doses?

The answers? Numerical simulation (*in silico*) can help...

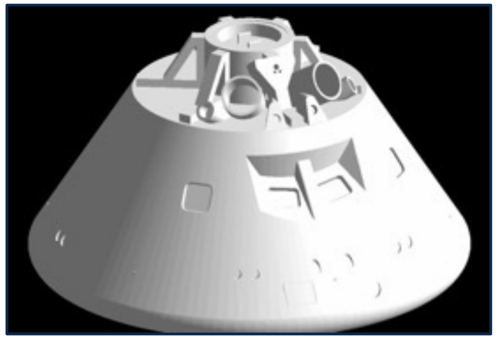
Objectives of the project

- A consortium of collaborators to develop a prototype of **multi-scale simulation platform** based on the **Geant4** Monte Carlo simulation toolkit (http://geant4.org)
  - General-purpose, open-source
  - International collaboration
  - Available on all recent OSs
  - A lot of experience in Korea and France (development & usage)
- The platform will allow the **mechanistic simulation of biological damage induced in the biological cells' DNA of the human body**, placed in a **realistic environment** exposed to **complex radiation fields**.
  - **« Space exploration » use case**: irradiation of a realistic human phantom placed inside a genuine spacecraft or habitat model and determine the early DNA damage induced in cells of several organs of the phantom.
  - **Fully included in Geant4, will be maintained over the years**
  - Extensible to other application domains involving ionising radiation
    - medical physics, environmental sciences…
- **Four stages** : a multi-scale approach

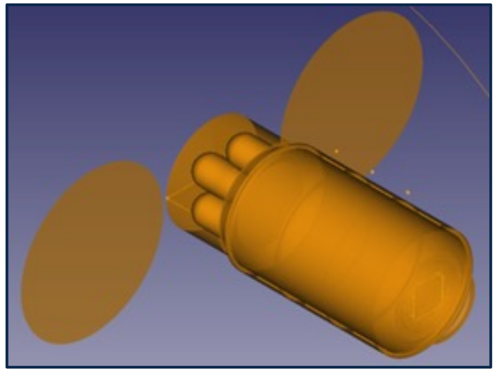
Realistic environment exposed to space radiation (Spacecraft, moon habitat) **SPACE / PLANET scale**	Simulation of absorbed dose in organs of human phantoms **BODY scale**	Simulation of early direct and non-direct DNA damage in these organs' cells **DNA scale**	Combination of the previous stages in a software user friendly application, to be included in Geant4

Stage #1: in space, on the Moon…

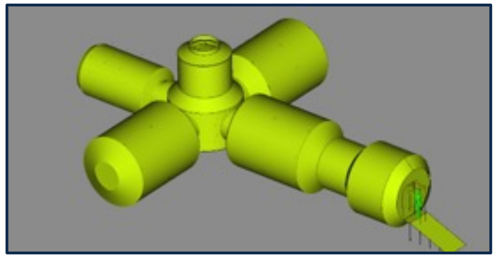
- First stage **tasks** (2025):
  1. **Implementation of two realistic habitats** in the GDML format in the **GORAD*** Geant4 advanced example:
     - **Spacecraft** : Orion from the NASA/ARTEMIS mission
     - **Lunar habitat** (on the ground) : ESA Moon habitat
     - In collaboration with
       - A. MANTERO, P. DONDERO, SWHARD SARL, **Italy**;
       - J. ARCHER, S. GUATELLI, J. M. C. BROWN, Wollongong & Swinburne U., **Australia**;
       - All are past collaborators of the BioRad3 ESA project 2021-2023 led by LP2i
  2. Simulation of **realistic incident spectra** – GCR & SPE - impacting the two habitats
     - Geant4 simulation of ion species transport and all their secondaries through the different materials of the geometries
- **Outcome**: realistic radiation field inside the habitat
- Expected duration: 6-9 months
- GORAD
  - GORAD (Geant4 Open-source Radiation Analysis and Design) was written as a turn-key application built on top of Geant4 by M. ASAI with a grant from NASA
  - https://geant4.web.cern.ch/docs/advanced_examples_doc/example_gorad



GORAD Orion NASA spacecraft



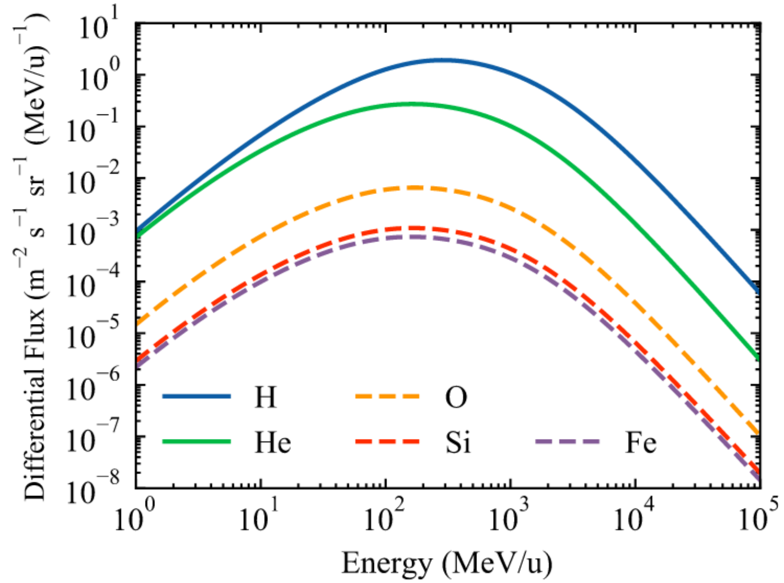
(ESA transfer module)



