ASNR Autorité de sûreté nucléaire et de radioprotection

MARS 2026 – JDT26 – STERCKX NICOLAS PSE-SANTE/SDOS/LDRI

TIME-RESOLVED DOSE RATE MODELING WITH GEANT4-DNA :

A STEP-BY-STEP APPROACH FOR RADIATION CHEMISTRY

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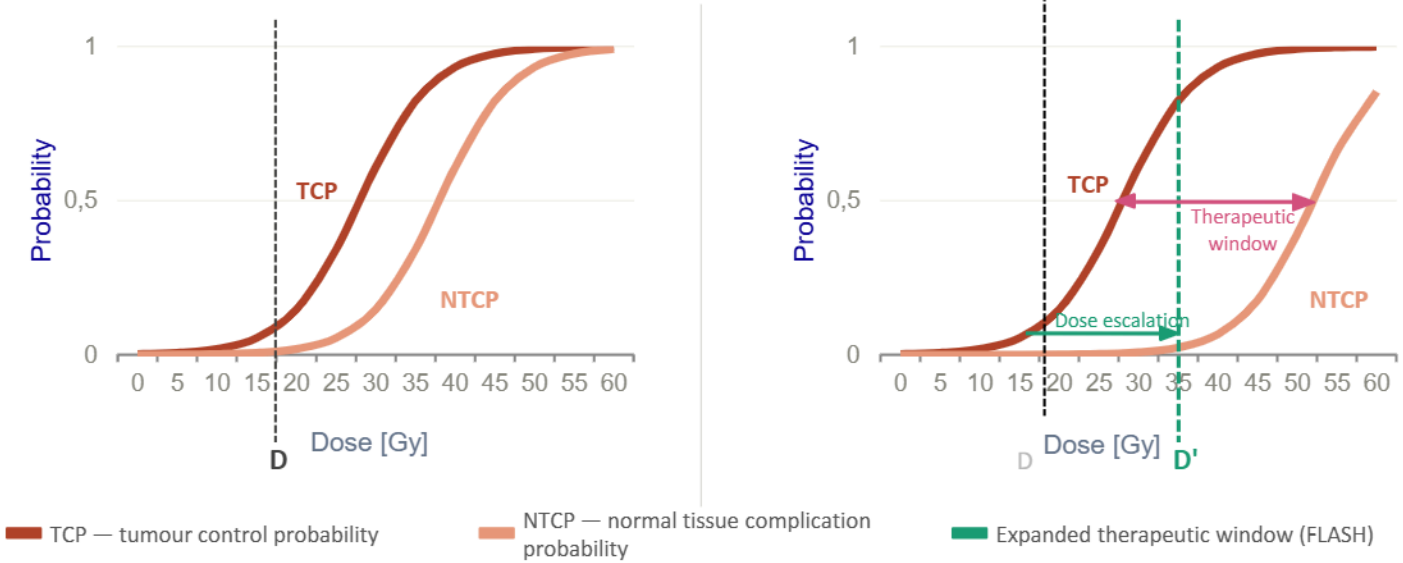
CHALLENGES OF MODERN RADIOTHERAPY (1)

- 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 : > 40Gy/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 damage and other biological endpoints at varying dose rates**
- Observe biological endpoints directly

