Geant4-DNA, Ultra-High Dose Rate & FLASH-RT

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INFN-LNS

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Roadmap

- A simple introduction to **water radiolysis, FLASH-RT.**

- Overview of Geant4-DNA
  - Radiobiology
  - Simulation toolkit
- UHDR example
- FLASH Radiation Therapy

Part I/1: Radiobiology &Geant4-DNA

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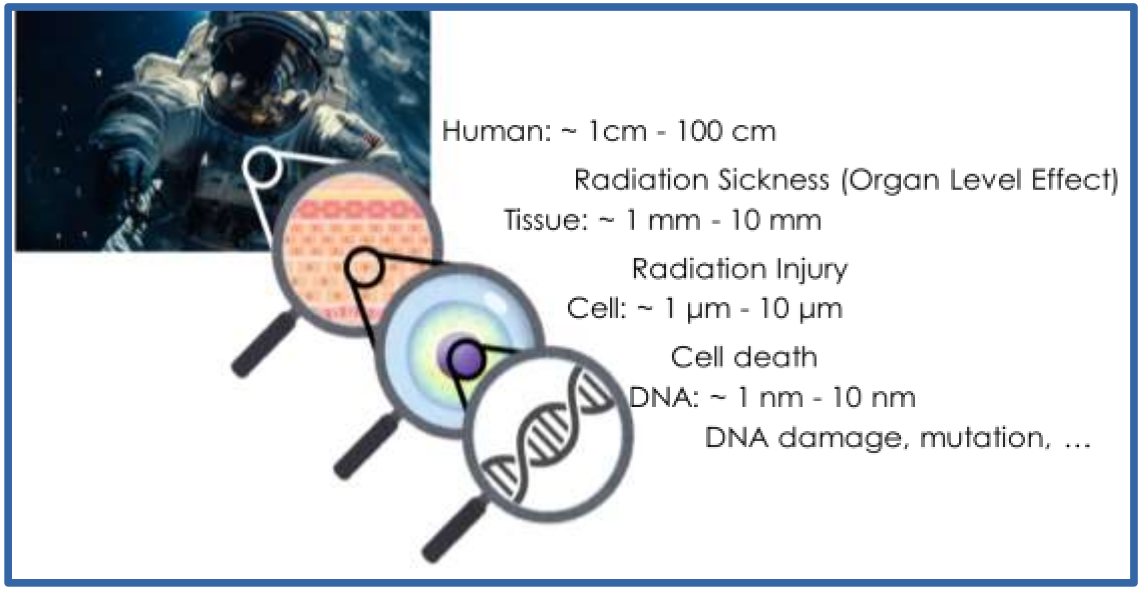
Radiobiology

- **Radiobiology** is a branch of science that connects the basic principles of **radiation physics with biology**.
- **Radiobiology** is related to the effects of radiation on biological tissues.
- **Radiobiological** mechanisms focuses on the biological effects produced by energy absorption in small volumes (microscopic scale).

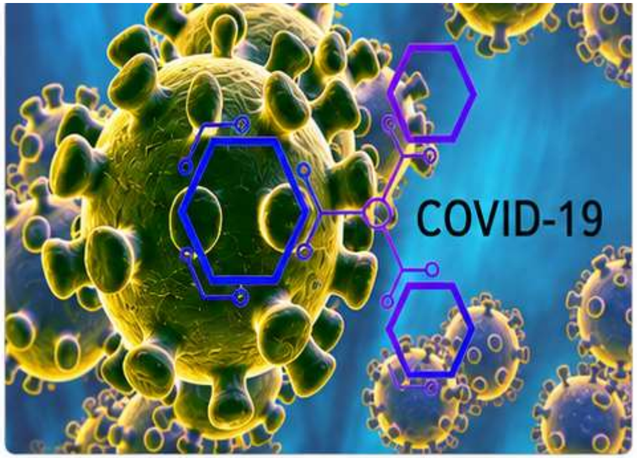


Radiobiology helps answer:

- where energy of radiation is deposited,
- what changes inside cells after irradiation
- how treatment can be made safer and more effective?

Applications of Radiobiology

From microorganisms to radiation protection and space environments and medical field



Microorganism inactivation

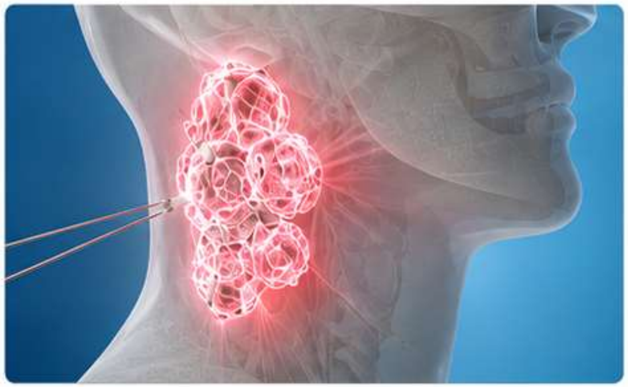
Study viral/bacterial response to ionizing radiation