ESA Moon habitat

Exemple of radiation spectra

- Incident isotropic radiation
  - **GCR** : p and He are the dominant species
    - Spectra from Space Environment Information System (SPENVIS) at 1 AU from the Sun during the last solar minimum (12/01/2008) using the default ISO-15390 model (https://www.spenvis.oma.be)
  - **SPE** at solar minimum & maximum (e.g. 1956 & 1989)
- Case of Moon
  - Influence of soil
  - Secondary radiation field : **neutrons**, gamma rays, x–rays, electrons, positrons and light nuclear fragments



*Energy spectra of example **GCR** ions as derived from the ISO-15390 model of SPENVIS.*

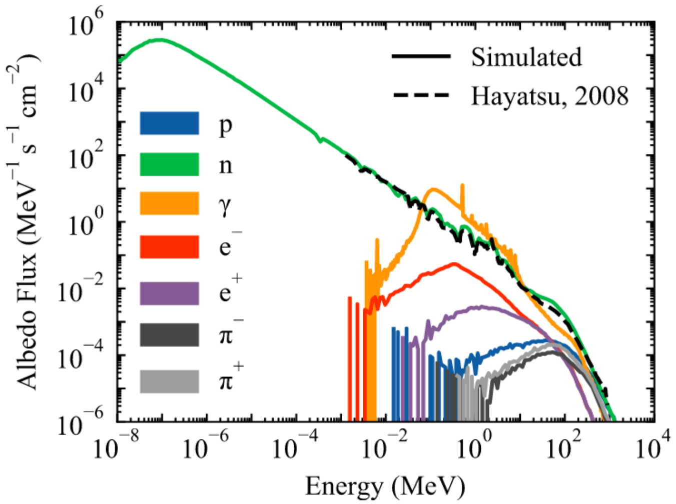
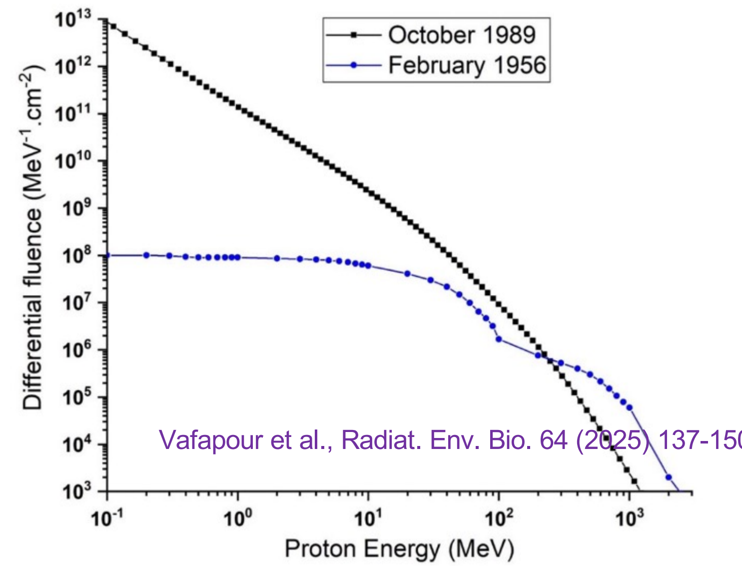


Table 1
The composition, density and thickness of the layers of the lunar volume as adapted from McKinney et al. (2006), Mesick et al. (2018).

	Layer 1	Layer 2	Layer 3	Layer 4
Start Depth (cm)	0	22	71	224
End Depth (cm)	22	71	224	1000
Density (g/cm^3)	1.76	2.11	1.78	1.79
O	0.41739	0.41557	0.42298	0.42636
Na	0.00292	0.00313	0.00307	0.00346
Mg	0.06162	0.06026	0.06156	0.06091
Al	0.06061	0.05977	0.07384	0.07598
Si	0.19026	0.18955	0.19668	0.20218
K (ppm)	726.24	789.65	920.11	1631.8
Ca	0.07541	0.07668	0.0802	0.07707
Ti	0.05144	0.04905	0.0338	0.03198
Cr	0.00287	0.00309	0.00264	0.00255
Mn	0.00176	0.00178	0.00152	0.00146
Fe	0.13496	0.1403	0.12277	0.11688
Sm (ppm)	8.3342	7.7459	7.3429	10.506
Eu (ppm)	1.8164	1.7821	1.5453	1.6997
Gd (ppm)	10.997	10.577	9.8178	13.547
Th (ppm)	0.9449	0.8022	1.3819	3.0065

***Albedo spectra** for incident GCR protons & Moon composition*



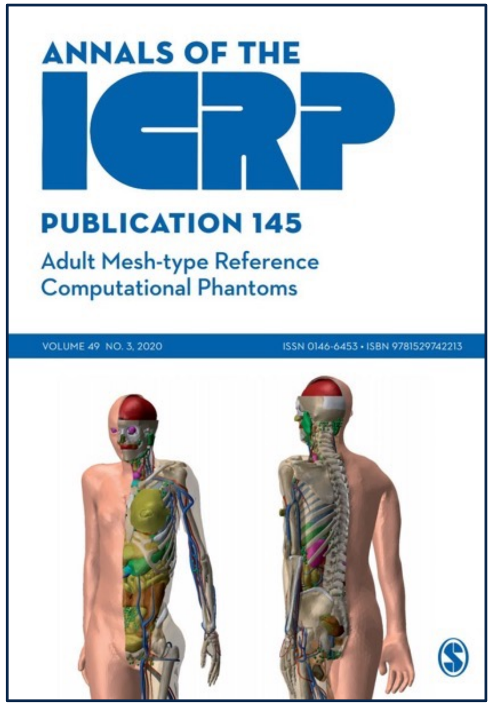
*October 1989 and February 1956 **SPE** energy spectra adapted from Atwell et al. (2011) and Townsend et al. (2018)*

