

JUNE 2026 – LARD26 – STERCKX NICOLAS

TIME-RESOLVED DOSE RATE MODELING WITH GEANT4-DNA :

A STEP-BY-STEP APPROACH FOR RADIATION CHEMISTRY

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CHALLENGES OF MODERN RADIOTHERAPY (1)

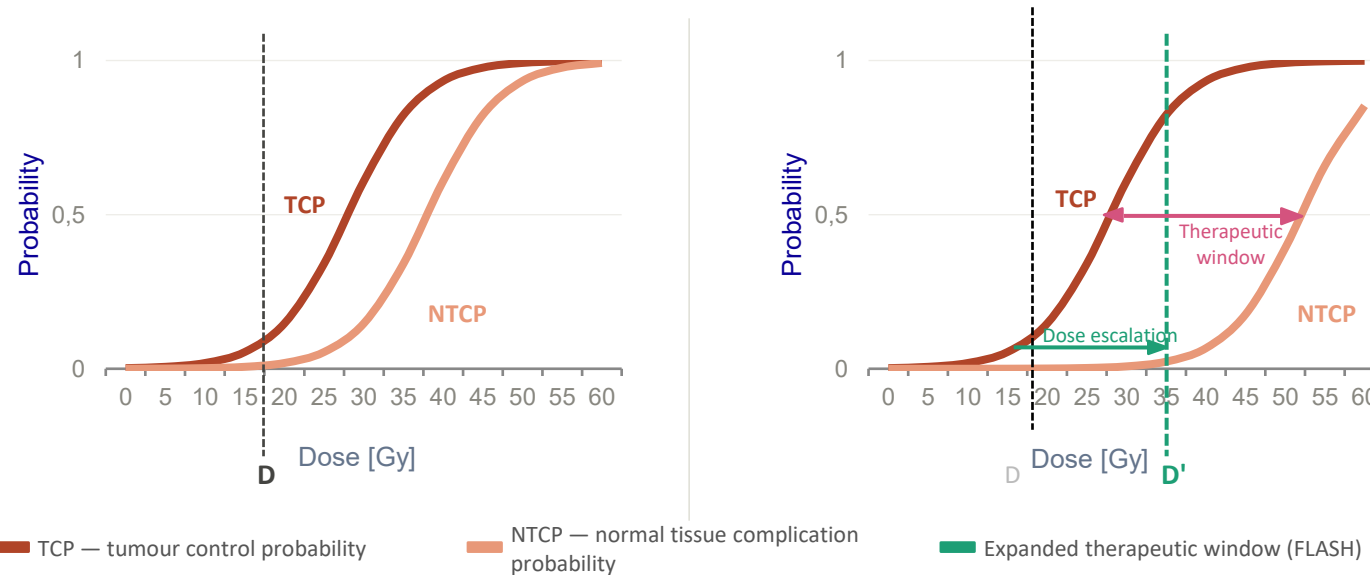
- CANCER INCIDENCE IS INCREASING WORLDWIDE
- EXTERNAL RADIOTHERAPY : ESSENTIAL TREATMENT FOR ~50% OF ALL CANCER PATIENTS



MULTIPLE DELIVERY METHODS:

Irradiation delivery at conventional dose rates : ~0.1-2 Gy/min (continuous delivery)

Ultra-high dose rates (UHDR) radiotherapy : > 40 Gy/s (short pulses)



CHALLENGES OF MODERN RADIOTHERAPY (2)

What is the action of dose rate?

The radiobiological mechanism is not yet elucidated.

Two approaches to investigate:

Experimentation

- **In vitro & in vivo** irradiation
 - Measure **DNA damages and other biological endpoints at varying dose rates**
 - Observe biological endpoints directly
- ✓ *Gold standard for biological insight*

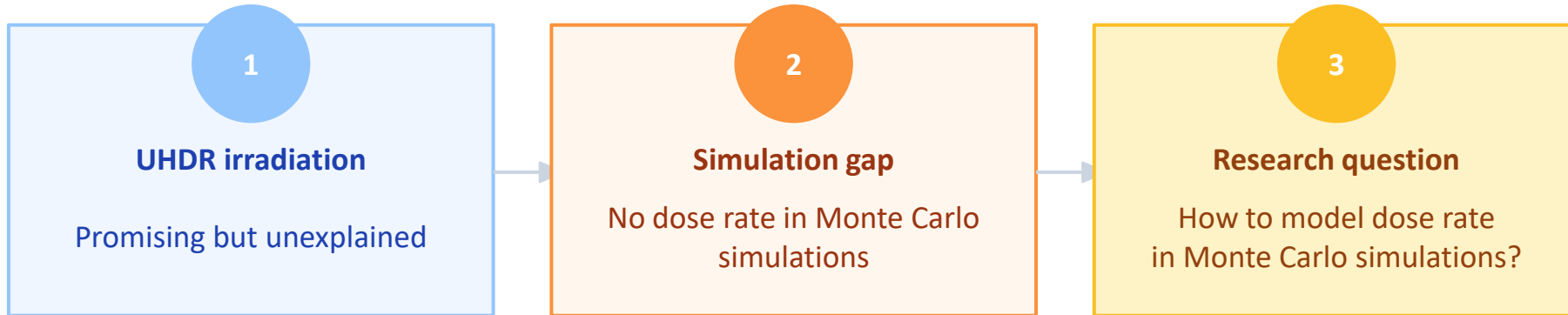
vs

Monte Carlo simulation

- Track **particle interactions** in silico
- Model **DNA damage** at the **nanoscale**
- Explore mechanisms computationally

✗ **Dose rate is not modelled in current simulations**

CHALLENGES OF MODERN RADIOTHERAPY (3)



Implement dose rate consideration in Monte Carlo simulations
to enable mechanistic exploration of the FLASH effect at the nanoscale

Key challenge: effect of dose rate on DNA damage is not accounted for in current mechanistic simulations — new chemical models are required.

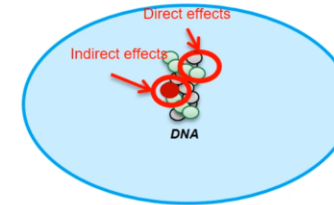
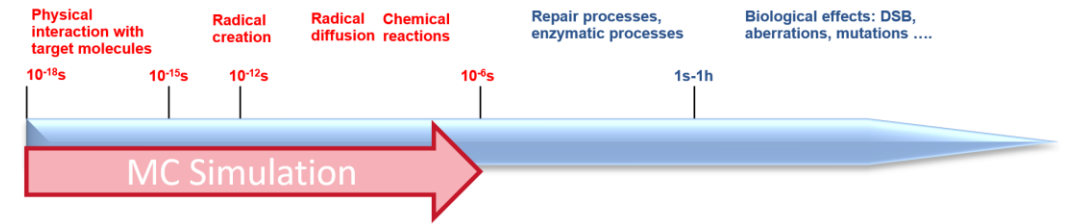
GEANT4-DNA: MONTE CARLO TRACK STRUCTURE SIMULATION TOOLKIT

- GEANT4-DNA = MCTS FRAMEWORK ADAPTED TO THE UNDERSTANDING OF THE ACTION OF RADIATIONS ON BIOLOGICAL MEDIA

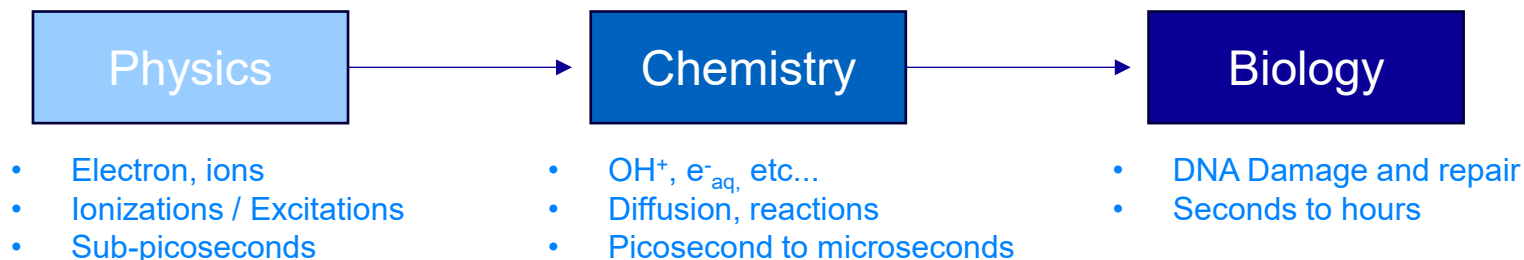
- FULLY INTEGRATES :

- Physical stage (fs) : ionizations, excitations, elastic scatterings
- Chemical stage (ps to μ s) : radical formation, diffusion, reactions
- (Optional) Biology stage : Repair of DNA damage

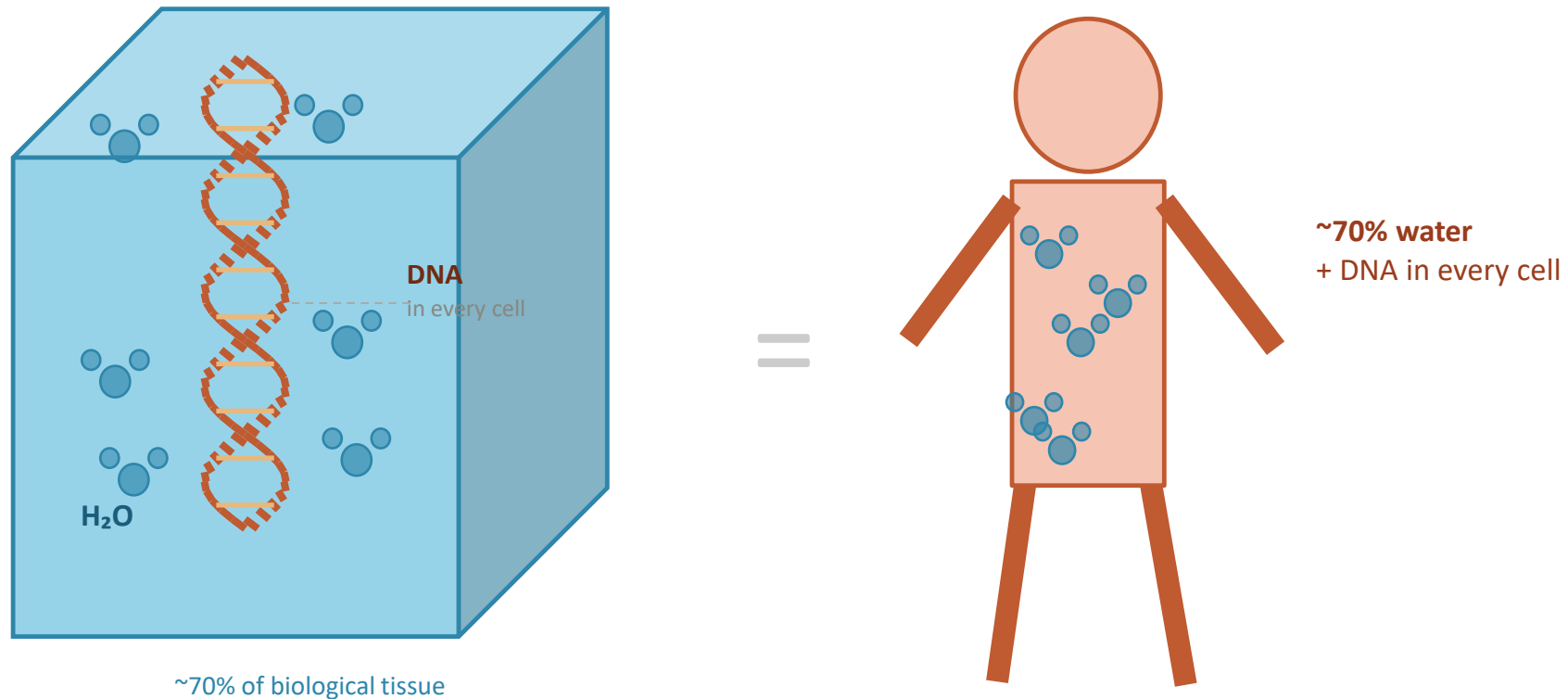
- FULLY SPATIALLY RESOLVED DOWN TO nm SCALE