Sterilization

Medical tools and materials can be sterilized by radiation

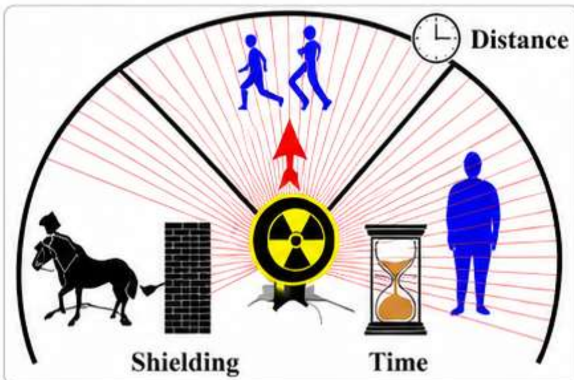
Food irradiation

Reduce microorganisms and extend shelf life



Radiation Therapy and Cell Biology

Understand cell response to radiation for better treatment outcomes



Radiation protection physics

Use principles of shielding, distance and time to reduce radiation exposure

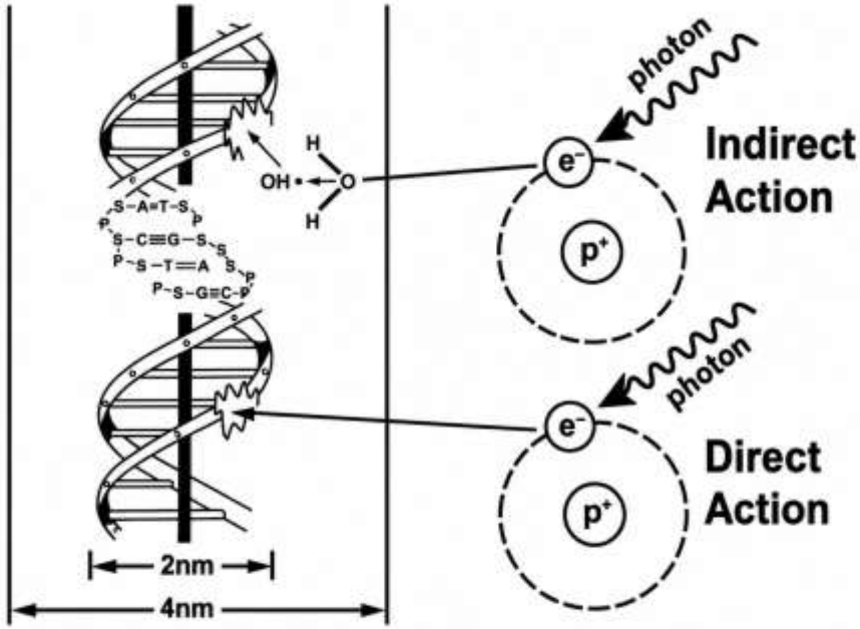
Space missions

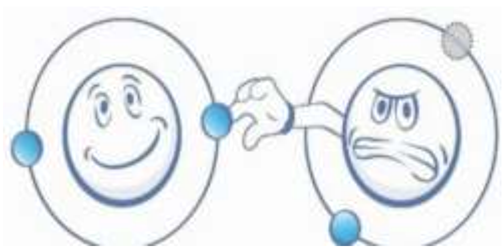
Study effects of cosmic radiation on astronauts and equipment

What happens when cells are irradiated?

Direct and indirect action

Radiation may hit DNA directly, or act through radicals made in





Free radicals can start chain reactions.

Water radiolysis

Energy absorbed in water produces reactive species such as e_{aq}^-, OH• and

$$H_2O \xrightarrow{h\nu} H_2O^+ + e^- \rightarrow H_2O^+ + e^-_{aq}$$

$$H_2O^+ \rightarrow OH^\bullet + H^+$$

$$H_2O \xrightarrow{h\nu} H_2O^* \rightarrow H^\bullet + OH^\bullet$$

Chemical stage: water radiolysis forms short-lived reactive species.

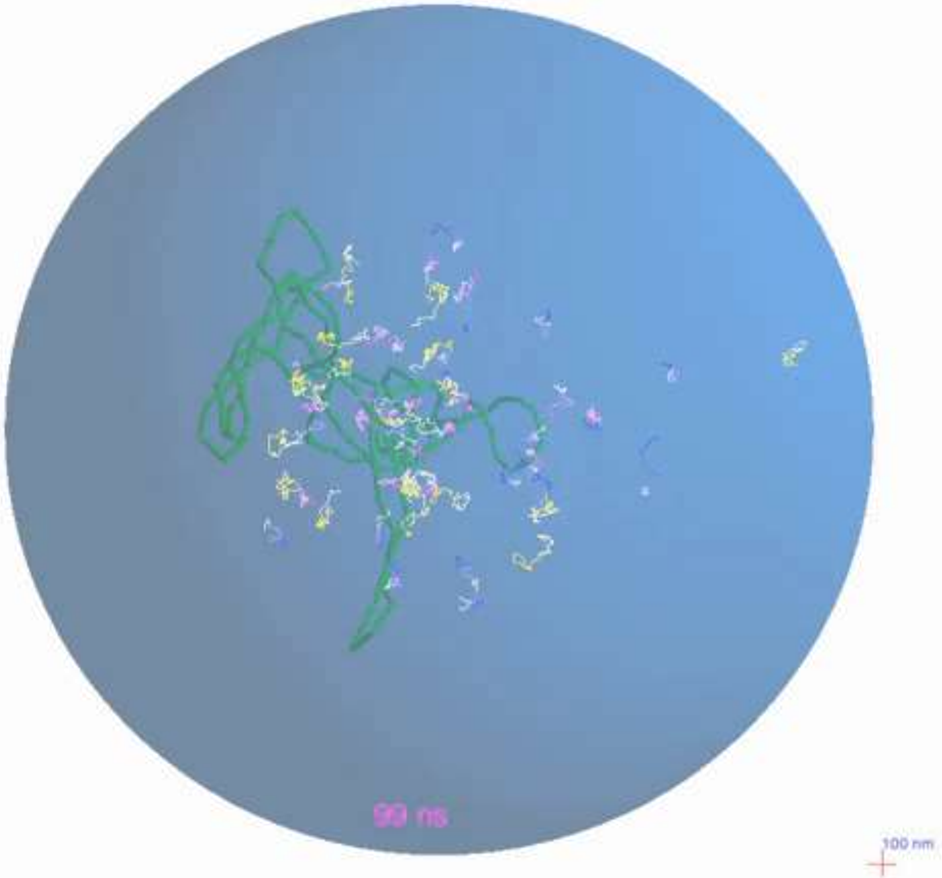
Oxygen effect:
dissolved O_2 changes radical pathways, e.g.
$H^\bullet + O_2 \rightarrow HO_2^\bullet$

Simple sequence of simulation:
radiation track → radicals → molecular damage → cellular response

Part I/2: Geant4-DNA simulation

Geant4-DNA

Modeling of biological damage induced by radiation at the DNA scale.



Radiation first creates reactive radicals in water, and then radicals diffuse toward the plasmid DNA and may damage it.

Irradiation of a **pBR322 plasmid**, including radiolysis

Why Geant4-DNA?

A Monte Carlo toolkit for **microscopic radiation biology**

Limits of standard Geant4 for radiobiology

- Uses a **condensed-history** approach for many charged-particle interactions.
- Has **low-energy limits** in common EM models: Livermore ≈ 250 eV; Penelope ≈ 100 eV.
- Does **NOT** explicitly describe target details such as **liquid water chemistry or DNA components**.
- **Does not cover the chemical reaction stage** after energy deposition.