Archer et al., Rad. Phys. Chem. 229 (2025) 112448

Stage #2: inside the habitat

- Second stage **tasks** (2025):
  1. Implement realistic **mesh-type human phantoms in both habitats** (spacecraft, lunar habitat)
     - State-of-the-art: **ICRP145 report**
     - Developed by Y. S. YEOM et al.
     - Available in Geant4 in the **ICRP145_HumanPhantoms** Geant4 advanced example
  2. **Score of the complex radiation fields** (including secondary particles) entering various organs of the phantom, for a complete coverage of the human body (male & female)
     1. **Absorbed dose** scoring at each organ level
     2. **Individual particles (including neutrons)** scoring in **micrometric/ cellular scale virtual volumes** placed in the different organs

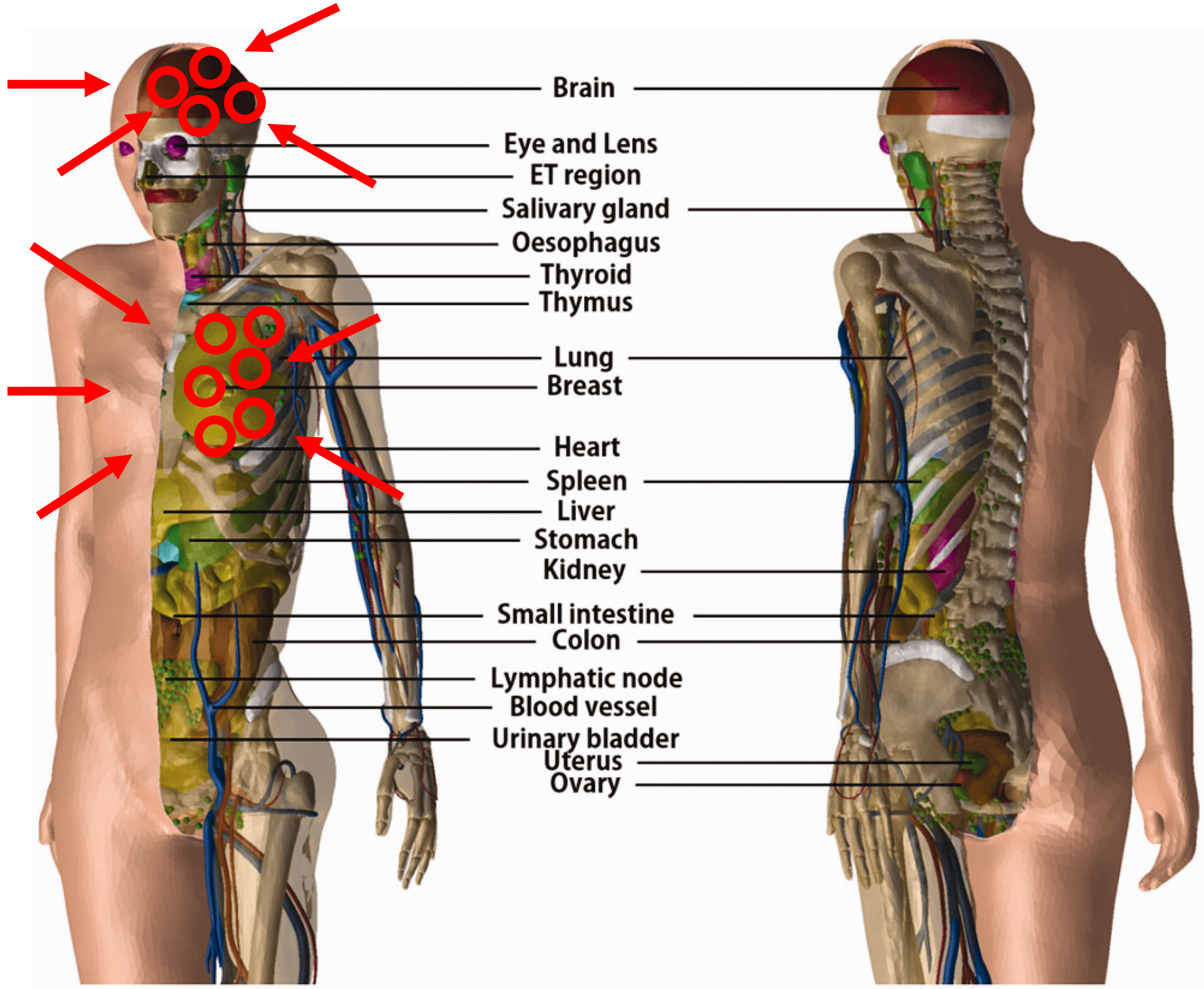
- **Outcome**: scoring of ionising radiation in organ volumes
- Expected duration: 6-9 months
- https://www.icrp.org/publication.asp?id=ICRP%20Publication%20145



https://www.icrp.org/page.asp?id=699

Example of phantom dosimetry

- From the resulting spectra of secondary particles (habitats), score
  - Particles entering **micrometric virtual volumes** of the geometry, in selected organs
    - Production of PSF files
  - Estimate **absorbed dose** at the organ level
- **Organs** of interest
  - Brain
  - Eyes
  - Breast…
- Testing **different phantoms**
  - Male / female
  - Standing up / sitting
  - Adult / children…