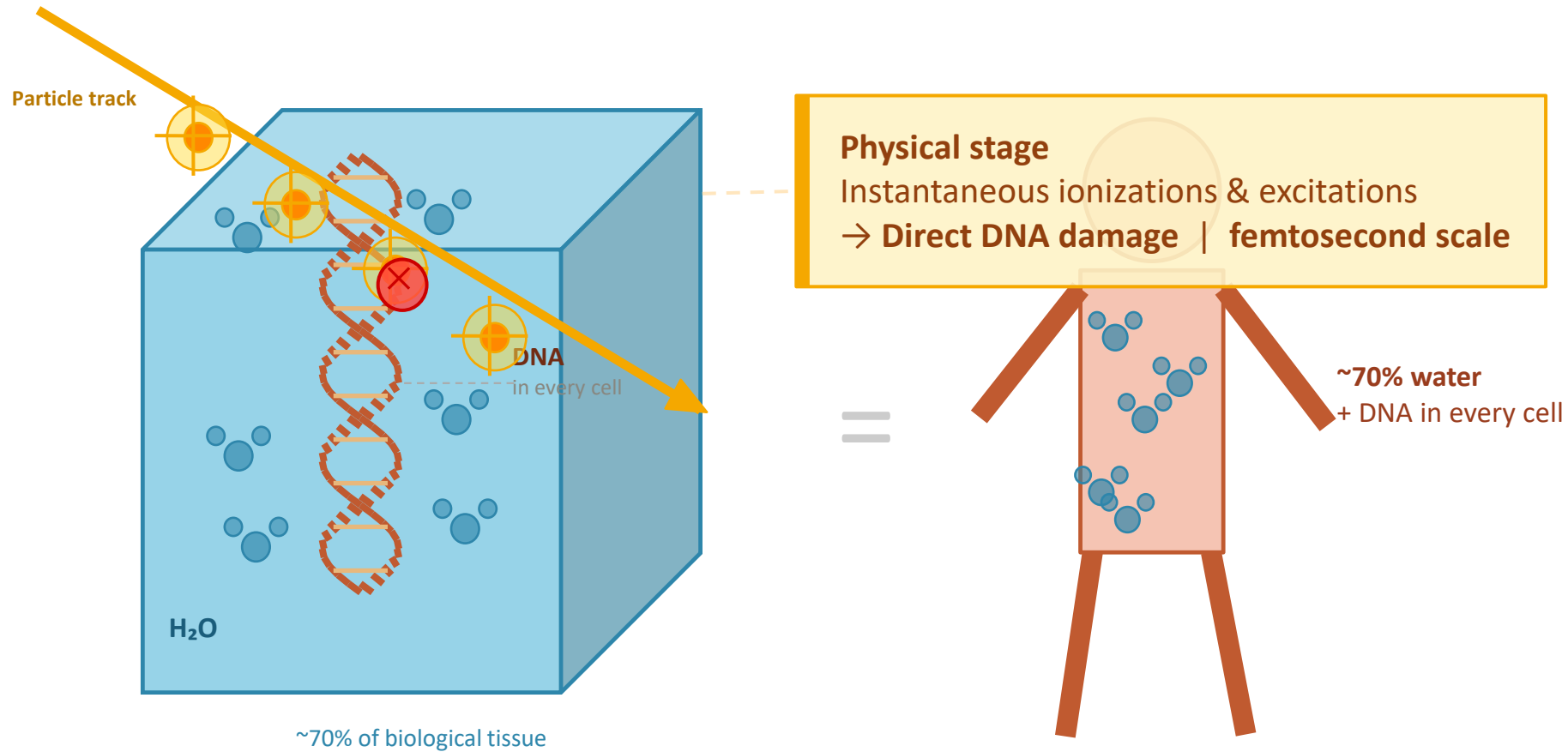
- OPEN-SOURCE, WIDELY USED IN RADIOBIOLOGY AND MEDICAL PHYSICS
-  LIMITATION : BY DEFAULT, ASSUMES ALL PARTICLES ARE INDEPENDENT



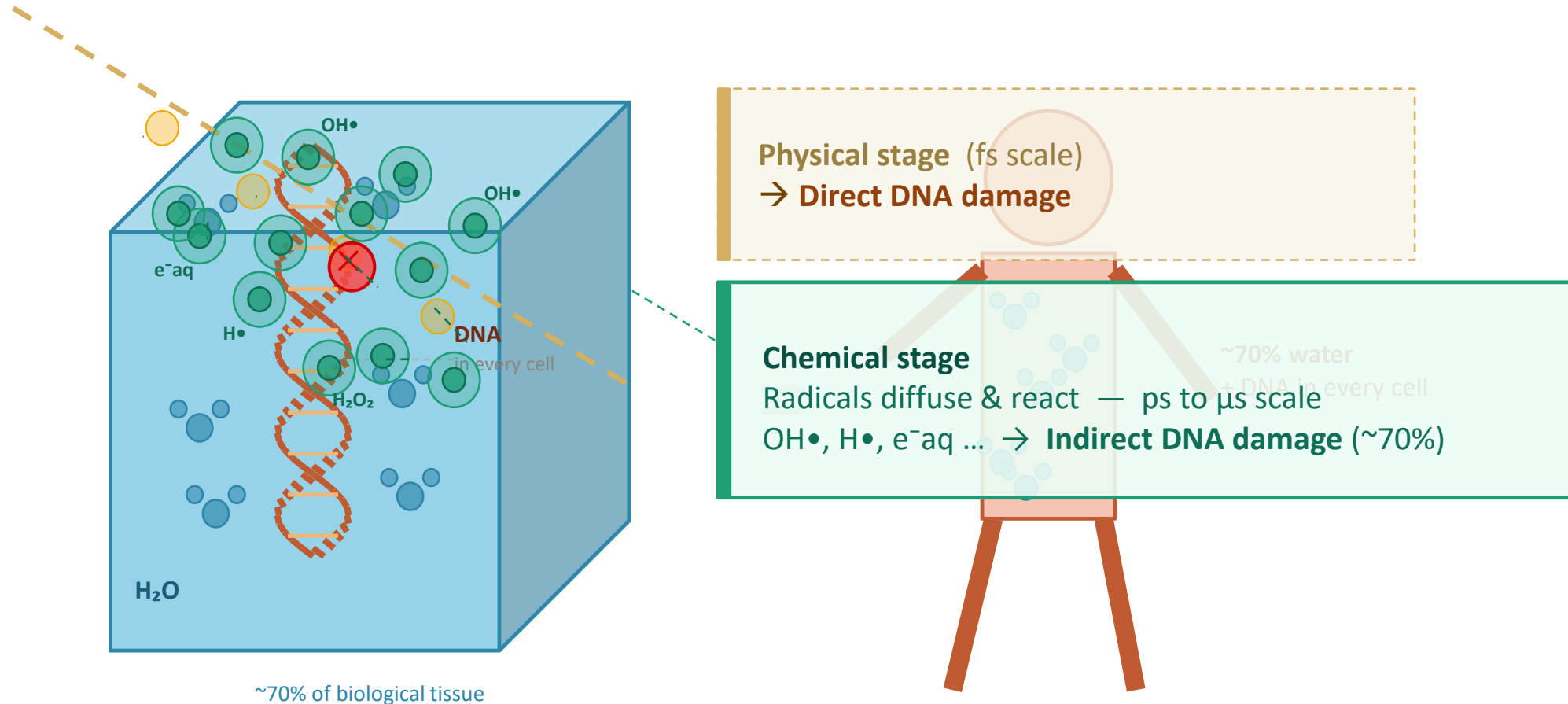
PHYSICS IS INSTANTANEOUS — CHEMISTRY IS TIME-DEPENDENT (1)



PHYSICS IS INSTANTANEOUS — CHEMISTRY IS TIME-DEPENDENT (2)

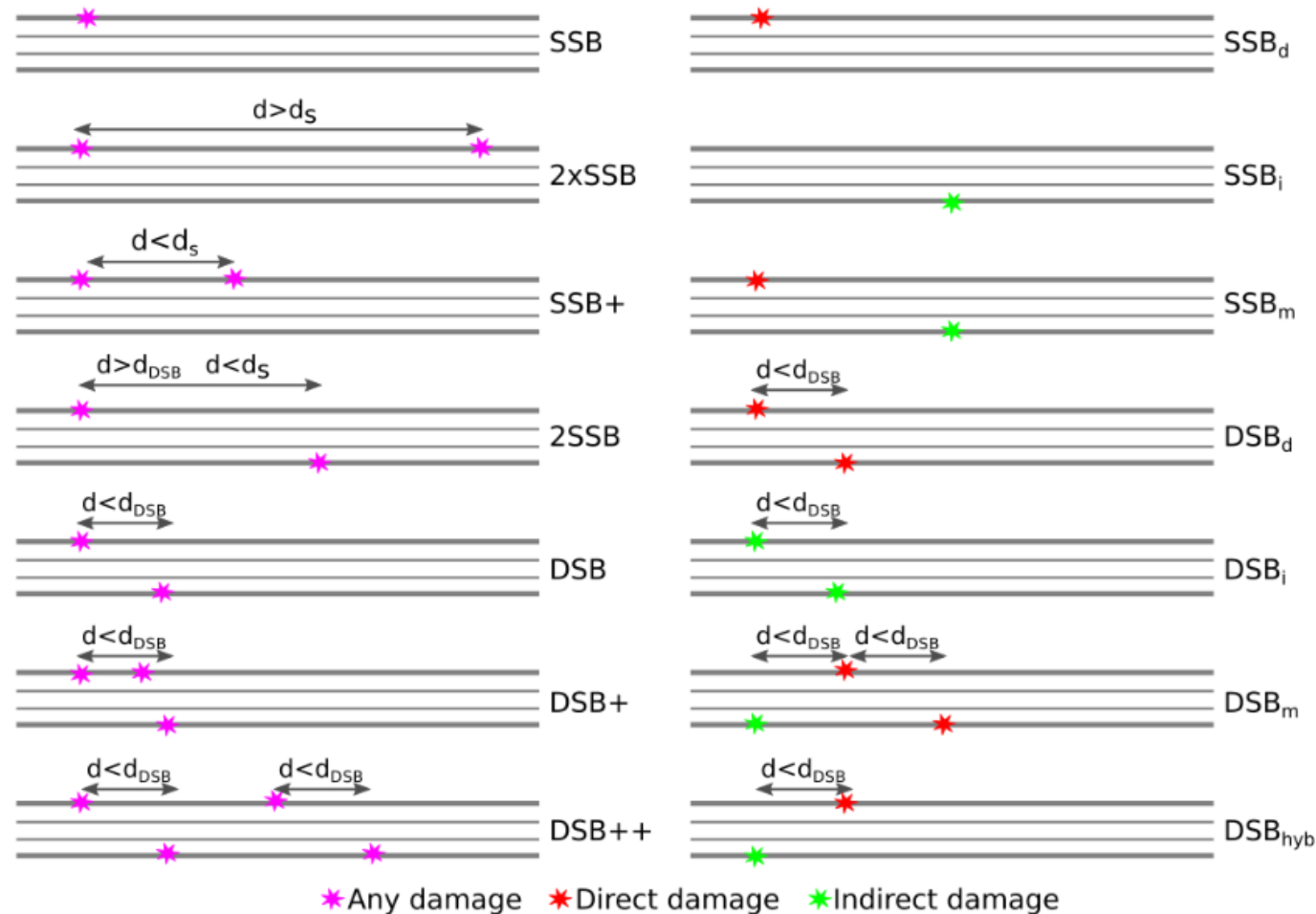


PHYSICS IS INSTANTANEOUS — CHEMISTRY IS TIME-DEPENDENT (3)