Geant4-DNA for radiobiology

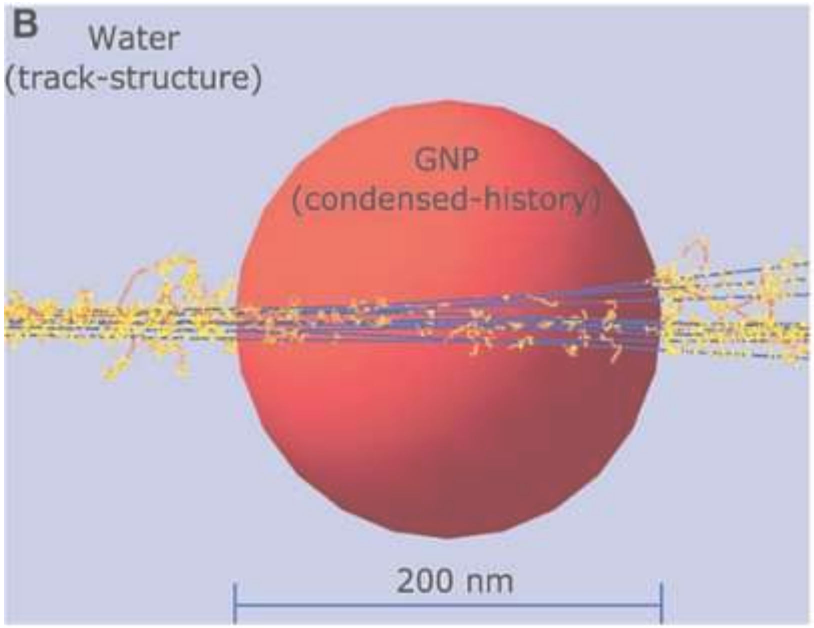
- **G4-DNA** was introduced in 2007 as a Geant4 extension for very **low-energy particle transport**.
- It provides detailed **physics models** (**Track structure** approach) for electrons, protons, hydrogen and helium in **liquid water**.
- It follows particle interactions at the eV and **nanometer scale**, making it useful for radiobiology and DNA-damage studies.

SO Geant4-DNA extends Geant4 from macroscopic dose calculation toward microscopic mechanisms of radiation damage.

Geant4-DNA: TS Monte Carlo

What is different between **track-structure (TS)** codes and **condensed-history (CH)** codes

CH *can be used inside* ***large objects****, while* ***TS*** *follows* ***detailed tracks in microscopic media*** *such as water.*



Track structure (TS) / Geant4-DNA

- Simulates individual physical interactions
- Slower, but much more detailed
- Gives nanometer-scale energy deposition
- Needed to connect radiation tracks to chemical and biological damage

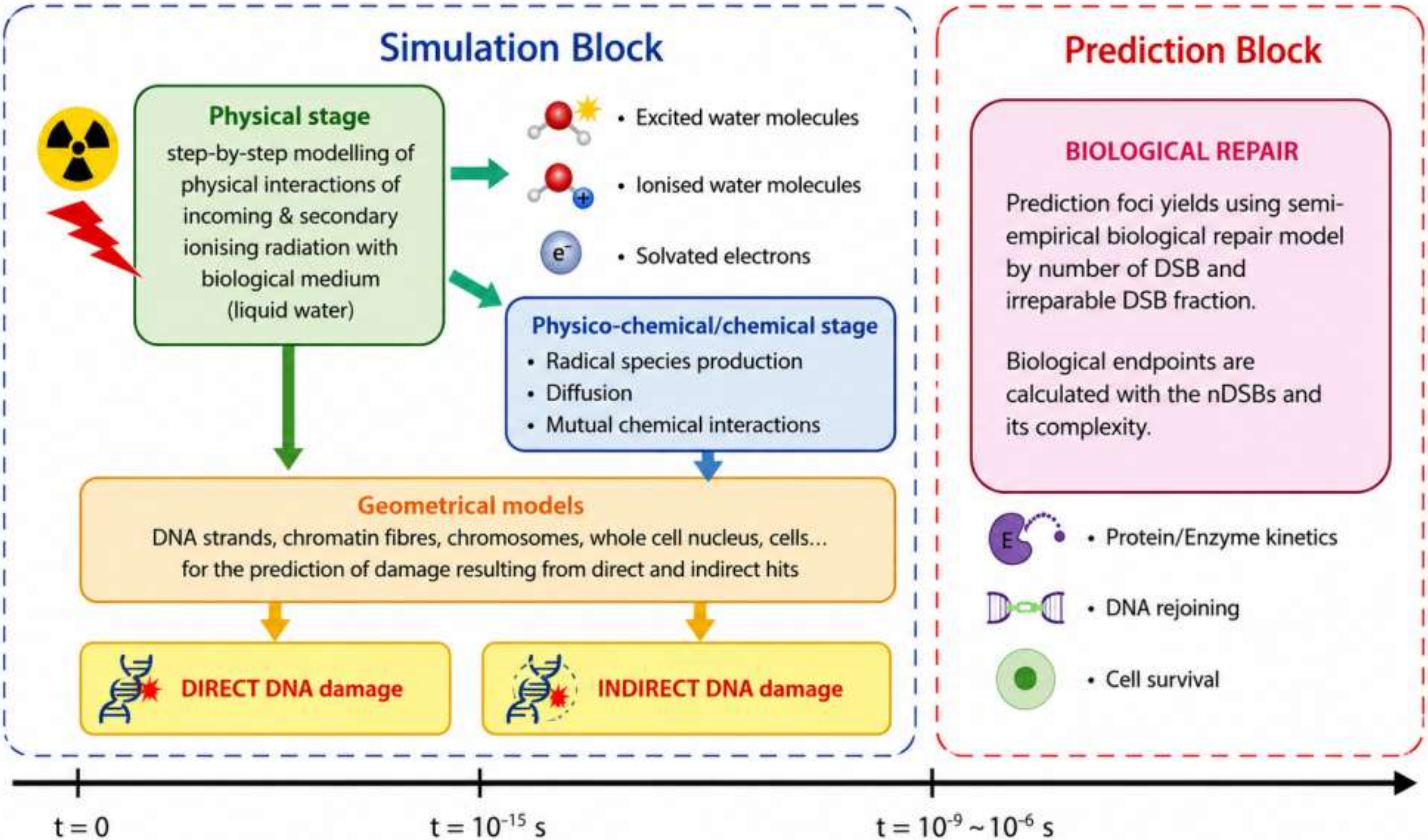
Condensed history (CH)