✓ *Gold standard for biological insight*

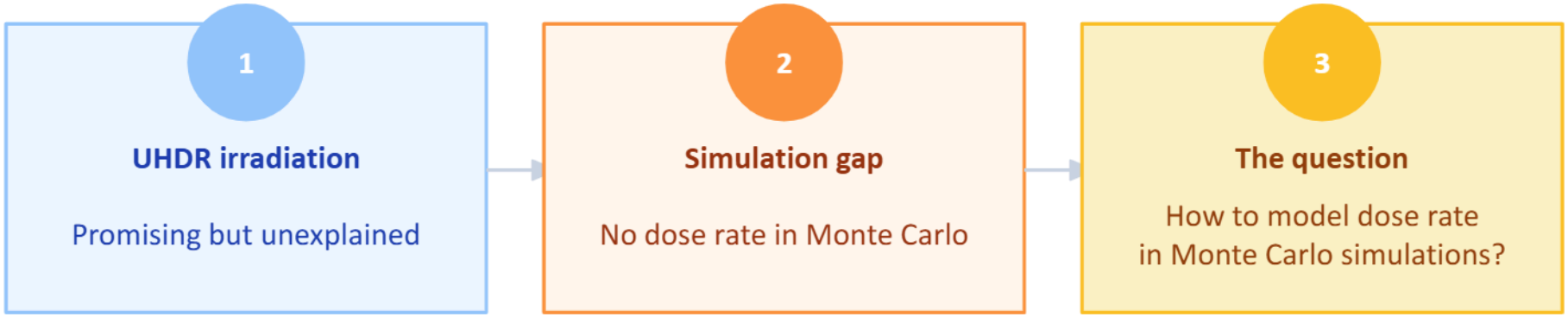
vs

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**

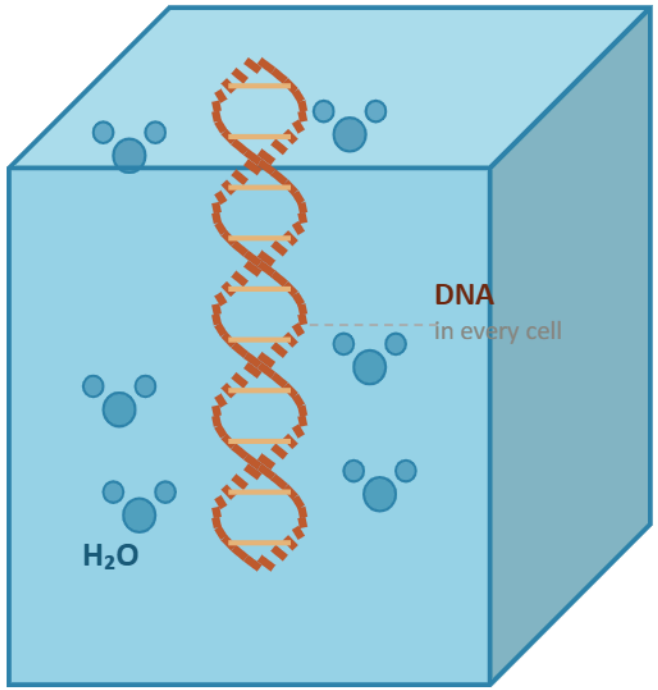
CHALLENGES OF MODERN RADIOTHERAPY (3)



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.

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



~70% of biological tissue

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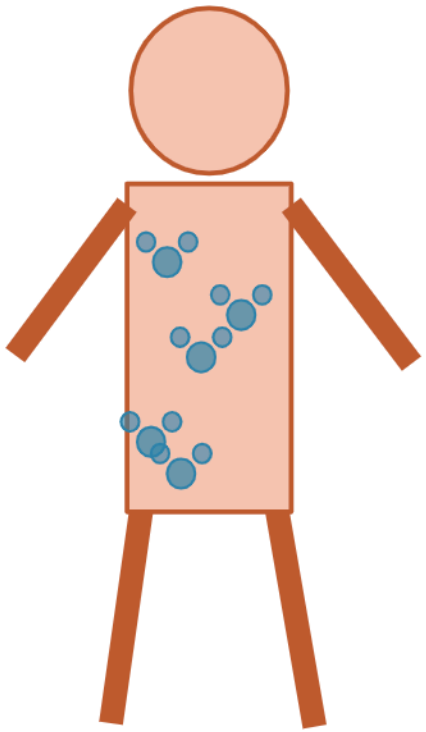
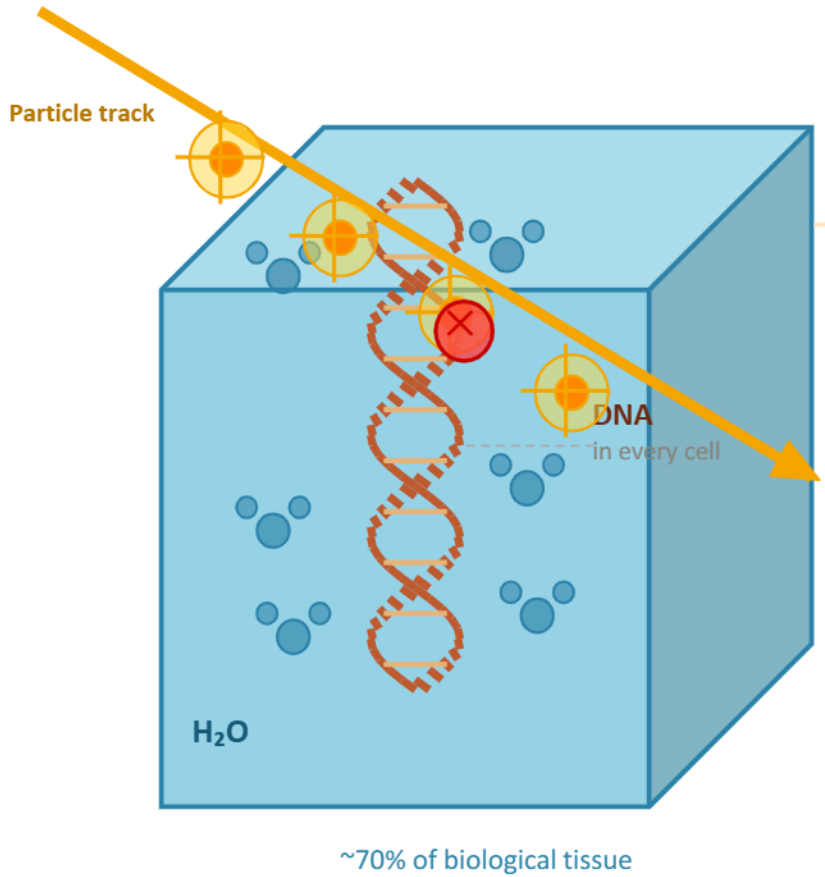