PHYSICS IS INSTANTANEOUS — CHEMISTRY IS TIME-DEPENDENT (4)

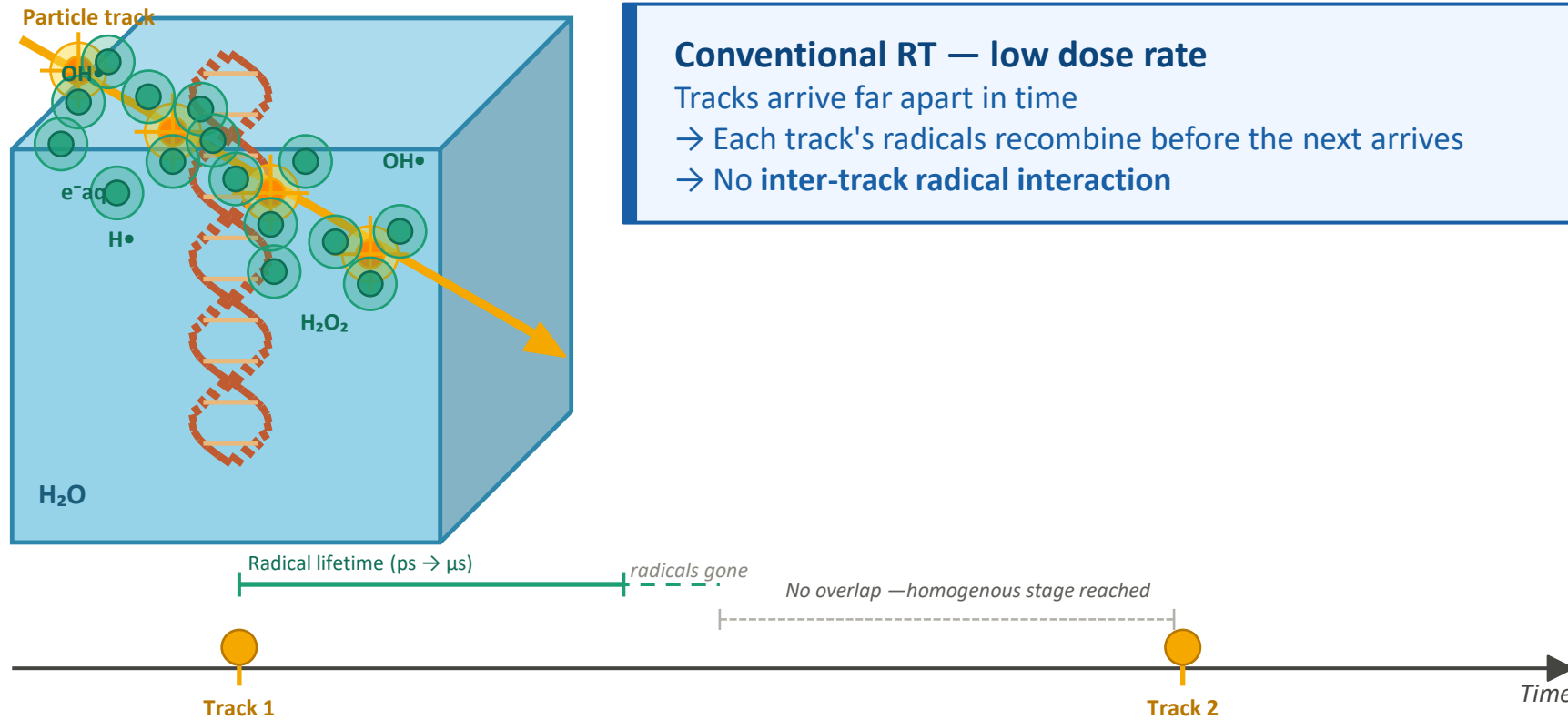
Damage classification model



Computational modelling of lowenergy electron-induced DNA damage by early physical and chemical events, H. Nikjoo et al., Int. J. Radiat. Biol. 71 (1997) 467–483 - [link](#)

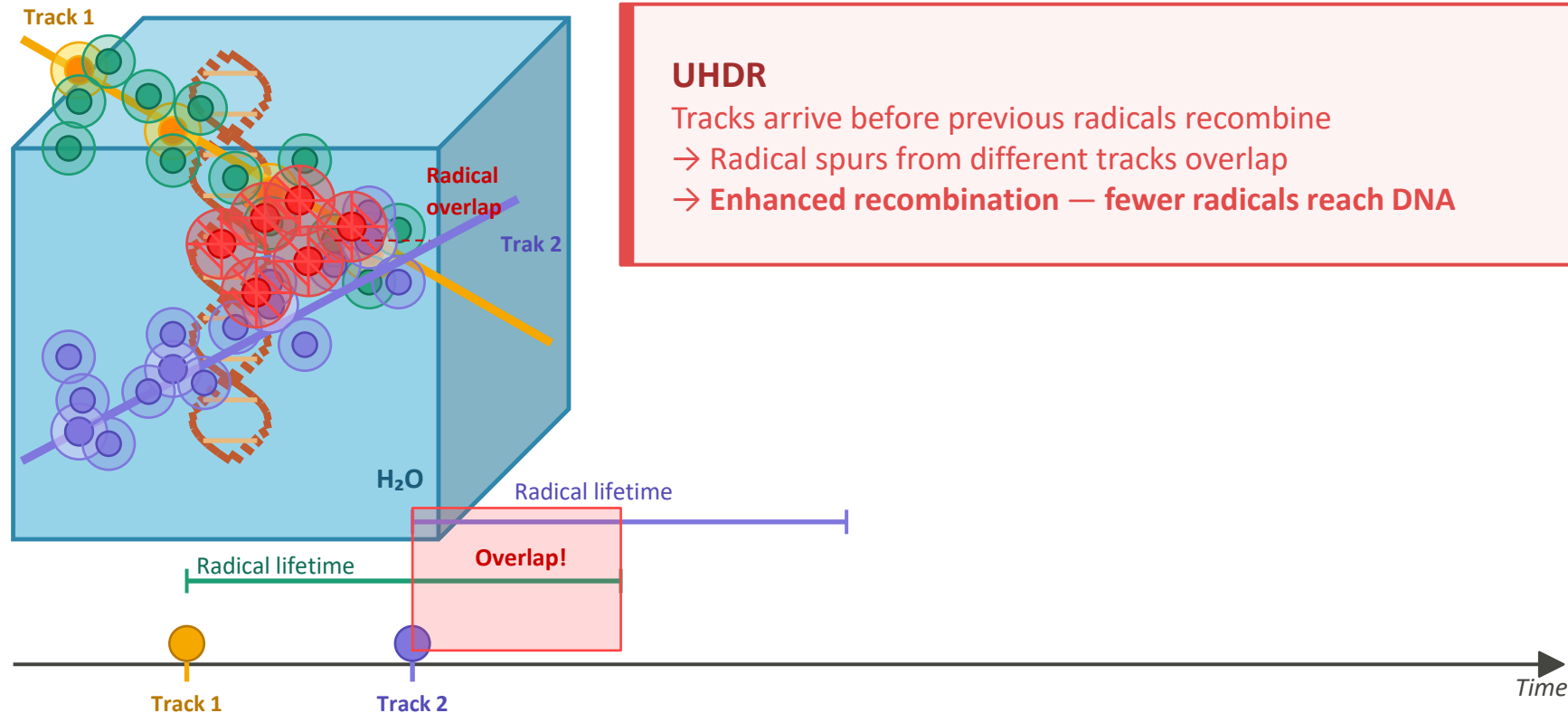
PHYSICS IS INSTANTANEOUS — CHEMISTRY IS TIME-DEPENDENT (5)

Low dose rate — tracks isolated in time



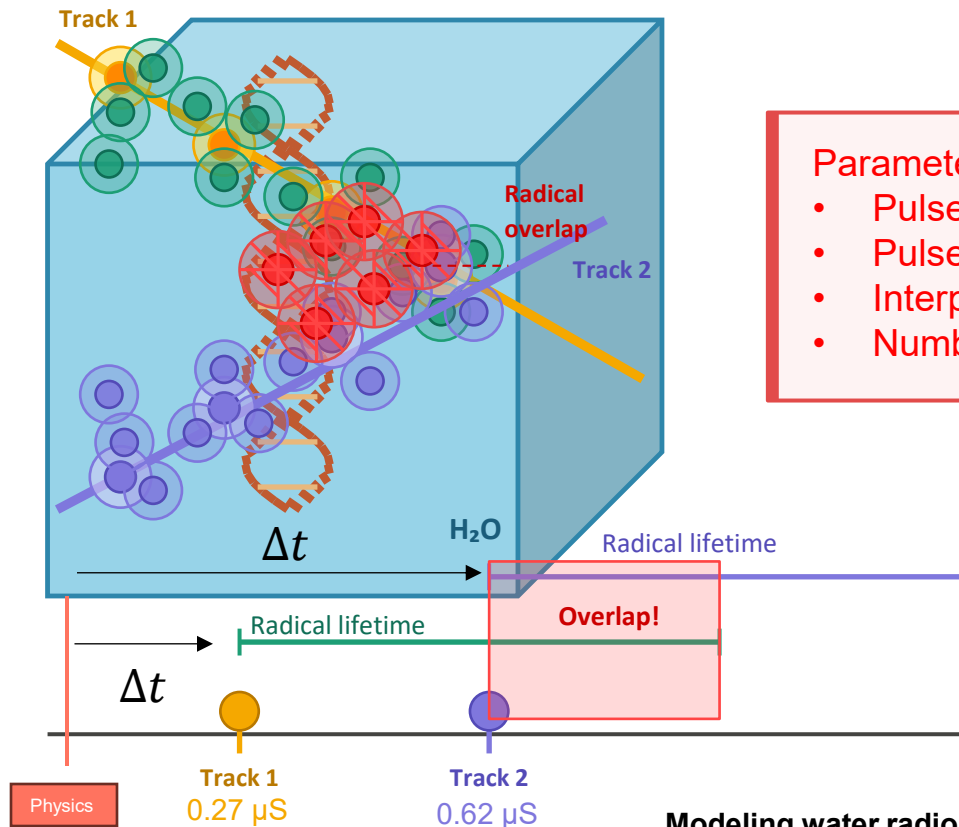
PHYSICS IS INSTANTANEOUS — CHEMISTRY IS TIME-DEPENDENT (6)