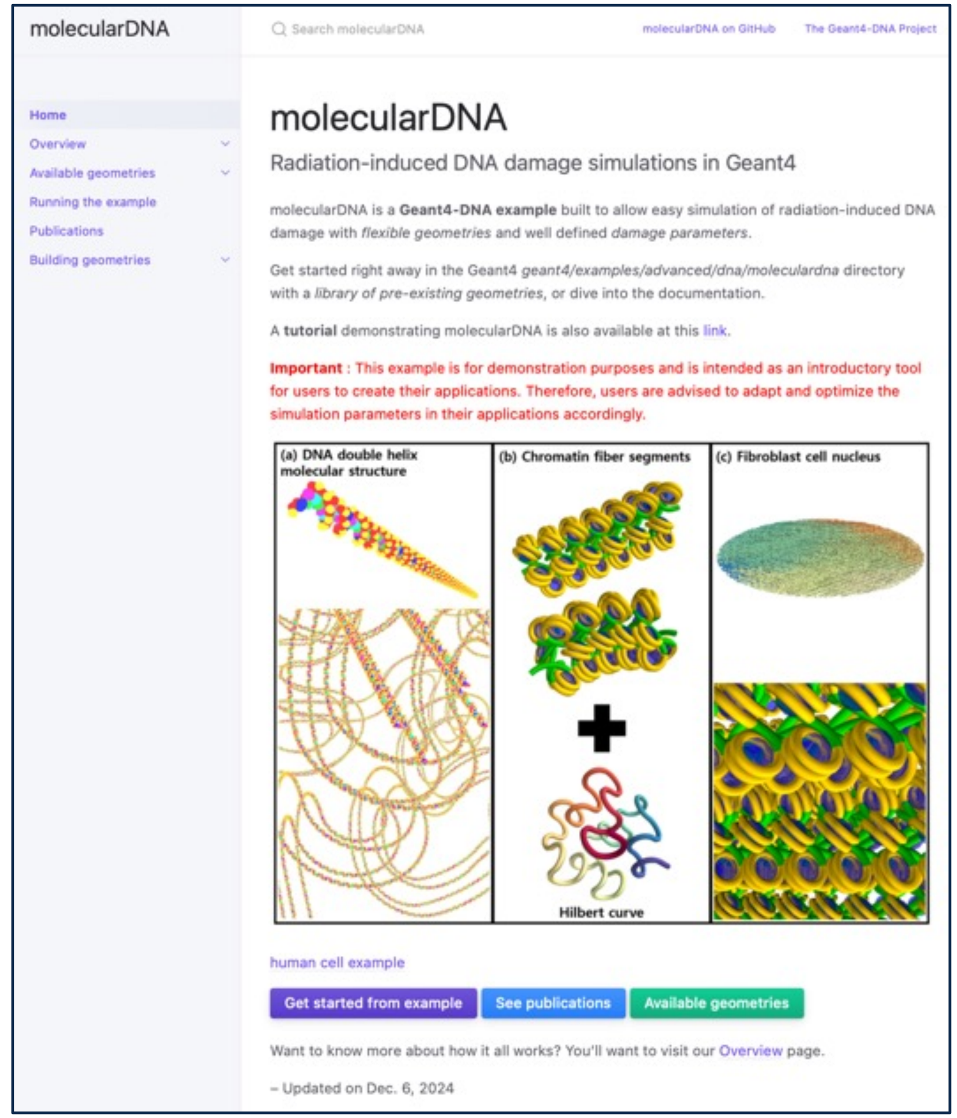


Mesh-type ICRP adult female reference phantom

https://journals.sagepub.com/doi/full/10.1177/0146645319893605

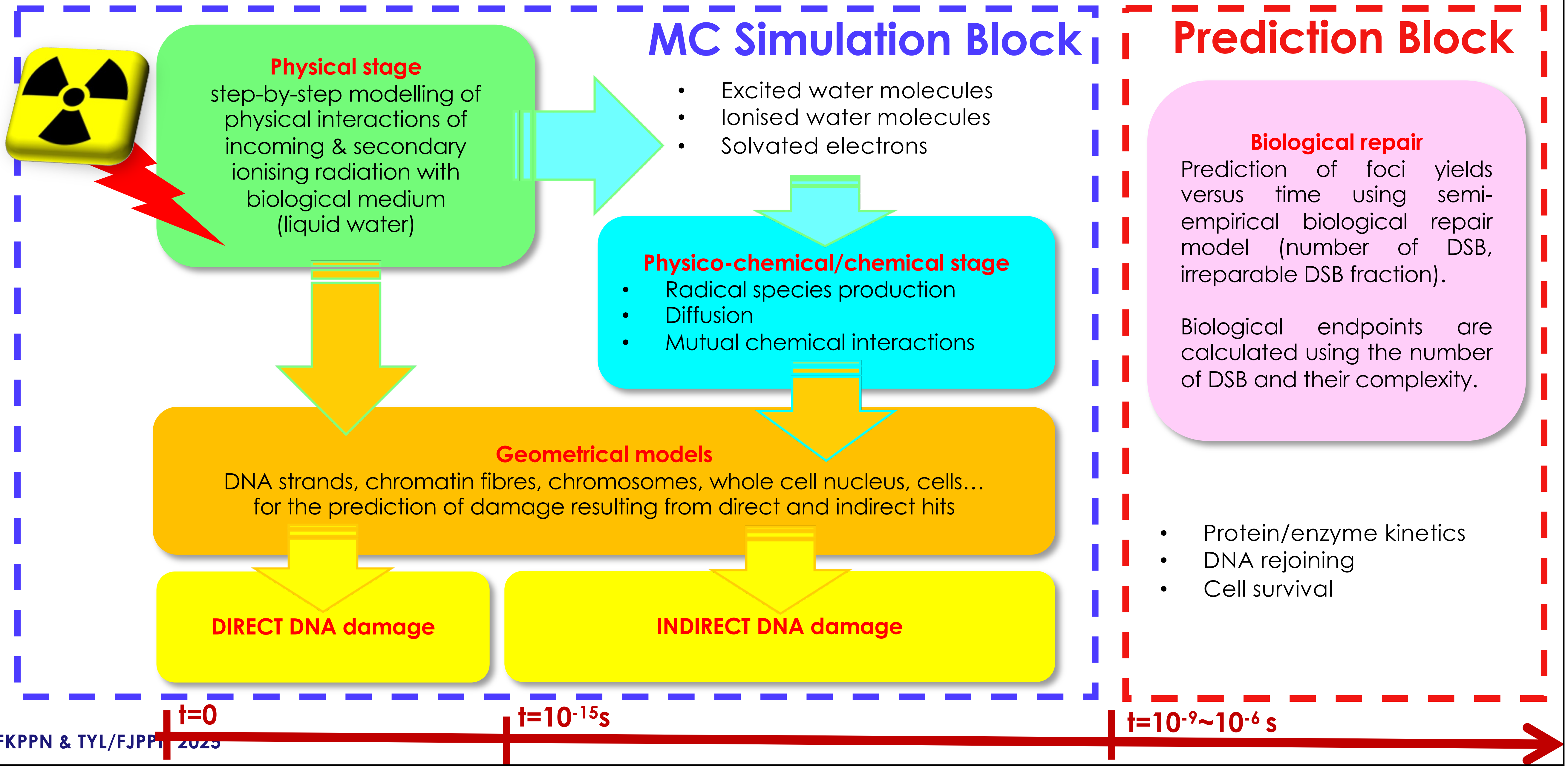
Stage #3: in phantom’s cells

- Third stage **tasks** (2026):
  1. Create a collection of **micrometric phase-space-files** (PSF) for each micrometric virtual volume in the different organs
  2. Implement **neutron interactions** in liquid water in Geant4-DNA simulations
  3. Use these PSF as **particle sources** in combination with the **molecularDNA** Geant4 advanced examples in order to predict direct (physics) and non-direct (chemistry) DNA damage induction