- Groups many interactions into one step
- Faster, good for macroscopic dose
- Uses stopping power + multiple scattering
- Less spatial detail at very small scales

CH answers "**where is the dose?**"; **TS** helps answer "**how radiation damage starts at molecular scale**"

Geant4-DNA implementation

A simple view of the physics, chemistry, geometry,



Processes in the Chemical Stage

CHEMICAL SPECIES

DIFFUSION

Species	Diffusion coefficient D (10^{-9} m^2 s^{-1})
H_3O^+	9.0
$H\bullet$	7.0
OH^-	5.0
e^-_{aq}	4.9
H_2	5.0
$\bullet OH$	2.8
H_2O_2	1.4

REACTIONS

REACTION BUILDERS

G4-DNA uses Reaction builders to define reaction lists for different applications.

ChemNO2_NO3ScavengerBuilder

→ Build reaction list with NO_2^-/NO_3^-

ChemPureWaterBuilder

→ Build the reaction list with pH

ChemOxygenWaterBuilder

→ Build the reaction list with ROS

ChemFrickeReactionBuilder

→ Build the reaction list of Fricke dosimeter

Builders define which species with which reaction rate can react

Chemistry Models

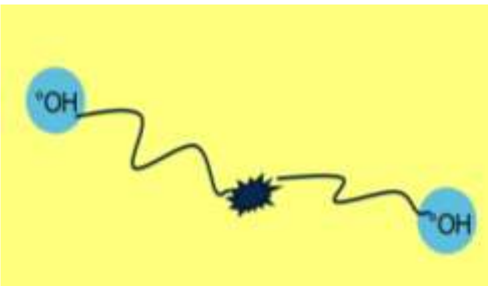
Geant4-DNA chemical stage: from step-by-step reactions to mesoscopic kinetics

SBS model

Step-by-step diffusion-controlled reactions

Core idea:

- At each step, the separation distance **d** for every reactant pair is checked.
- Two species react when **d** is smaller than the reaction radius **R**.
- Brownian-bridge correction compensates for possible missed reactions.



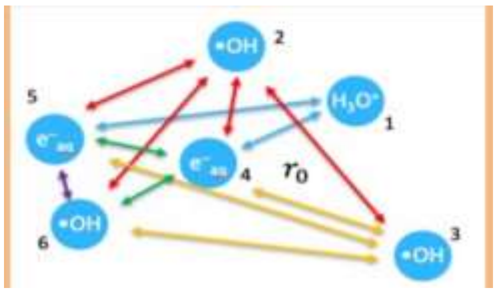
Ref: Karamitros et al., JCP 2014

IRT model

Independent reaction-time method

Core idea:

- Build an event table from initial species positions and probabilistic reaction times.
- Sort reactions in ascending reaction-time order, then process them.
- Sample product positions randomly within a sphere centered at the reaction site.



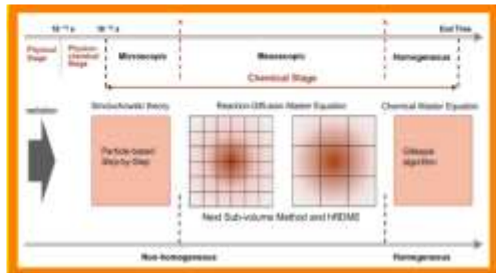
Refs: Karamitros et al., arXiv 2020; Ramos-Méndez et al., MP 2020

SBS/IRT+ mesoscopic model

Hybrid microscopic + mesoscopic approach

Core idea:

- Combines the microscopic model with mesoscopic compartment-based RDME model.
- Designed for larger spatial scales and longer chemical evolution.
- On-lattice stochastic chemistry beyond the microscopic regime.



Ref: Tran et al., IJMS 2021

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Geant4-DNA chemistry examples

Example	Main purpose	Method / feature
chem1	Activates the simulation of water radiolysis.	Step-by-step chemistry
chem2	Sets minimum time-step limits on water radiolysis.	Step-by-step chemistry time-step control
chem3	Implements user actions in the chemistry module.	Step-by-step chemistry custom user actions
chem4	Computes radiochemical yields (G values) versus time.	Step-by-step chemistry ROOT graphical interface
chem5	Computes G values versus time using alternative physics and chemistry lists.	Step-by-step chemistry physics/chemistry list comparison
chem6	Computes G values versus time and LET.	IRT method LET scoring
scavenger	Simulates scavenging with an easy-to-use interface.	IRT method scavenger concentration studies
UHDR	Activates the chemistry mesoscopic model to simulate reactions beyond 1 µs post-irradiation.	FLASH / UHDR chemistry mesoscopic approach

Progression: step-by-step water radiolysis → G-value scoring → IRT scavenging → UHDR / FLASH chemistry.

Part II: UHDR example

UHDR Example

Tran, H. N. et al. (2021), IJMS 22(11), 6023. DOI: 10.3390/ijms22116023

Simulation setup and chemistry controls

Core UHDR features

- ✓ World volume: water box with two optimized dimensions
- ✓ Mesoscopic approach implemented with SBS/IRT-RDME
- ✓ Time structure activated by implementing a delayed time
- ✓ Scavenger molecules and pH included
- ✓ Beam stops automatically by setting dose cut off
- ✓ Each event can contain multiple incident particles

Scoring output

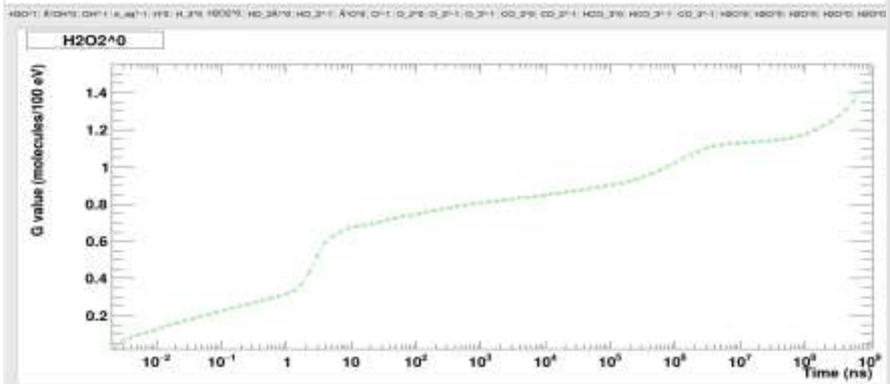
Radiochemical yield G

scoring G as a function of time:

$$G = \frac{\text{Number of species X}}{\text{100 eV of deposited energy}}$$

Example output plot

Chemical evolution vs. time



G-value curve reaches the post-irradiation over microsecond region.