High dose rate — tracks overlap in time



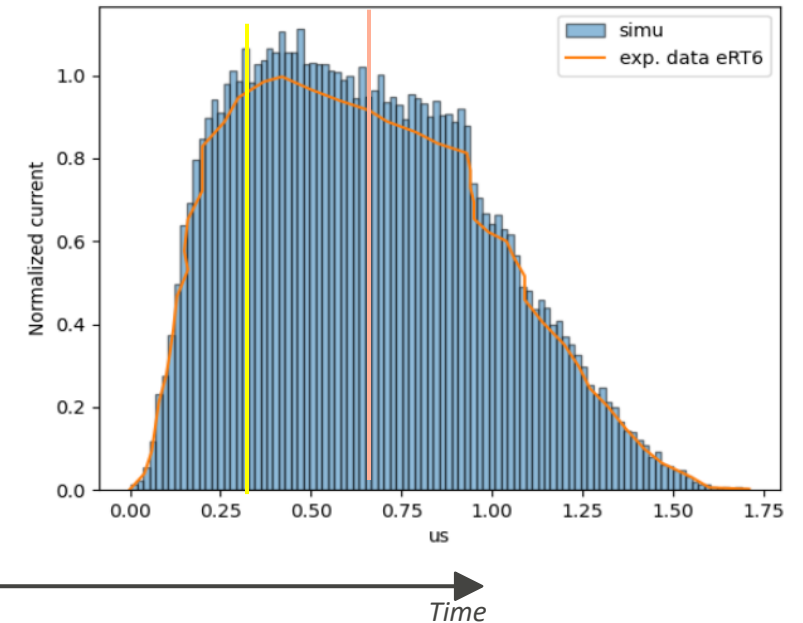
PHYSICS IS INSTANTANEOUS — CHEMISTRY IS TIME-DEPENDENT (7)

Dose Rate implementation



Parameter :

- Pulse shape
- Pulse length
- Interpulse
- Number of pulses



Modeling water radiolysis with Geant4-DNA: Impact of the temporal structure of the irradiation pulse under oxygen conditions, T. A. Le, H. N. Tran, S. Fattori, V. C. Phan, S. Incerti (2024) ([arXiv:2409.11993](https://arxiv.org/abs/2409.11993))

DNA DAMAGE SIMULATION CODES IN GEANT4-DNA

DSBANDREPAIR

- Monte Carlo simulation framework developed by LDRI based on Geant4-DNA and released as an advanced example
- Designed to study DNA single-strand and double-strand breaks (SSB & DSB) induction in realistic nuclei models and repair.
- Three-stage simulation framework, voxel-by-voxel chemistry
- DNAFabric geometry
- **New implementation of dose rate methods**
- Time scale limited to ~5 ns

→ The inability of the voxel to “communicate” with each other limit the maximum simulation time to 5 ns.

At longer time scales, reactive species would diffuse further and may need to interact across neighboring voxels, which is currently not supported.

« dsbandrepair » - an updated Geant4-DNA simulation tool for evaluating the radiation-induced DNA damage and its repair, T. A. Le, N. H. Tran, Y. Thibaut, K. Chatzipapas, D. Sakata, S. Incerti, C. Villagrasa, Y. Perrot, Phys. Med. 124, 103422 (2024) ([link](#))

Geant4-DNA simulations using complex DNA geometries generated by the DnaFabric tool, S. Meylan, U. Vimont, S. Incerti, I. Clairand, C. Villagrasa, Comput. Phys. Commun. 204 (2016) 159-169 ([link](#))

MOLECULARDNA

- Example developed withing the Geant4 collaboration based on Geant4-DNA and released as an advanced example
- Allow to study DNA single-strand and double-strand break (SSB & DSB) induction.
- Single integrated simulation block
- Fractal geometry
- Octree spatial lookup for efficient navigation
- New implementation of dose rate methods
- Time scale up ~1s

Simulation of DNA damage using Geant4-DNA: an overview of the “molecularDNA” example application, K. P. Chatzipapas, N. H. Tran, M. Dordevic, S. Zivkovic, S. Zein, W.-G. Shin, D. Sakata, N. Lampe, J. M. C. Brown, A. Ristic-Fira, I. Petrovic, I. Kyriakou, D. Emfietzoglou, S. Guatelli, S. Incerti, Prec. Radiat. Oncol. 7 (2023) 4-14 ([link](#))

INTEGRATION OF DNAFABRIC GEOMETRIES INTO MOLECULARDNA

Objective :

- Enable DNAFabric geometries in MolecularDNA for nanometric DNA damage simulations

Motivation :

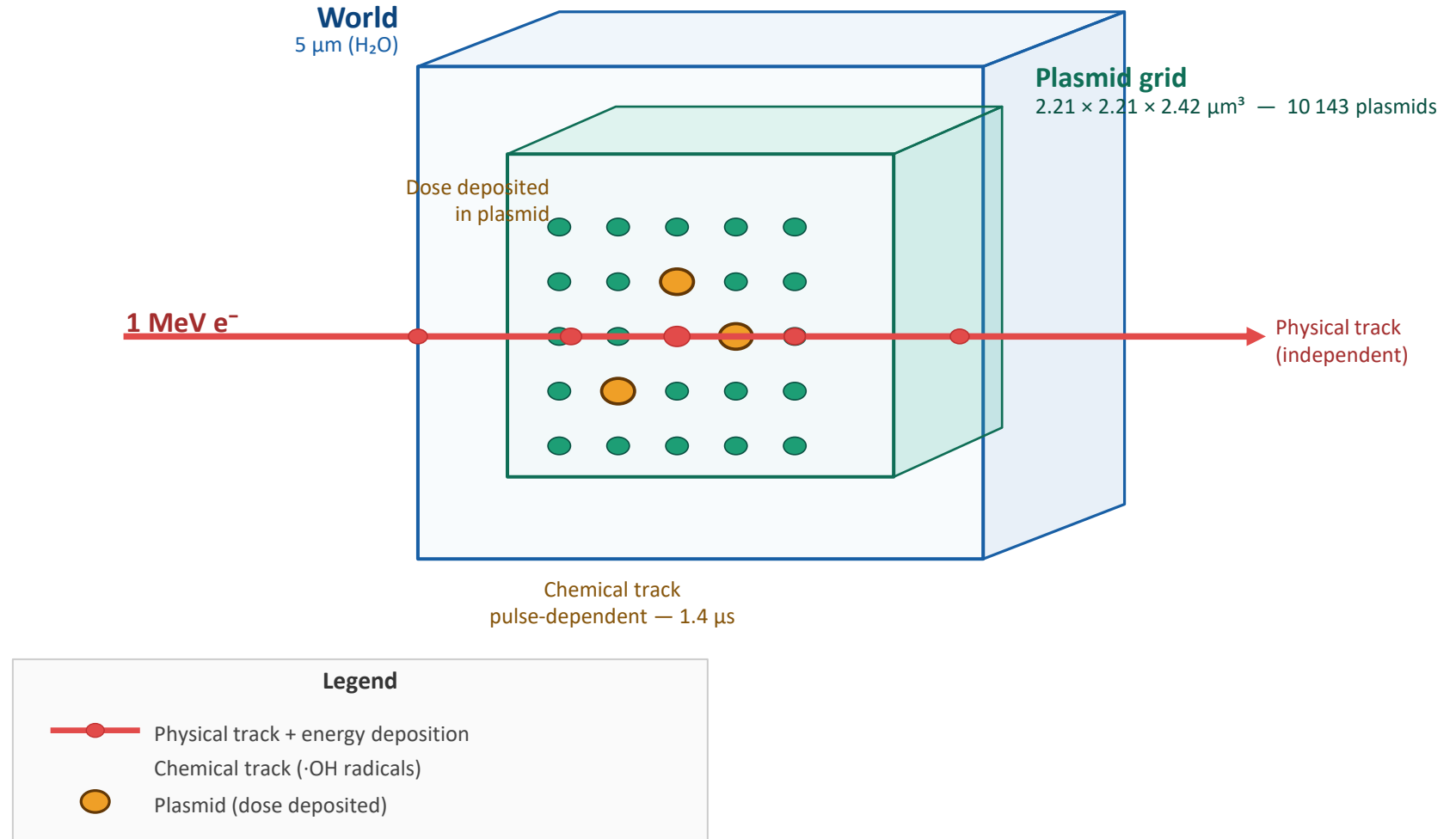
- Accurate modeling requires realistic chromatin structures
- FractalDNA geometries are procedurally generated and may lack nucleosome/fiber-level detail
- DNAFabric provides explicit DNA, nucleosome, and fiber structures

Method / Implementation :

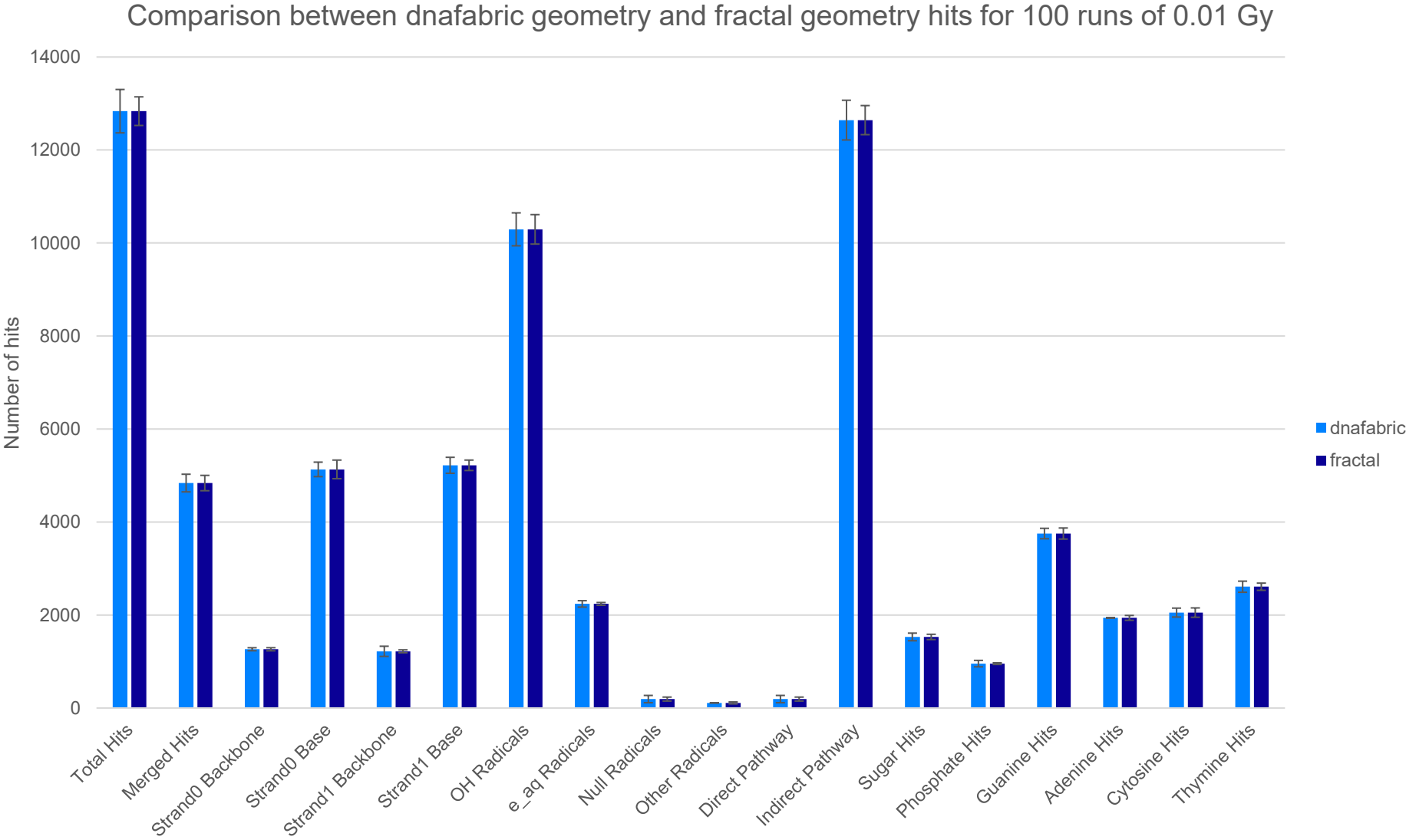
- MolecularDNA code adapted to read DNAFabric files directly
- Preserves strand topology, base-pair organization, and nucleosome/fiber structure