     - A step towards **RBE calculations** in such complex environments
- **Outcome**: early direct and non-direct DNA simple & complex damage in organs cells
- Expected duration: 6-9 months
- https://moleculardna.org



molecularDNA website

Damage to cells : the Geant4-DNA approach



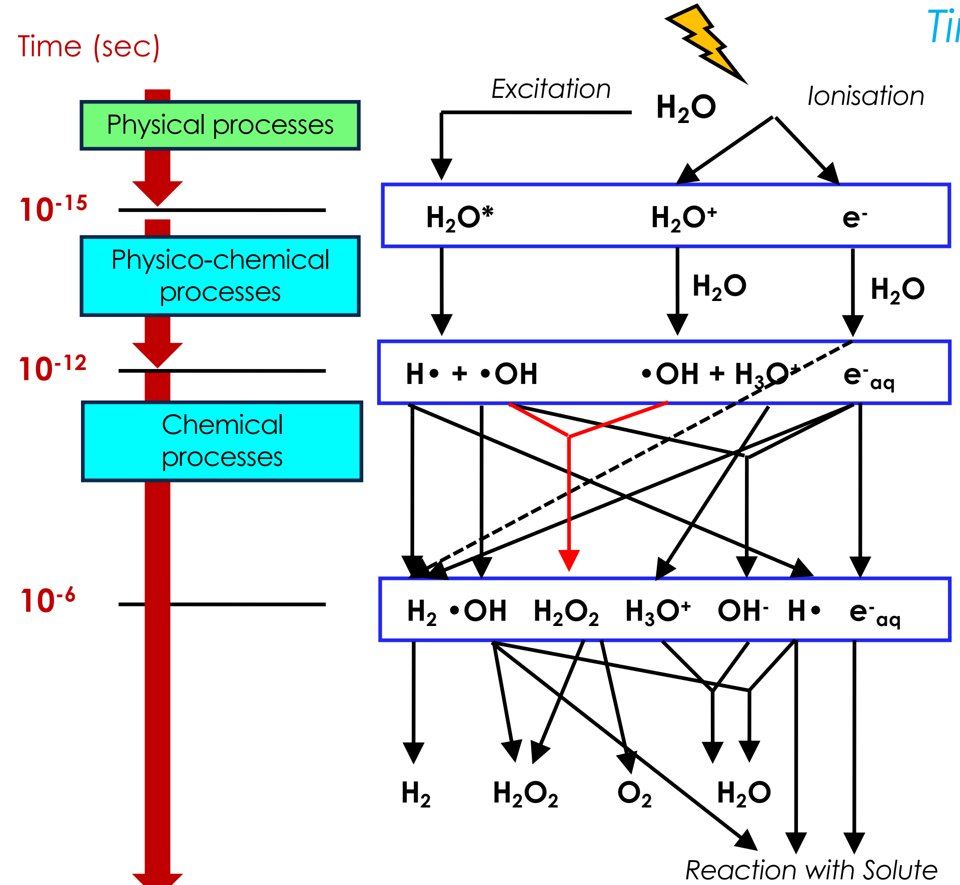
Geant4-DNA Physical stage

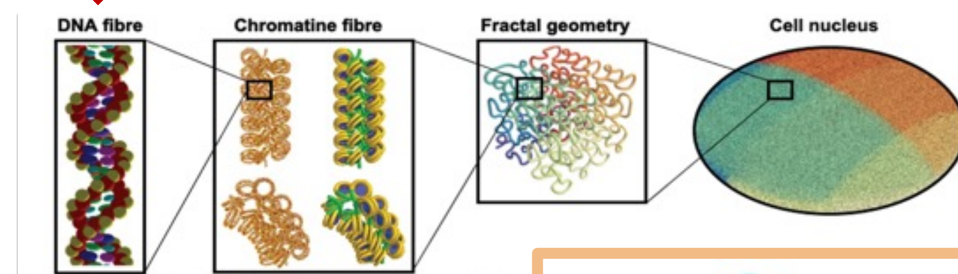
- Recommendation: use Geant4-DNA physics constructors
  - `G4EmDNAPhysics_option2`
  - `G4EmDNAPhysics_option4`
  - `G4EmDNAPhysics_option6`