~70% water
+ DNA in every cell

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



Physical stage
Instantaneous ionizations & excitations
→ **Direct DNA damage** | **femtosecond scale**

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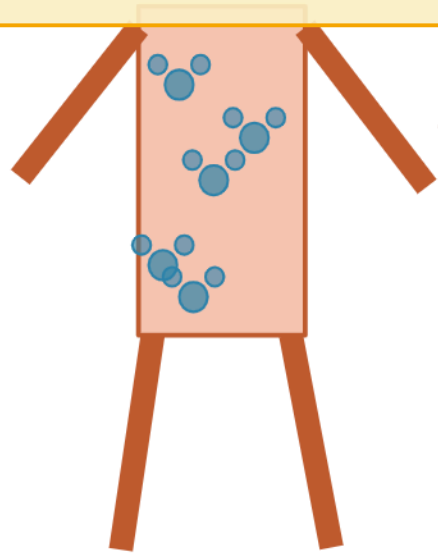
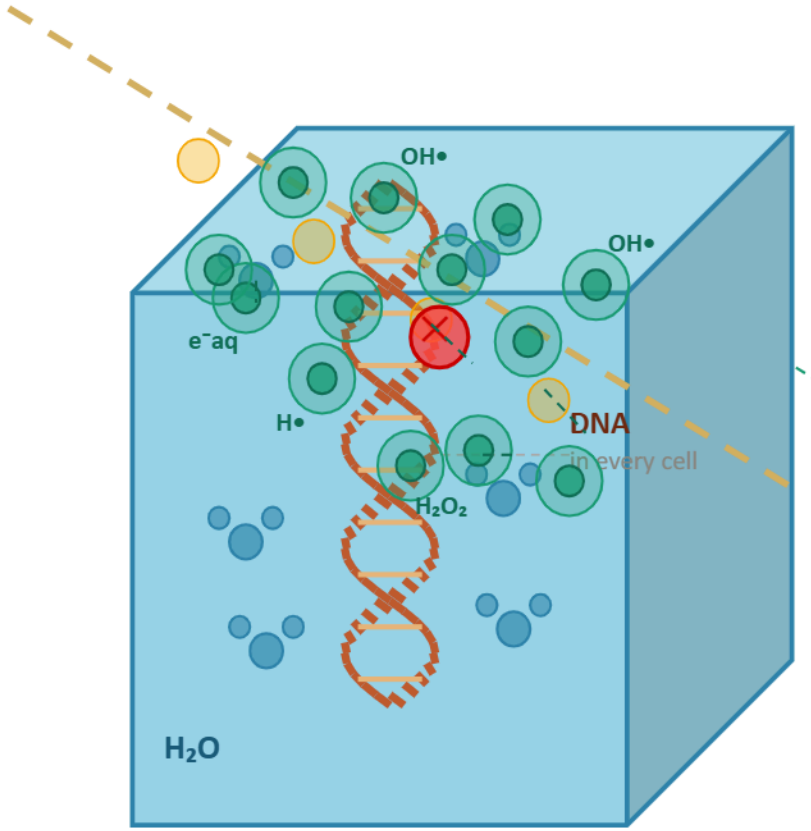