DNAFABRIC GEOMETRY COMPARISON

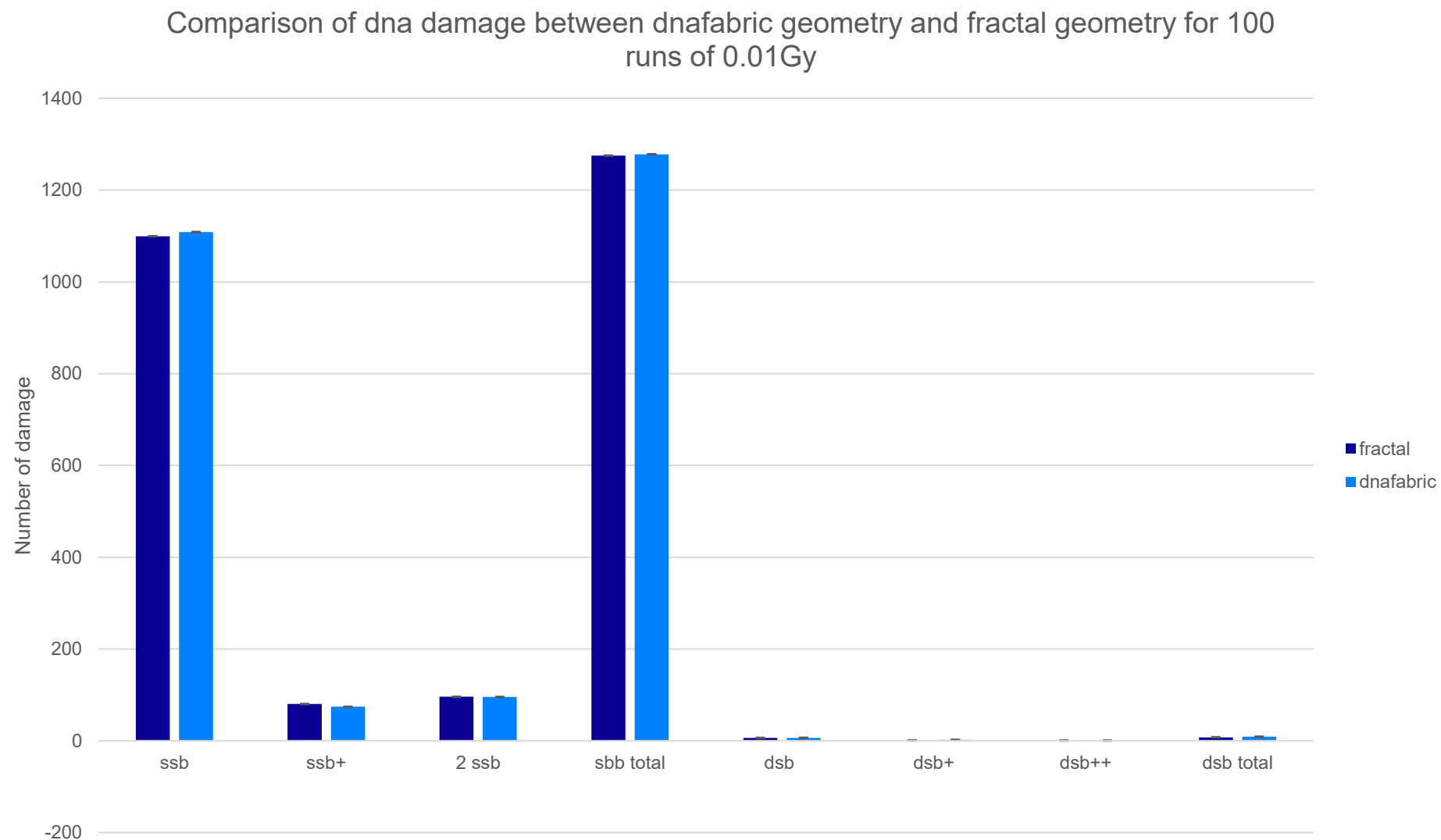
- World volume: 5 μm side
- DNA geometry: 10143 plasmids
pBR322 arranged in a $4.42 \times 4.42 \times 4.84 \mu\text{m}^3$ cube
- Primary particles: 100 runs of 1 MeV electrons
- Dose per run: 0.01 Gy
- Total dose : 1 Gy
- Pulse duration: 1.4 μs
- Dose rate $\sim 1,4\text{e}6$ Gy/s
- Physics list: Geant4-DNA Option 2
- Chemistry list: Geant4-DNA Option 3



RESULT OF THE GEOMETRY IMPLEMENTATION (1)



RESULT OF THE GEOMETRY IMPLEMENTATION (2)



SCAVENGER HANDLING (1)

Towards realistic biological environments and experimental validation



Introduce O_2 , H_3O^+/OH^- (pH of the medium) and other scavengers

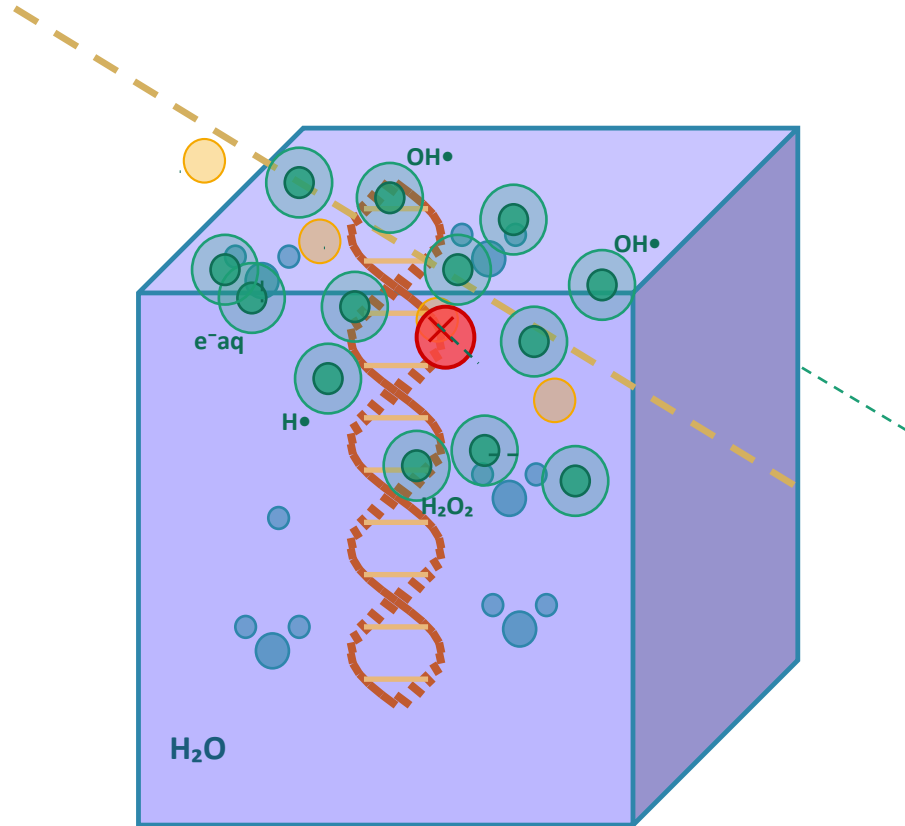


Handle concentration, diffusion, and reaction rates



Extend chemistry aqueous solution

SCAVENGER HANDLING (2)



~70% of biological tissue

Scavengers

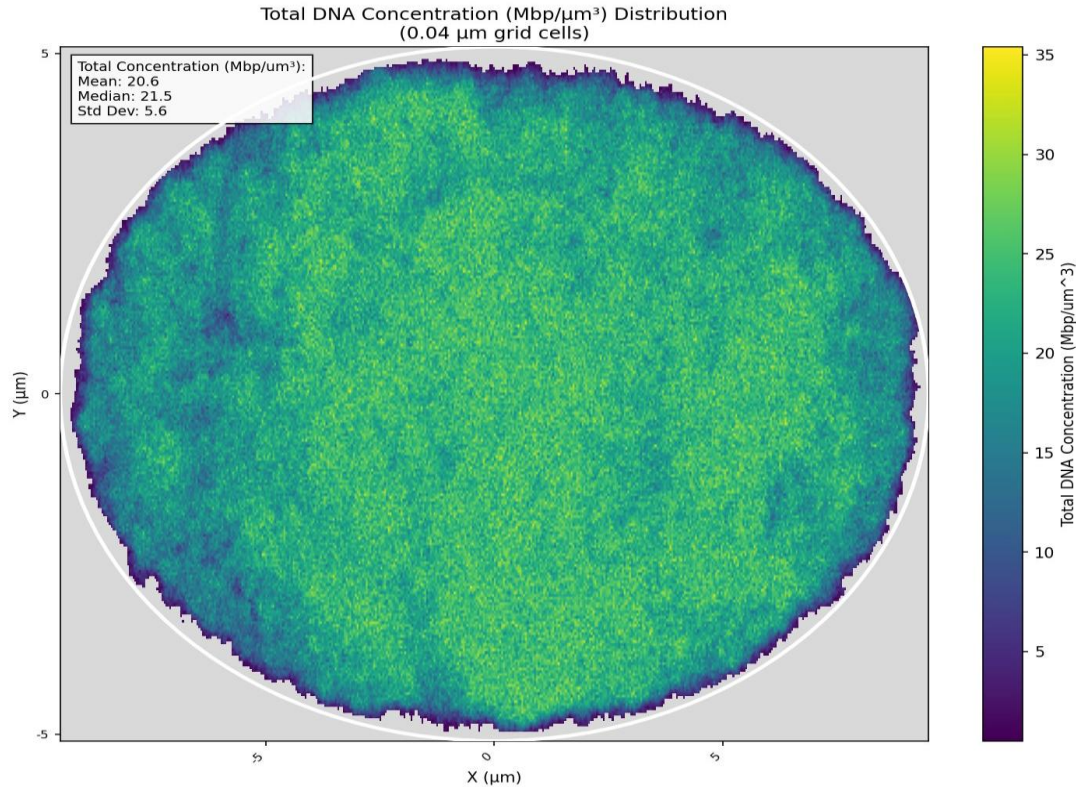
- uniformly distributed throughout the medium
- Has a probability of interacting with radical species.

→ By capturing these radicals, they act as chemical traps, reducing radical availability and significantly altering the reaction kinetics.