UHDR chemistry connects deposited energy and pulse timing to time-dependent radical yields

Useful for comparing **conventional irradiation** with **ultra-high dose-rate** pulse structures for **FLASH RT**

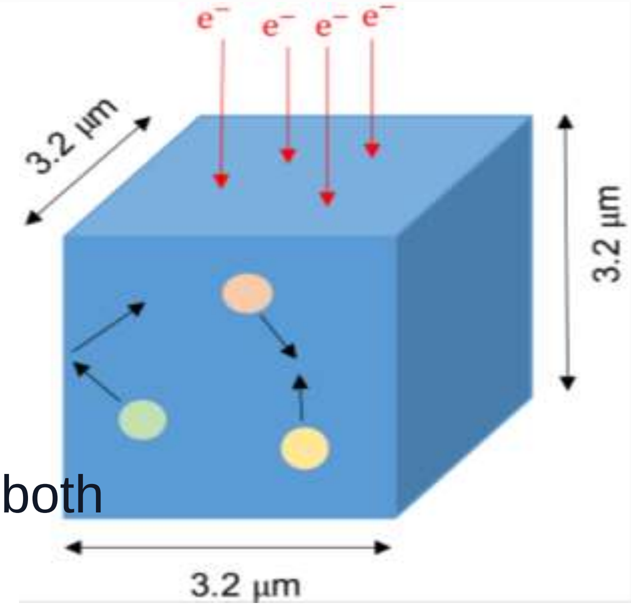
UHDR- Geometry

$1.6 \times 1.6 \times 1.6\ \mu m^3$

UHDR

$3.2 \times 3.2 \times 3.2\ \mu m^3$

CONV



- Chemical species diffuse and react in a bounded volume meaning diffusion is limited by geometrical boundaries.
- The bouncing at the volume borders is applied in both microscopic and mesoscopice sub-stages.

Represents a closed system of test cells for in vitro measurements.

```
# Set the simulation volume (half Side Length)
#/UHDR/env/volume 0.8 um # for UHDR
/UHDR/env/volume 1.6 um # for CONV
```

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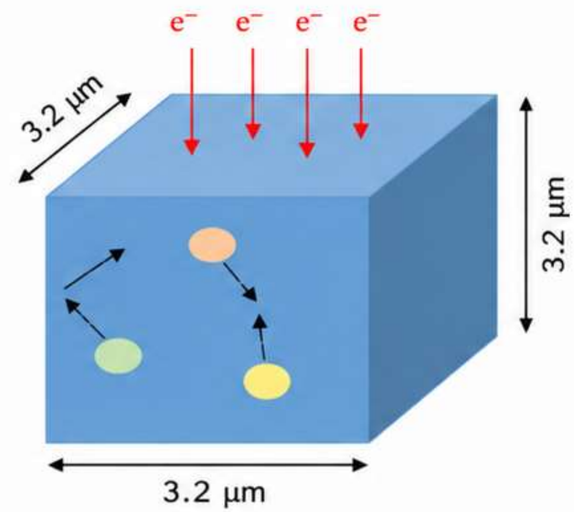
UHDR- Particle source

Modeling of ultra-high dose rate (UHDR) electron beams:

- Default source: 1 MeV electron beam
- Instantaneous pulse:
  - Each event consists of multiple incident particles shot at the same time.
  - All species are produced simultaneously at 1 ps.



- Cut-off dose: Primary particles are shoot until the sum of all energy deposits in the volume reaches a given absorbed dose:
  - 0.01 Gy is considered for conventional irradiation
  - 1-10 Gy is considered for UHDR irradiation

Modalities	Volume (μm^3)	Dose rate (Gy/pulse)	Incident electrons (tracks)	Deposited energy (keV)
CONV	3.2 × 3.2 × 3.2	0.0109812	6	2.246
UHDR	1.6 × 1.6 × 1.6	1.00273	110	25.637
		5.01636	562	128.254
		10.0076	1063	255.866

beam.in macro

UHDR example provides **user interface** to **control** the simulation:

- Irradiated geometries
- Pulse structure
- pH control
- Oxygen concentration
- Cut-off dose

```
#/run/numberOfThreads 10
/process/dna/e-SolvationSubType Meesungnoen2002
#/process/dna/e-SolvationSubType Ritchie1994
#/process/dna/e-SolvationSubType Terrisol1990

# Set the simulation volume (half Side Length)
#/UHDR/env/volume 0.8 um # for UHDR
/UHDR/env/volume 1.6 um # for CONV

/run/initialize

# time structure
/UHDR/pulse/pulseOn true
# push structure file
/UHDR/pulse/pulseFile 1.4us

# pulse structure
/UHDR/pulse/multiPulse false
#/UHDR/pulse/pulsePeriod 2 s
#/UHDR/pulse/numberOfPulse 2
#/UHDR/pulse/pulseInHisto pulseHisto.txt

# pH and Scavenger
/UHDR/env/pH 5.5

# Oxygen concentration
/UHDR/env/scavenger O2 19 %

/chem/reaction/print

#/run/verbose 1
/tracking/verbose 0
/scheduler/verbose 0
/scheduler/endTime 1 ms

# set false if many beamOn in medium
/scheduler/ResetScavengerForEachBeamOn true

/scorer/6values/nOfTimeBins 80

/run/printProgress 10

/scorer/Dose/cutoff 0.01 Gy
/UHDR/source/particle e-
/UHDR/source/energy 0.999 MeV
/run/beamOn 2
```