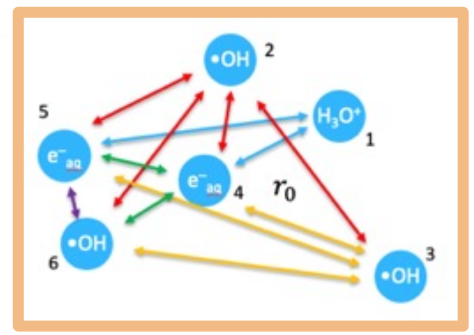
Geant4-DNA Chemical stage

- Independent Reaction Times (« IRT ») approach
  - From the 1980's by Clifford, Green et al., widely used today
  - Iterative process where the approximation of « independent pairs » is assumed: calculates the reaction times between all possible pairs of reactive species, as if they were isolated.
  - No longer necessary to diffuse the molecular species and to calculate the possible reactions between the species at each time step.
  - A « synchronous » alternative **hybrid version** (« **IRT-sync** ») **is used**: it gives all spatio-temporal info on radicals, as it is required to combine with the DNA geometries
    - E.g. a human cell nucleus containing **6.4 Gbp of DNA**

Timeline







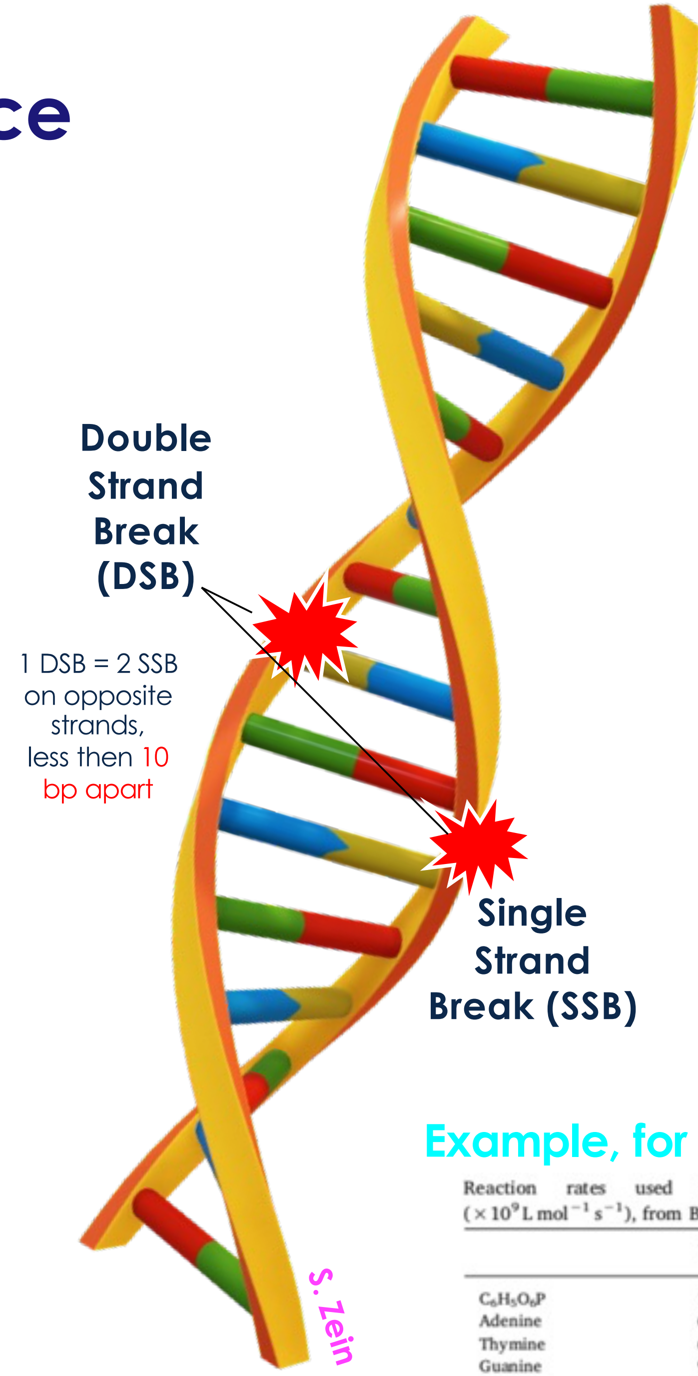
Principle of IRT

Geant4-DNA : parameter choice

Physics

DIRECT damage induction

1. **Choice of G4DNA physics constructor**
2. **Volume for energy deposition scoring in DNA backbone (D or P molecule)**
3. **Probability of Single Strand Break induction in DNA backbone**
   - Threshold, linear…

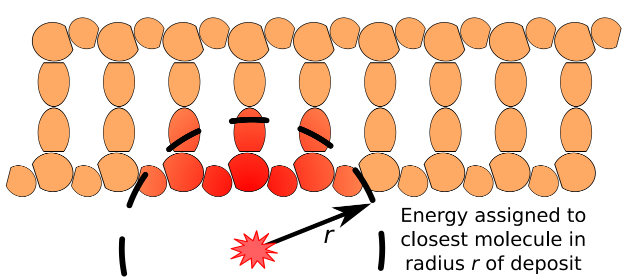


Chemistry

NON-DIRECT damage induction

1. **Choice of G4DNA chemistry constructor**
   - Including reactions with DNA components
2. **Probability of non-direct SSB induction**
   - •OH on DNA backbone : e.g. 40.5 %
3. **Distance from DNA to kill radicals (mimic scavenging in cells)**
4. **Histones considered as full scavengers (in cells)**
5. **Radiolysis maximum time steps**
6. **Chemical stage end time**

Example, for item 2:



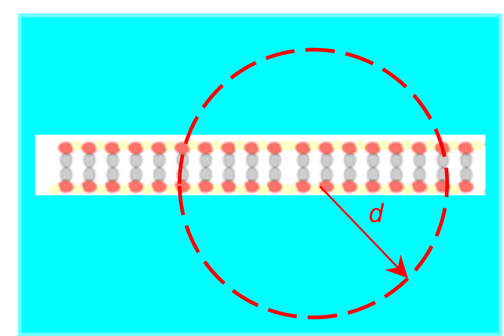
E.g. 6 A° for ~3 hydration shell

Example, for item 1:

Reaction rates used between radicals and DNA components ($\times 10^9$ L mol^{-1} s^{-1}), from Buxton et al. [65].