~70% water
+ DNA in every cell

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



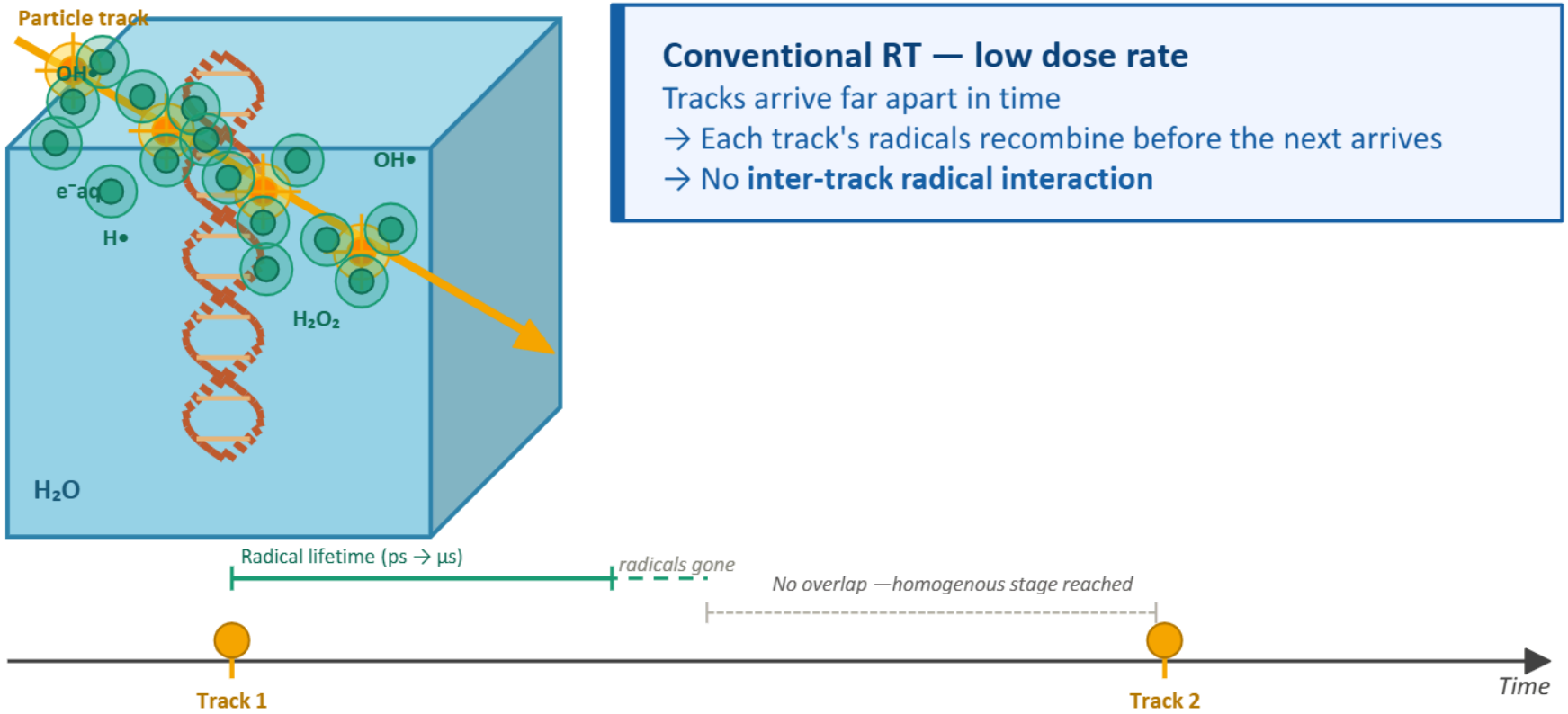
~70% of biological tissue

Physical stage (fs scale)
→ **Direct DNA damage**

Chemical stage
Radicals diffuse & react — ps to µs scale
OH•, H•, e⁻aq … → **Indirect DNA damage** (~70%)