Irradiated geometries
Pulse structure
pH control
oxygen control
Cut-off Dose

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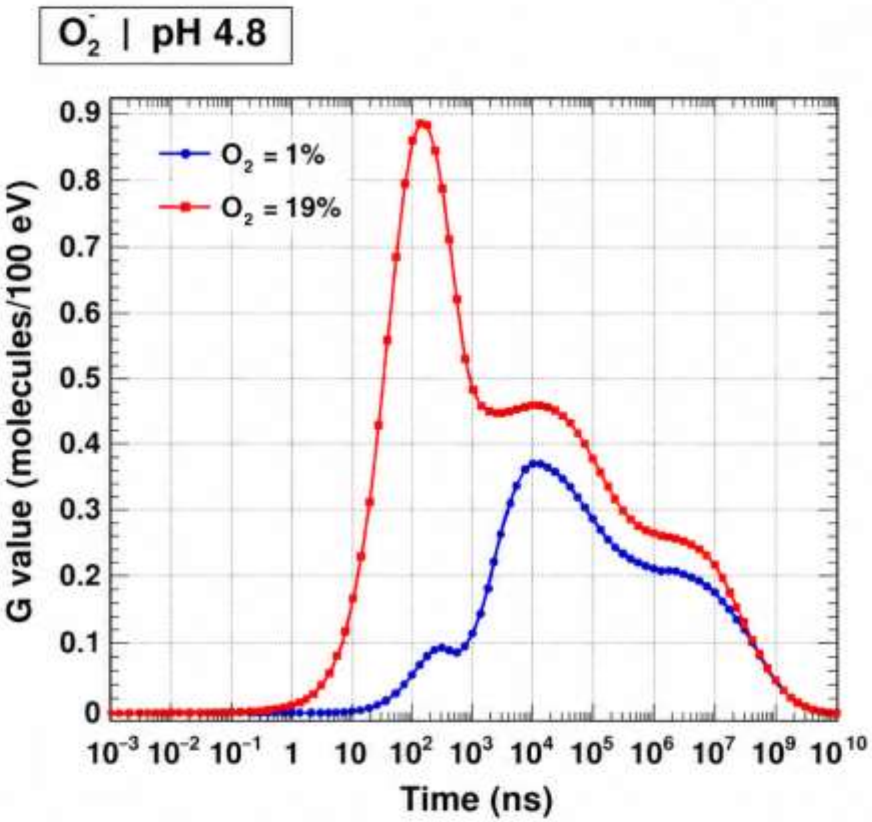
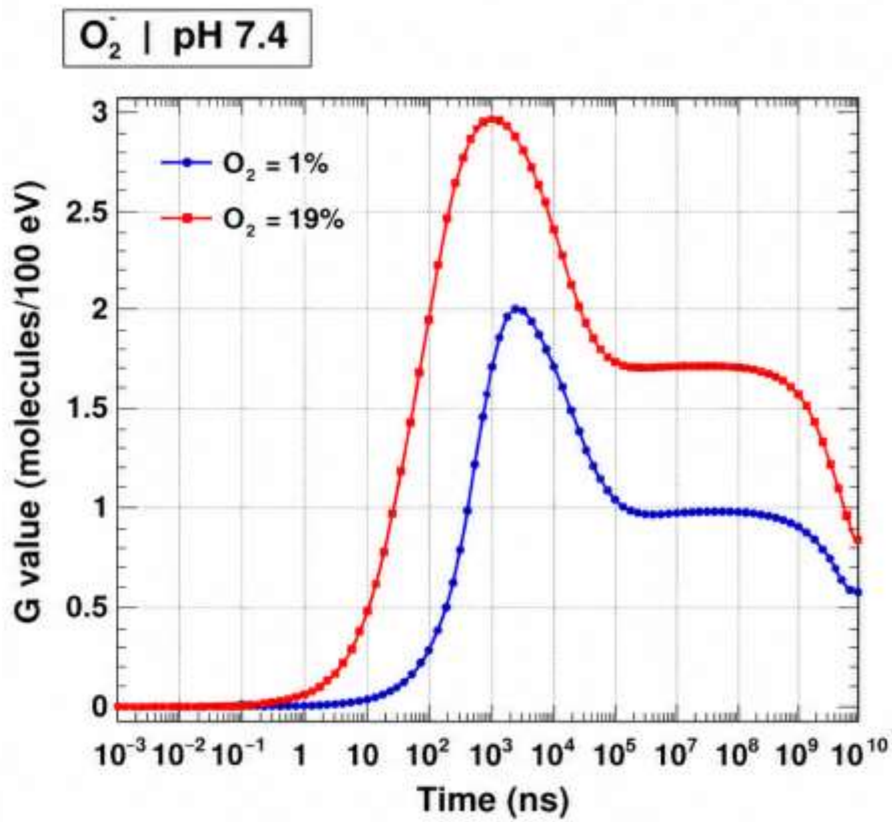
Output- G-values vs time for different pH





Time-dependent G-values of the chemical species for two different oxygen concentrations and different pH

Part II: FLASH Radiation Therapy

Introduction

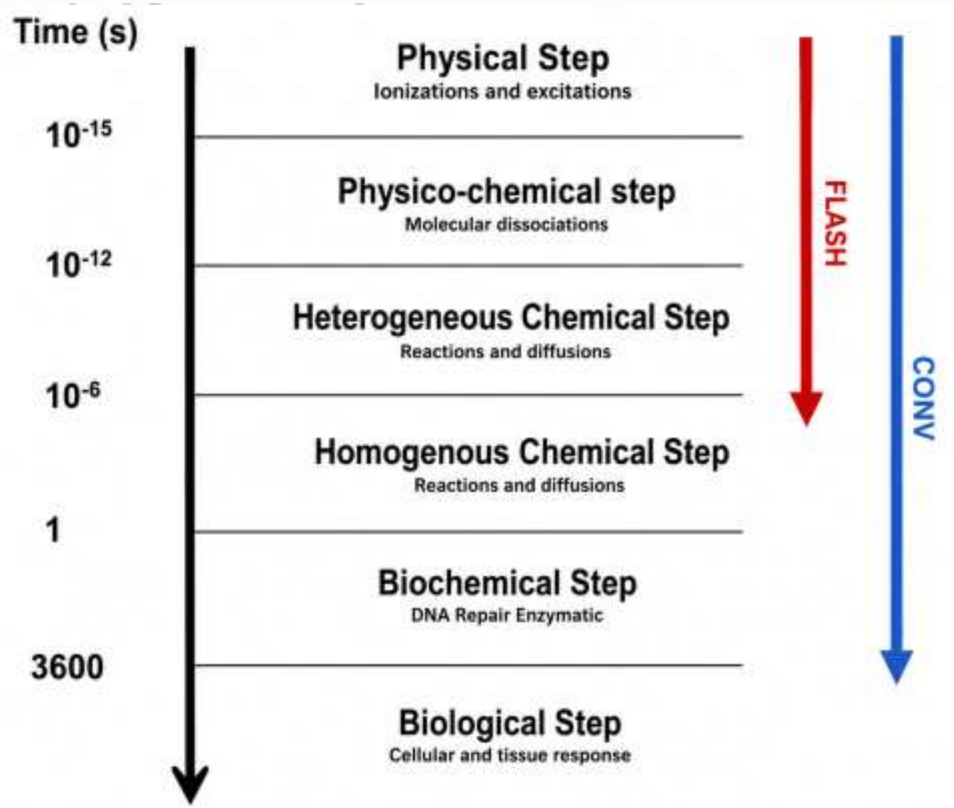
FLASH Radiotherapy (FLASH-RT) is a revolutionary approach in cancer treatment that involves delivering ultra-high doses of radiation in extremely short durations (typically less than a second), **with the high biological sparing of healthy tissue** while the same effect of conventional radiation on tumor.