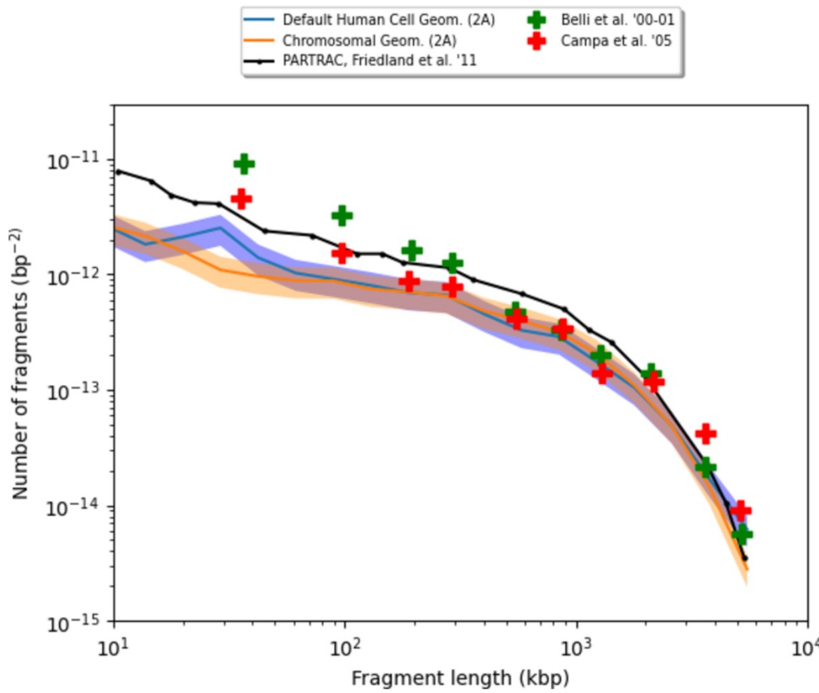
	$^{\cdot}$OH	H$^{\cdot}$	e^-_{aq}
$C_6H_5O_6P$	1.8	0.029	0.01
Adenine	6.1	0.10	9.0
Thymine	6.4	0.57	18.0
Guanine	9.2	–	14.0
Cytosine	6.1	0.092	13.0

Example, for item 3:



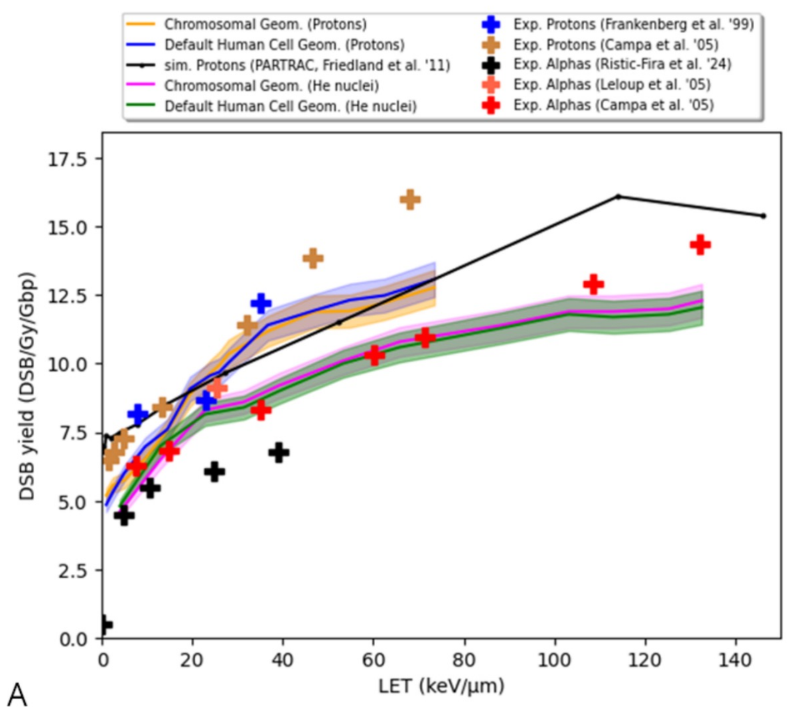
Examples of cell damage prediction using Geant4-DNA

DNA fragment size



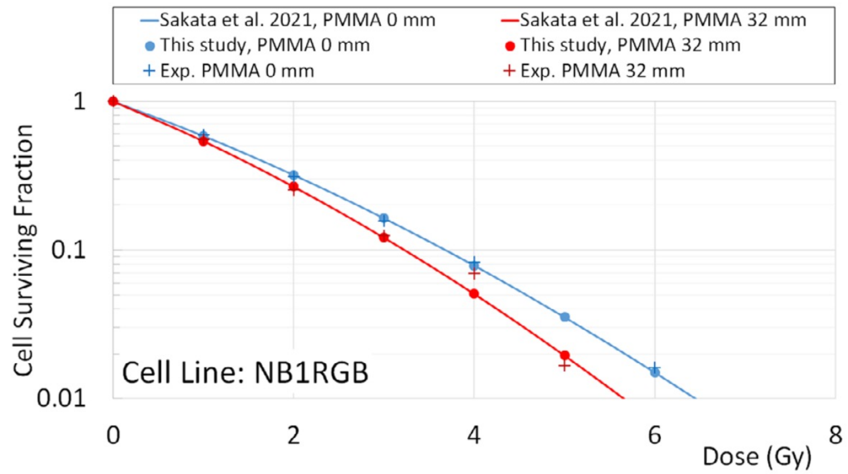
Histograms of the ***DNA fragment length frequency*** *distribution for* ***1 MeV incident protons****.*