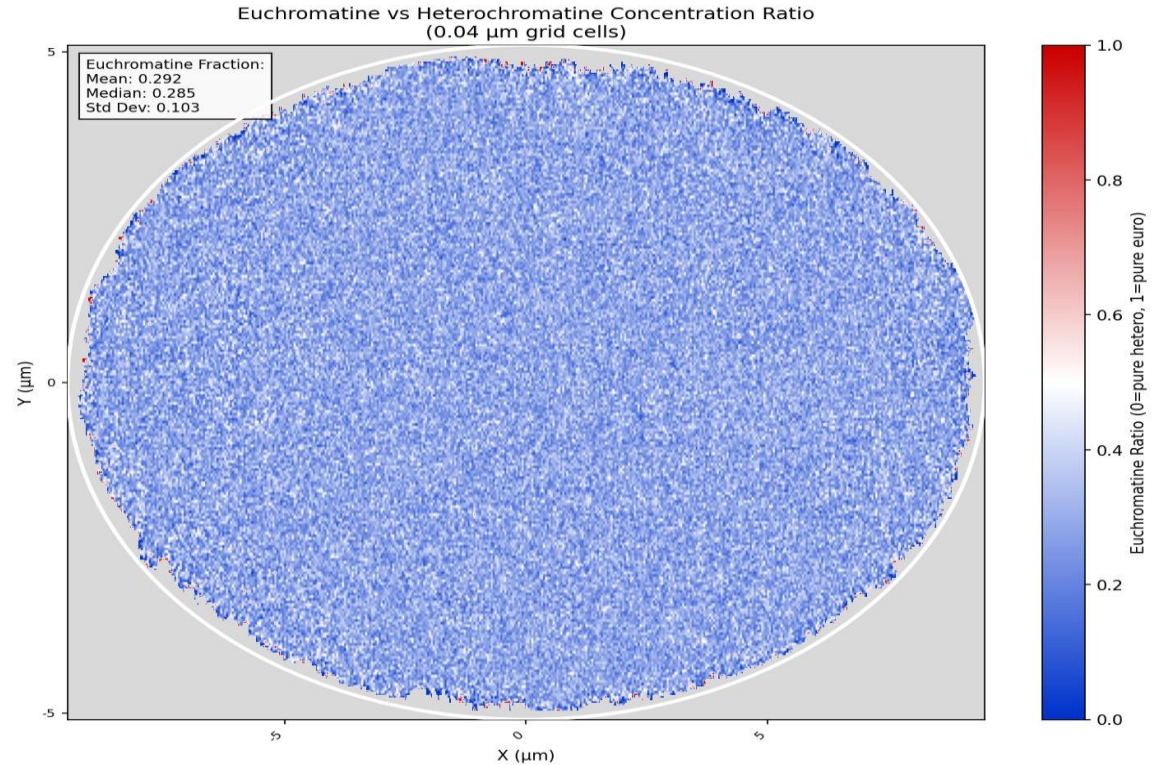
Currently implemented scavenger :
O₂, pH, HCO₃m, GSH, DMSO, TRIS, EDTA

Mapping chromatin organisation and DNA concentration across the entire endothelial nucleus

Total DNA Concentration · 40 nm grid



Euchromatin / Heterochromatin Ratio · 40 nm



What this cartography tells us

- DNA is densely packed at the nucleus core, sparser at the periphery
- Chromatin ratio is spatially heterogeneous — ~29% euchromatin on average
- This map guides which sub-volumes to select for MC simulation

2 574 583 Voxel

6.06805 Gbp

20.6 Mbp/ μm^3
mean DNA conc.

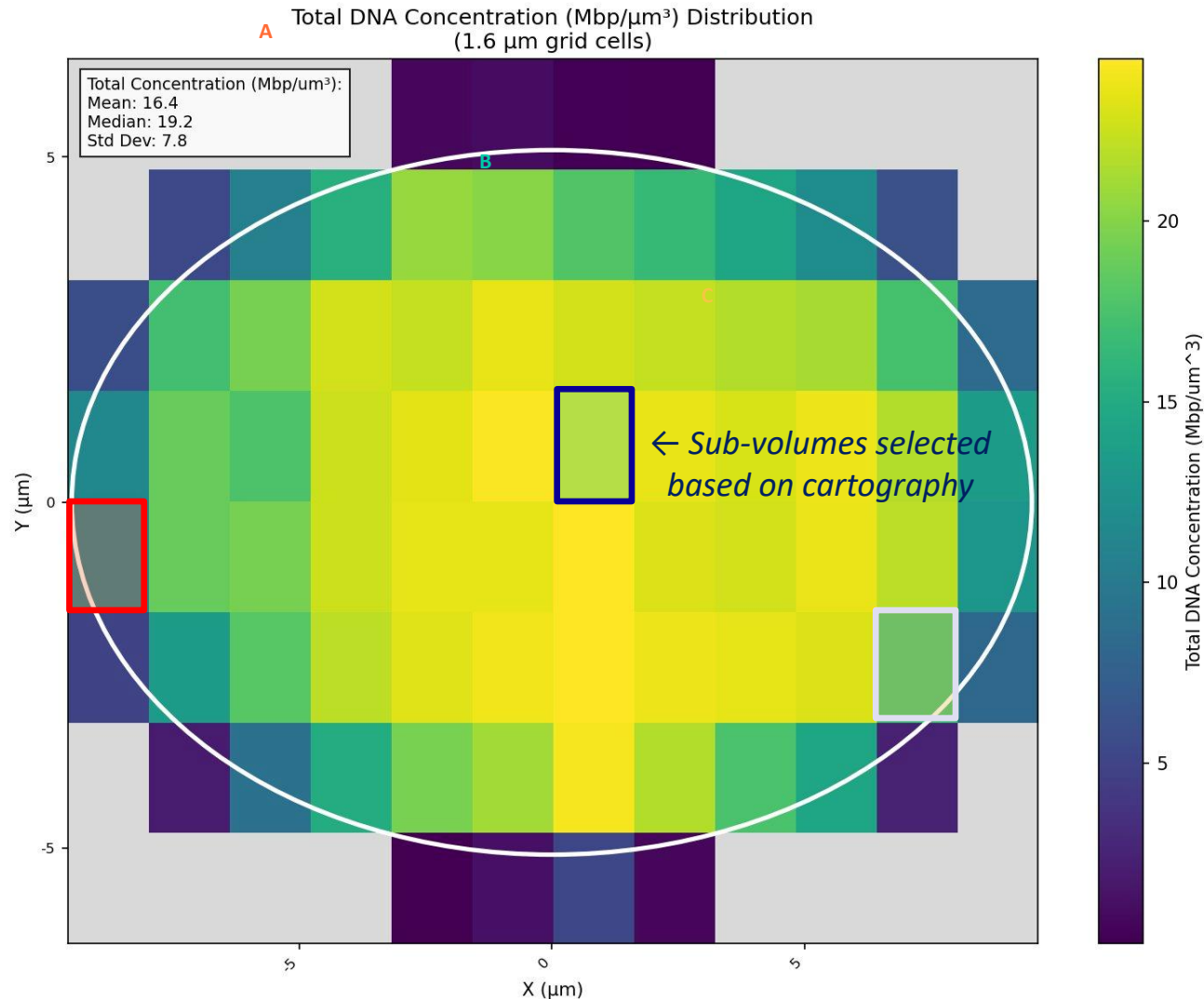
29.2%
euchromatin fraction

0.04 μm
grid resolution

→ Full geometry is too computationally demanding

Representative 3D sub-volumes are selected from the cartography map and simulated independently via Monte Carlo

Coarse Cartography Map · 1600 nm grid



① Cartography

Full-cell heatmaps at 40nm & 1.6 μm identify spatial heterogeneity in DNA density and chromatin state

② Sub-volume Selection

3D boxes (sub-volumes) are chosen to represent different regions: dense core, sparse periphery, mid-zone

③ Independent MC Simulation

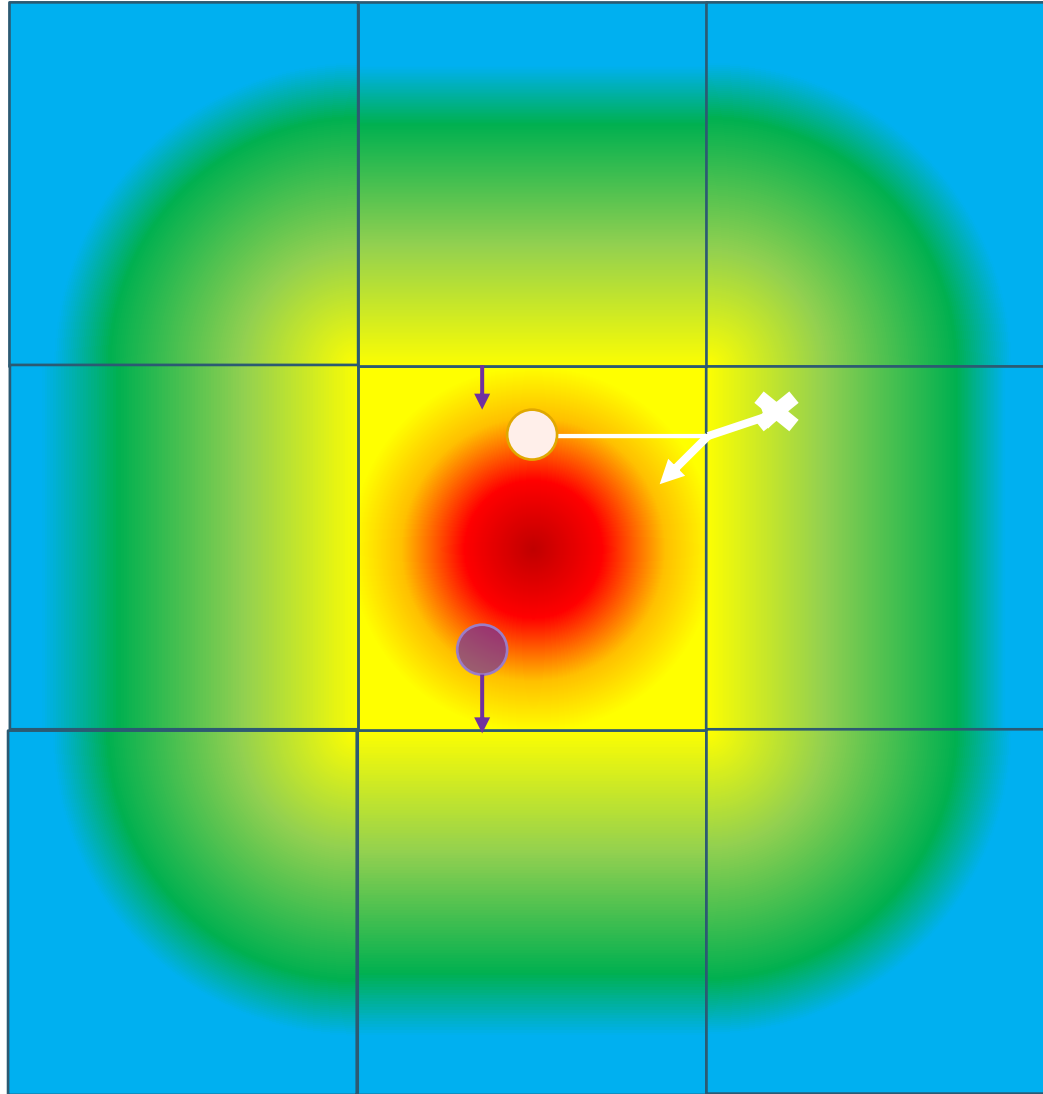
Each sub-volume is simulated separately — feasible compute time per box

④ Aggregation → Full Estimate

Results are combined weighted by volume fraction to reconstruct a full-cell Monte Carlo estimate

Periodic Boundary Conditions (PBC)

Preserving physical accuracy at sub-volume boundaries during Monte Carlo simulation



Why PBC is essential

⚠ Problem: artificial boundaries

Without PBC, molecules reaching the edge of a sub-volume would be absorbed or reflected — creating unphysical boundary effects that distort the MC statistics, even more so as the time pass.