Conventional RT

Radiation delivered over **seconds to minutes. Dose rate is lower** and **pulses are not extremely intense.**

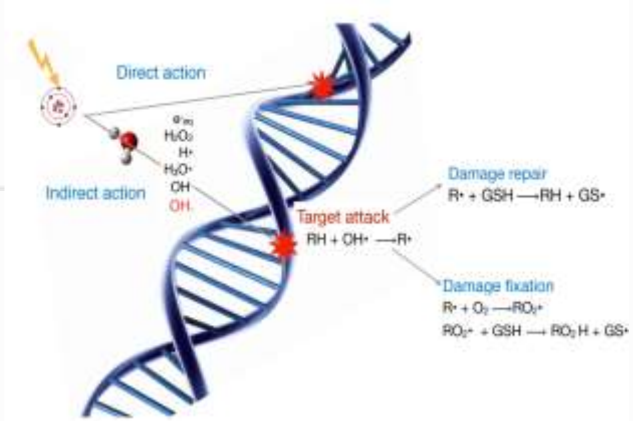
Pulsed FLASH-RT delivery parameters	
Dose per pulse (pulse duration × Dose rate within the pulse)	$\geq 1\,Gy$
Total dose (Dose per pulse × number of pulse)	$\geq 10\,Gy$
Total delivery time	$\leq 0.1\,s$
Mean dose rate $\left(\frac{Total\ dose}{Total\ delivery\ time}\right)$	$\geq 100\,\frac{Gy}{s}$

Wilson et al., Front. Oncol. 9, 1563 (2020)



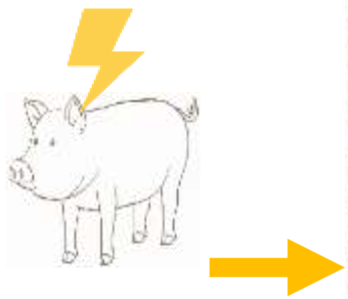
Same target dose, very different time structure

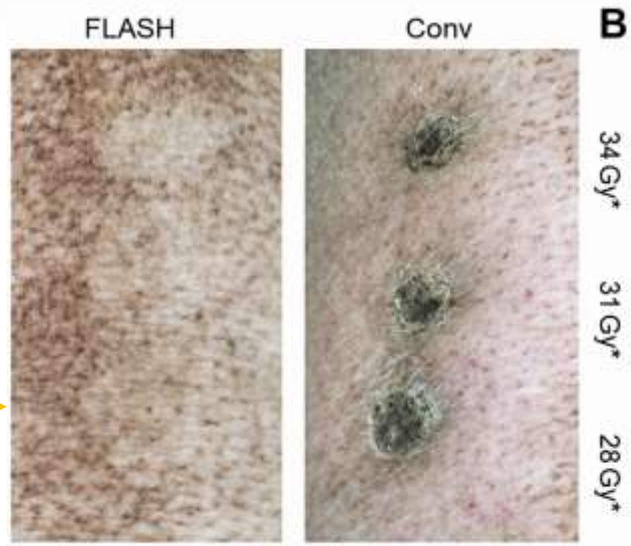
FLASH Effect



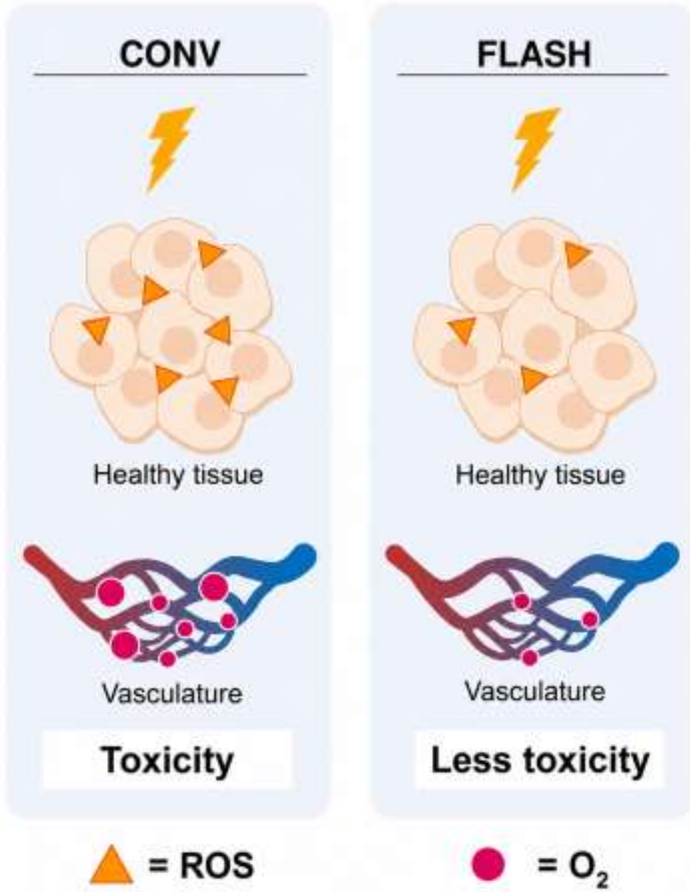
Main mechanistic hypothesis:

- Organic radical-radical recombination
- Inter-track Effects ► **Radiochemistry**
- Transient Hypoxia (O2 Depletion)
- Immune system driven ► **Radiobiology**





M. C. Vozenin et al., Clin. Canc. Res. (2019)



Part II: pulse laser-driven protons & FLASH-RT

From pulse laser-driven protons to DNA damage in FLASH-RT

Geant4 **Geant4-DNA**

- **Simulation bridge For FLASH study:**

Geant4 can model the **beamline and dose delivery**;

Geant4-DNA can model **water radiolysis** using simplified local source conditions (chemistry, `pulse timing, oxygen/scavengers and G-value scoring.`)

- **Geant4-DNA chemistry** to model chemical reactions relevant to radiobiology with special focus on oxygen effect
- **G4UserEventAction** implementing a delayed time and pulse structure

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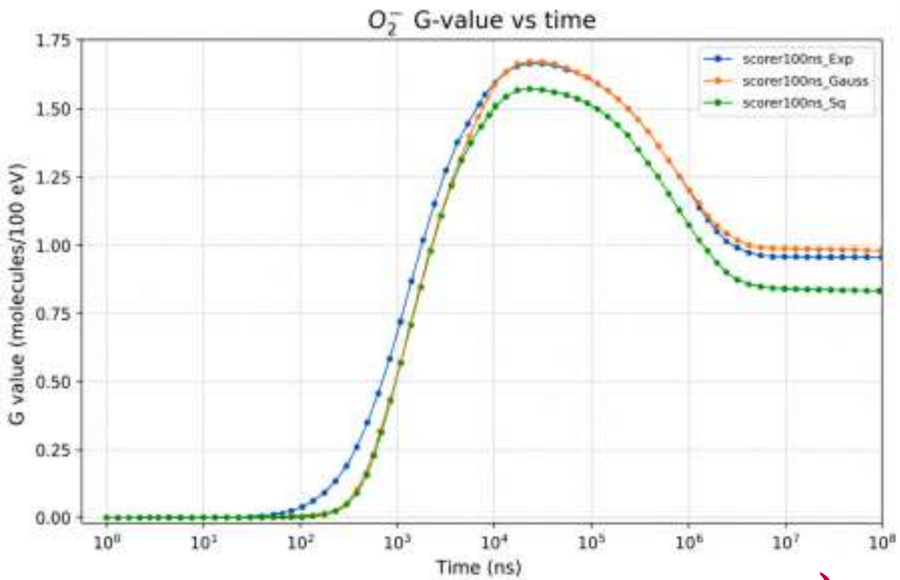
G-values vs time for different pulse structure

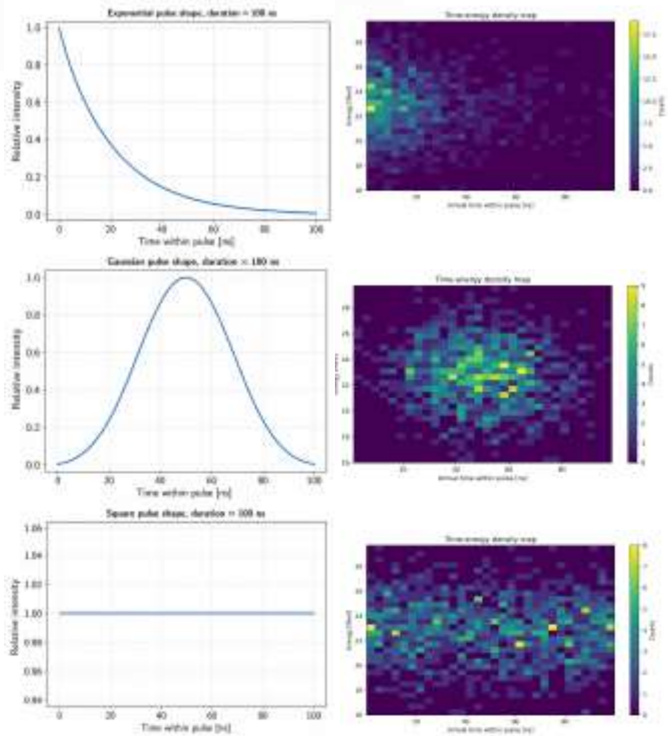


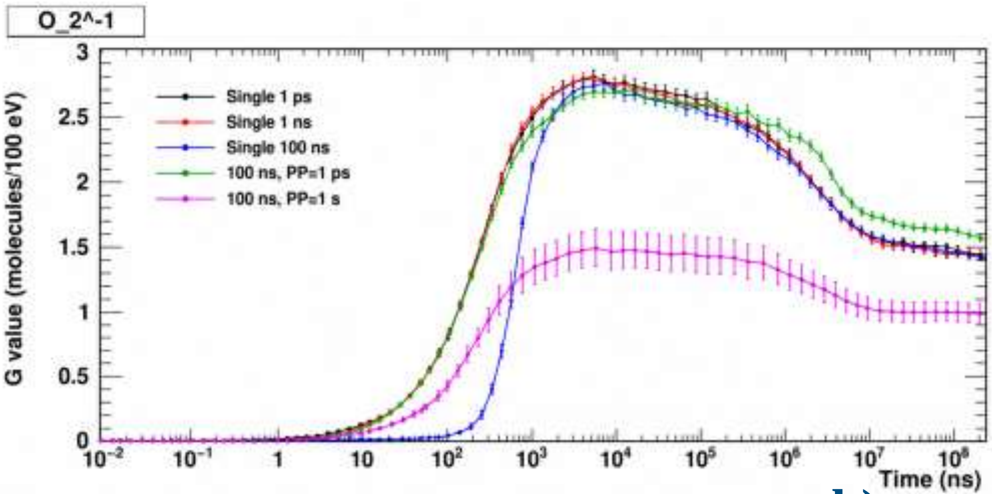
a)

a) Exponential,

b) Gaussian

c) Square





b)

a) Different pulse shape

b) Different pulse period (PP) &
Different pulse duration (PD)
For single and double pulse for O2.-

Thank you!

INFN LNS + GEANT4-DNA A SIMULATION TOOLKIT = INFN GEANT

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