DNA DSB vs LET



Quantification of ***DSB yields*** *for both the chromosomal and the default human cell models, irradiated by* ***protons and alphas*** *for several values of LET.*

Survival fraction vs dose



Survival fraction *of human fibroblast cells against absorbed dose, following irradiation by* ***70 keV protons****.*

Chatzipapas et al., Phys. Med. 127 (2024) 104389
Chatzipapas et al., Prec. Radiat. Oncol. 7 (2023) 4-14

Stage #4: combination of stages

- Fourth **stage** (2026, …):
  - **Combine the three above stages in a user-friendly application** that does not require (or reduces to a minimum) C++ coding
    - Sequence
      1. Implementation of a GDML habitat (spacecraft, Moon)
      2. Placement of a human phantom in the habitat
      3. Irradiation of the habitat and scoring of doses and particles in organs
      4. Prediction of early DNA damage
    - This application could be proposed as a new Geant4 example
    - Will serve as a base example for **other application domains**
      - Medical physics treatment rooms, environmental applications…
      - Combining **"GDML geometries + realistic phantoms + DNA damage"**
- **Outcome**: platform & software released in Geant4
- Expected duration: 6 months

An interdisciplinary project & team

- The consortium gathers experts in Geant4 and Geant4-DNA development and applications, and experts in radiation protection & medical physics.
  - **Geant4 & Geant4-DNA core development**
    - M. ASAI (former spokesperson of Geant4)
    - S. INCERTI (spokesperson of Geant4-DNA)
    - H. TRAN (TC of Geant4-DNA)
    - Y. S. YEOM (ICRP phantom expert)
  - **Geant4 & Geant4-DNA application**
    - Same
    - C. H. CHOI (Med. Phys.)
    - S. B. LEE (Med. Phys.)
  - **Radiation protection and medical Physics**
    - C. CHOI (Med. Phys.)
    - S. B. LEE (Med. Phys.)

Collaborator	Stage #1 (6-9 months)	Stage #2 (6 -9 months)	Stage #3 (6-9 months)	Stage #4 (6 months)
M. ASAI	X			X
C. H. CHOI		X	X	X
J. W. CHOI	X	X	X	X
S. INCERTI	X	X	X	X
S. B. LEE		X	X	X
H. TRAN	X	X	X	X
Y. S. YEOM	X	X	X	X
Postdoc	X	X	X	X

- **Past history** of collaboration
  - PHC-STAR 2023-2024 SNU-LP2i
  - PHC-STAR 2012-2013 NCC-LP2i-LPCA
  - FKPPL over the 2009-2019 period ("protontherapy" project)
  - 11 co-publications, 1 co-tutelle PhD between Bordeaux U. & Yonsei U. (W. G. SHIN)

Open science & outreach

- Boost the visibility & usage of Geant4 in Korea
  - All software available in open access in Geant4 after publication
    - equal access, reproducibility of results
- Opportunities
  - **Geant4 & Geant4-DNA international tutorials**
    - Last one in **February 2025** at the **Pohang Accelerator Laboratory**
    - One per year or every two years ?
    - Nice occastion to showcase the multiscale simulation platform (lecures & hands-on)
  - Series of conferences **« International Geant4 User Conference at the Physics – Medicine – Biology Frontier »**
    - **2028: first time in Seoul, Korea ?**
    - 2026: Melbourne, Australia (tba)
    - 2024: Osaka, Japan
    - 2022: Napoli, Italy
    - 2018, Bordeaux, France
    - 2013: Bordeaux, France
    - 2005: Bordeaux, France

Geant4 & Geant4-DNA tutorial, Pohang Accelerator Laboratory, 2025

Budget request

- From **Korea** side
  - 2 one-week trips to Bordeaux: 9000 kWon to **Yonsei U.** (Y. S. YEOM, J. W. CHOI)
  - 1 one-week trip to Bordeaux: 4500 kWon to **Seoul National U.** (C. H. CHOI)
  - 1 one-week trip to Bordeaux: 4500 kWon to **National Cancer Center** (S. B. LEE)

- From **France** side
  - 2 one-week trips to Seoul: 6000 euros to **IN2P3** (H. TRAN, S. INCERTI)

- Additional support (confirmed)
  - **PhD student** @ Yonsei University: **Ms Ji Won CHOI**
    - **Secured a grant for a 6-month stay in France at LP2i in 2026**
  - **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
  - Meeting with Dr Makoto Asai (Jefferson Lab., US) expected **this autumn at the annual Geant4 CM (US)**

References

- Key software components
  - https://geant4.org
  - https://geant4-dna.org
  - Applications
    - GORAD: https://geant4.web.cern.ch/docs/advanced_examples_doc/example_gorad
    - ICRP145: https://www.icrp.org/publication.asp?id=ICRP%20Publication%20145
    - molecularDNA: https://moleculardna.org

- We recently co-authored a simulation **feasibility study** for the Moon (Wollongong U.)
  - Archer et al., Rad. Phys. Chem. 229 (2025) 112448 (link)
  - Colleagues will be invited to join this project as collaborators

Thank you very much !

정말 감사합니다 !