✓ Solution: infinite periodic lattice

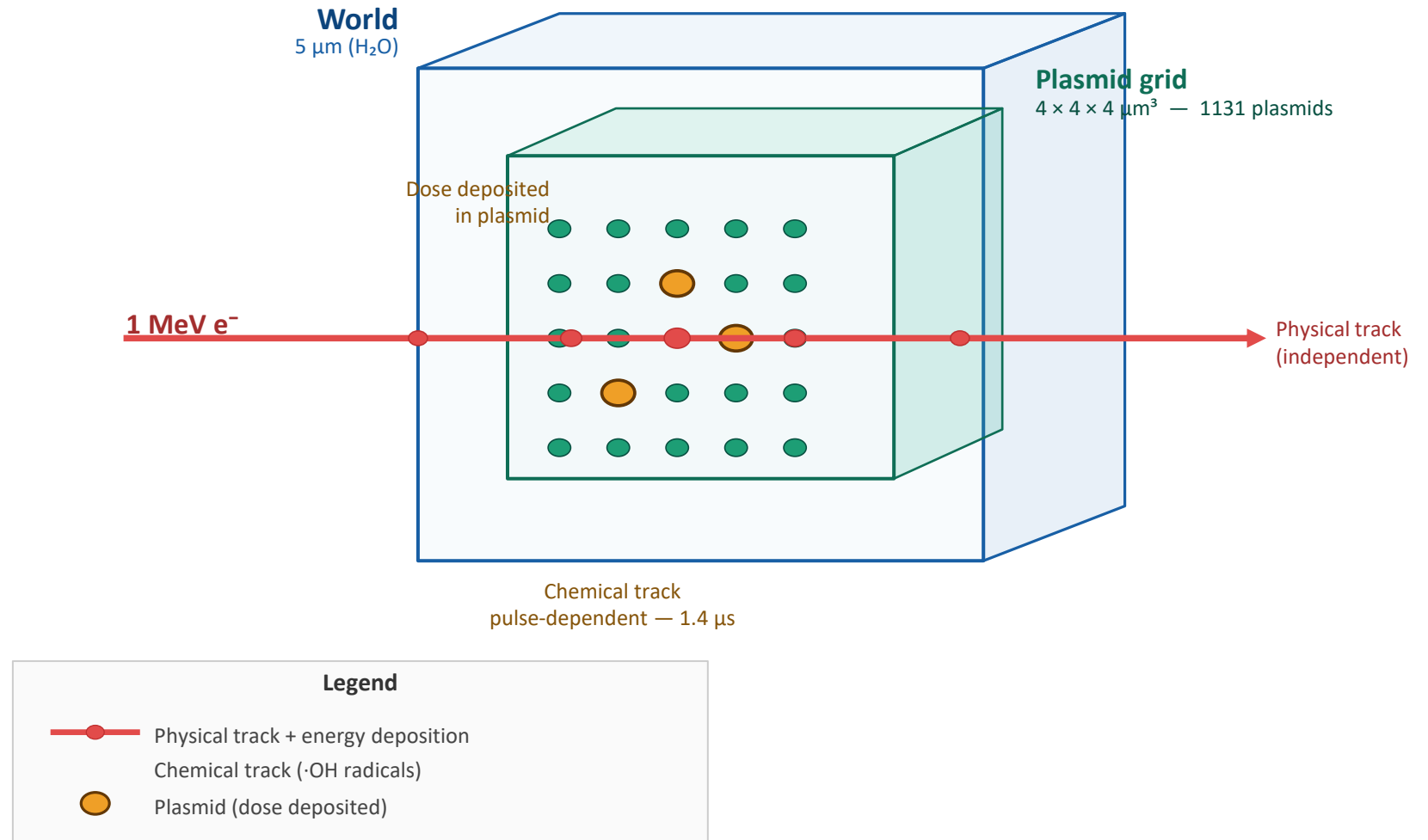
PBC makes each sub-volume surrounded by exact copies of itself. A molecule leaving one face instantly re-enters from the opposite face — mimicking bulk nuclear conditions.

⚙ Physical justification

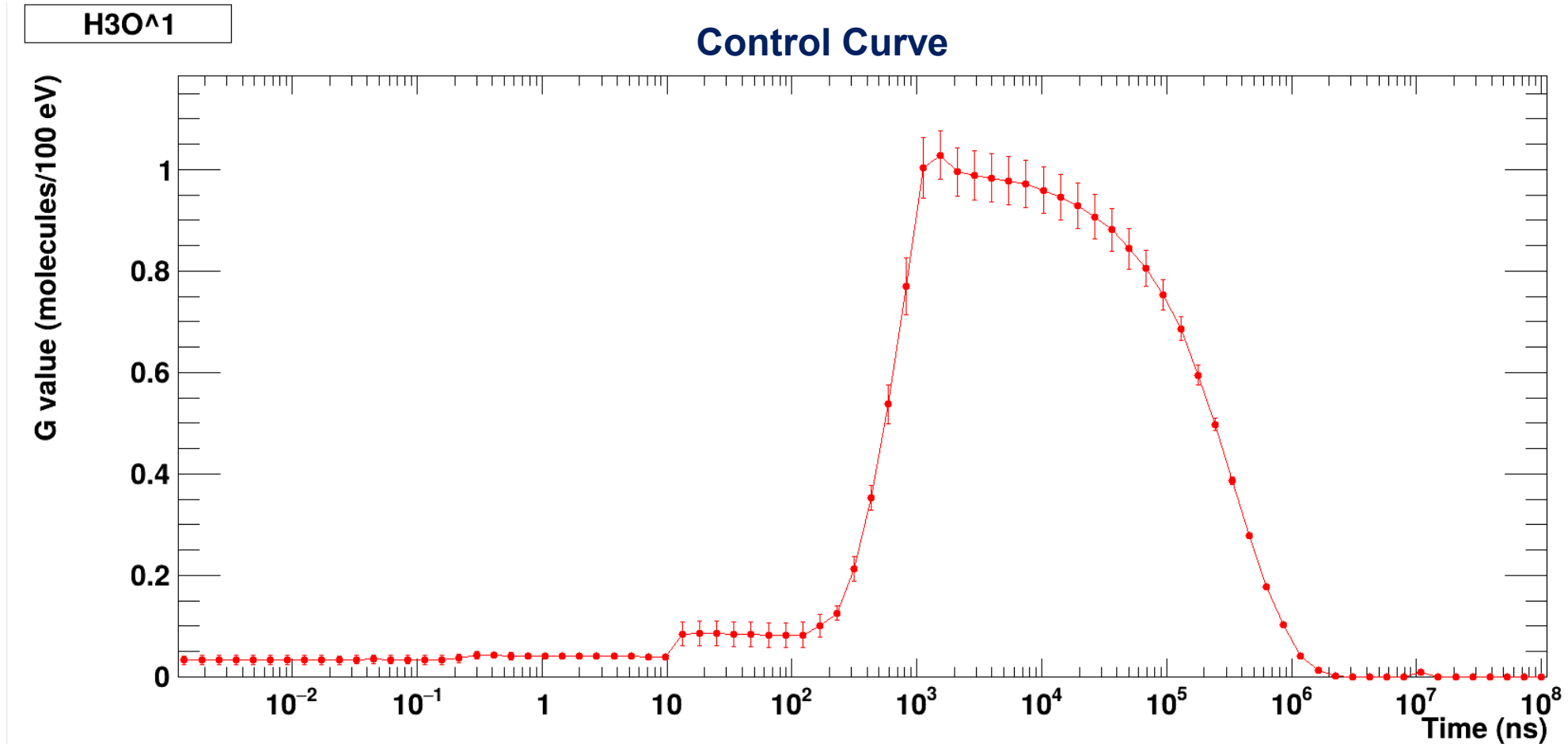
Chromatin domains in the nucleus sub-set are approximately homogeneous at the scale of a sub-volume ($\sim 1.6 \mu\text{m}$). PBC is the standard in molecular dynamics and radiation transport.

PBC COMPARISON PARAMETERS

- World volume: 5 μm side
- DNA geometry: 1131 plasmids
pBR322 arranged in a $4 \times 4 \times 4$ μm^3 cube
- Primary particles: 10 runs of 1 MeV electrons
- Dose per run: 0.5 Gy
- Total dose : 1.23 Gy
- Pulse duration: 1.4 μs
- Dose rate $\sim 1,4\text{e}6$ Gy/s
- Physics list: Geant4-DNA
Option 2
- Chemistry list: Geant4-DNA
Option 3

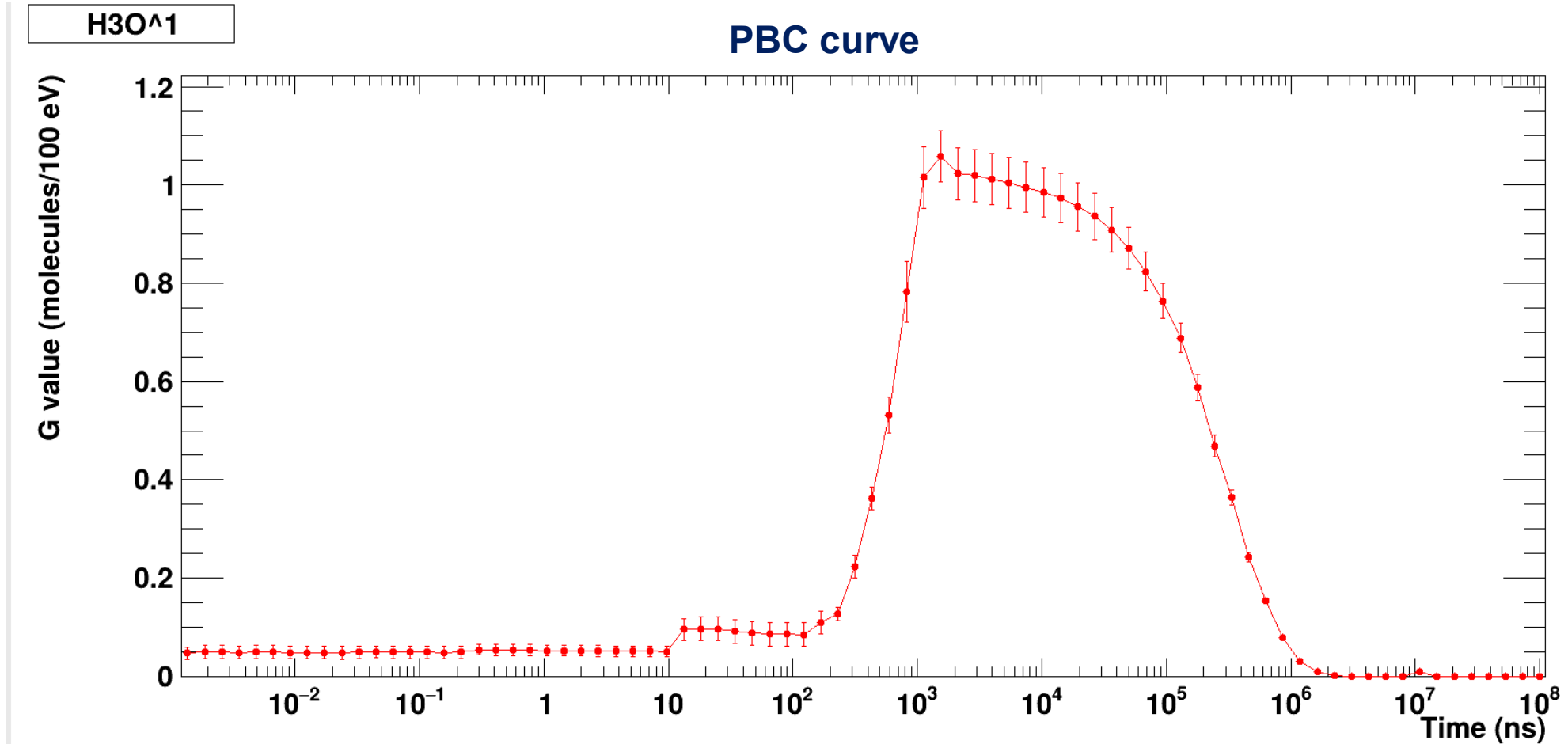


RESULT OF THE PBC IMPLEMENTATION (1)



Curve representing the H3O⁺ G-value with bouncing boundary condition

RESULT OF THE PBC IMPLEMENTATION (2)



Curve representing the H3O⁺ G-value with periodic boundary condition

RESULT OF THE PBC IMPLEMENTATION (3)

```
Dose Absorbed (Gy): 1.23306
Particle : e-   Energy (MeV) : 0.9999   Number of Primaries : 10
Output Damage :
  Number of plasmids:      1331
  Unbroken plasmids:      1123
  Broken plasmids:        208
  Rate of damages per plasmid 0.174305
  Rate of damages per plasmid per dose 0.14136 plasmid-1Gy-1
  Rate of damages per dose per Mbp 32.3701 Gy-1Mbp-1
  Species Hits
  EaqBaseHits 0
  EaqStrandHits 0
  OHBaseHits 591
  OHStrandHits 280
  HBaseHits 0
  HStrandHits 0

  Damage number
  SSB 201
  SSB+ 14
  2SSB 13
  SSB total 228
  DSB 2
  DSB+ 2
  DSB++ 0
  DSB total 4

  Breaks number
  SSB direct 1
  SSB indirect 226
  SSB mixed 1
  SSB total 228
  DSB direct 0
  DSB indirect 3
  DSB mixed 0
  DSB hybrid 1
  DSB total 4

  SSB/DSB 57
```

DNA damage for bouncing boundary (control)

```
Dose Absorbed (Gy): 1.23306
Particle : e-   Energy (MeV) : 0.9999   Number of Primaries : 10
Output Damage :
  Number of plasmids:      1331
  Unbroken plasmids:      1121
  Broken plasmids:        210
  Rate of damages per plasmid 0.168295
  Rate of damages per plasmid per dose 0.136486 plasmid-1Gy-1
  Rate of damages per dose per Mbp 31.2539 Gy-1Mbp-1
  Species Hits
  EaqBaseHits 0
  EaqStrandHits 0
  OHBaseHits 641
  OHStrandHits 262
  HBaseHits 0
  HStrandHits 0

  Damage number
  SSB 203
  SSB+ 7
  2SSB 11
  SSB total 221
  DSB 2
  DSB+ 1
  DSB++ 0
  DSB total 3

  Breaks number
  SSB direct 2
  SSB indirect 218
  SSB mixed 1
  SSB total 221
  DSB direct 0
  DSB indirect 3
  DSB mixed 0
  DSB hybrid 0
  DSB total 3

  SSB/DSB 73.6667
```

DNA damage for Periodic boundary

CONCLUSION & PERSPECTIVE

1. WHAT HAS BEEN DONE :

- Implementation of an initial framework to model various dose rate.
- allow the use of complex geometry (Human endothelial cell nuclei)
- Scavenger
- PBC

2. LIMITATIONS

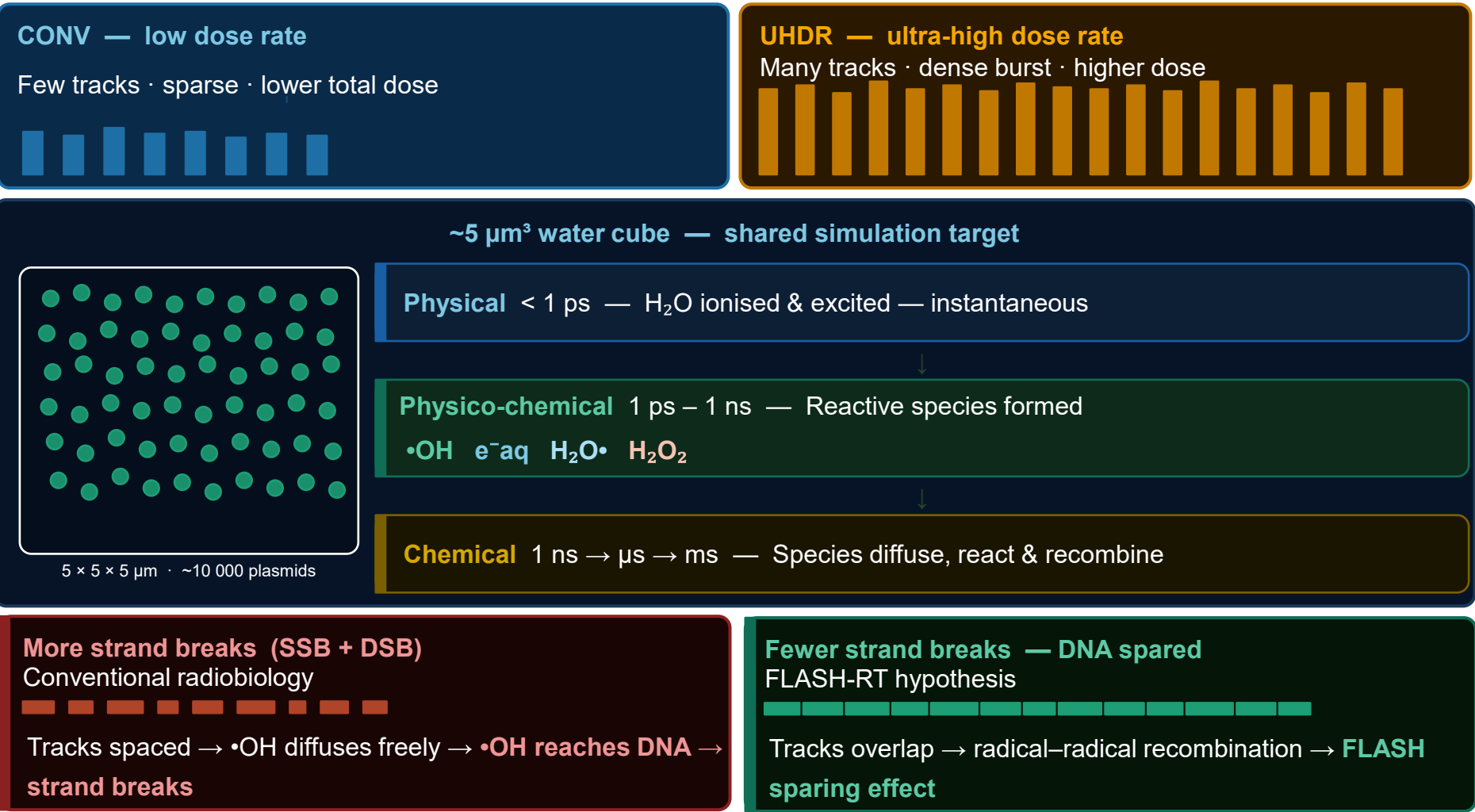
- pure medium vs biological medium
- No inclusion of cellular environment yet nor their reaction (mitochondrial reoxygenation for instance)

3. WHAT'S NEXT

- Implementation of oxygenated damages
- Validation of the code with experimental data
- Exploration of UHDR vs CONV impact on complex dna geometry
- Exploration of the impact of irradiation parameters on the DNA damage in function of its concentration

ILLUSTRATION OF THE DOSE RATE EFFECT

Geant4-DNA · Dose rate & DNA damage in a $\sim 5 \mu\text{m}^3$ water cube



HOW DOES IT WORK ?

Particle transport

- Simulates radiation tracks at the nanometer scale.

2. Energy deposition → Direct DNA damage

- Clustering of ionizations/excitations mapped onto DNA geometry.

3. Chemistry evolution → Indirect DNA damage

- Water radiolysis → radicals diffuse, react, and attack DNA.

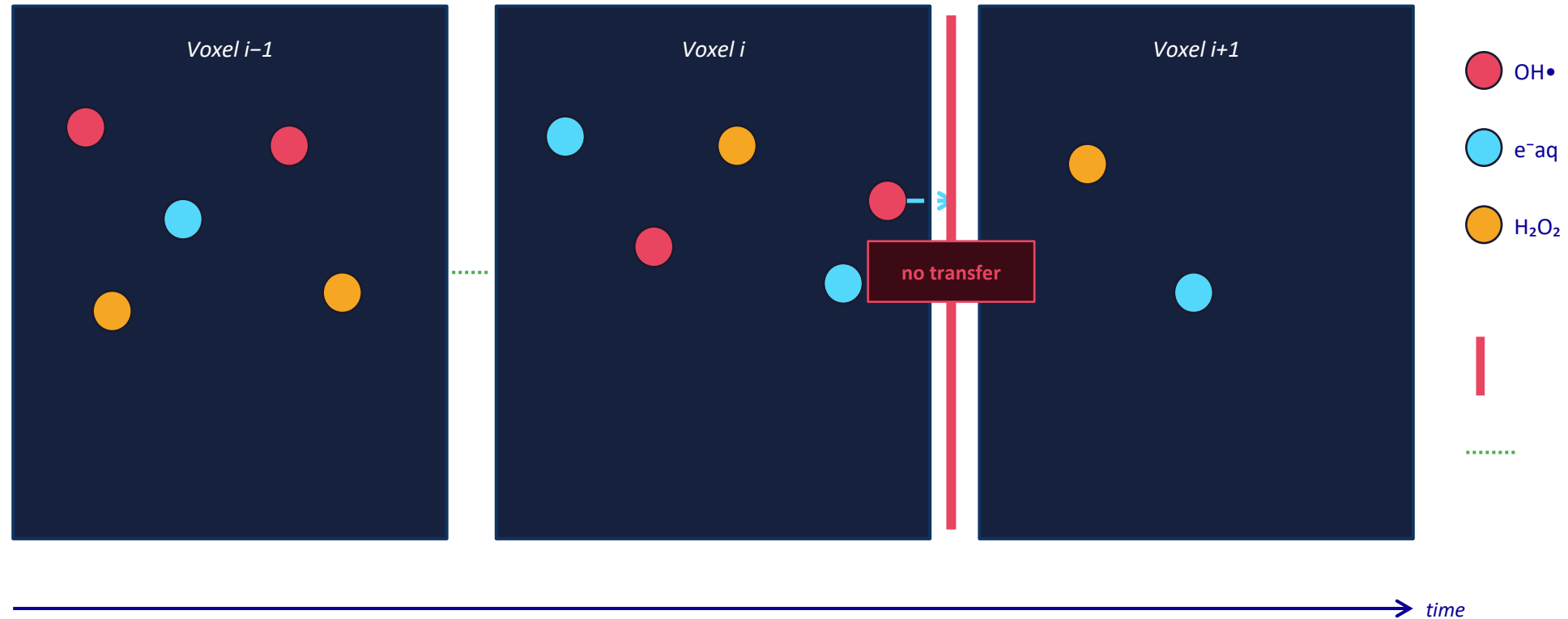
4. Conversion of strand breaks into DSBs and SSBs

- Clustering Algorithm

5. Repair modelling

- Built-in models (TLK, LEM-IV).
- DNA break induction passed to repair module.

VOXEL LIMITATION



Limitation: molecules diffuse within their own voxel, but voxel boundaries block inter-voxel species transfer

DIFFERENT MODELS FOR RADIATION CHEMISTRY

- SEVERAL METHODS EXIST TO MODEL CHEMICAL STAGE :

Model	Spatial Correlation	Diffusion	Reaction Kinetics	Computational Cost
Bulk (homogeneous ODE)	✗ None	✗	✓ Yes	● Very fast
IRT (Independent Reaction Times)	⚠ Approximate	✗	⚠ Semi-explicit	●
IRT-Sync	⚠ Semi-spatial	⚠ Limited	⚠ Partially synchronized	●
SBS (Step-by-Step)	✓ Full	✓ Explicit	✓ Fully explicit	● Heavy

Necessary of SBS for high dose rates where tracks overlap in time and space ?

→ Only SBS fully preserves spatial and temporal radical dynamics