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

Low dose rate — tracks isolated in time



Conventional RT — low dose rate

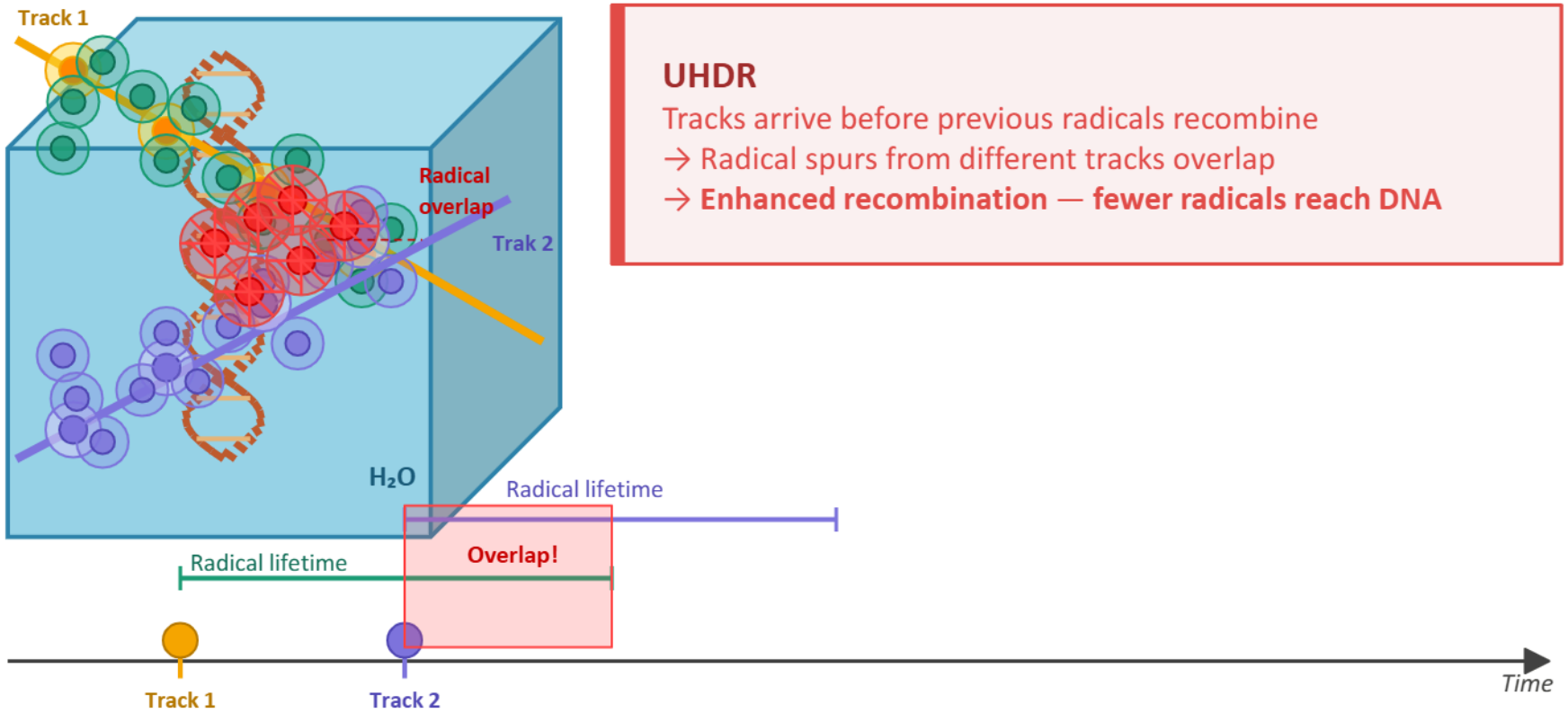
Tracks arrive far apart in time

→ Each track's radicals recombine before the next arrives

→ No **inter-track radical interaction**

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

High dose rate — tracks overlap in time



UHDR

Tracks arrive before previous radicals recombine

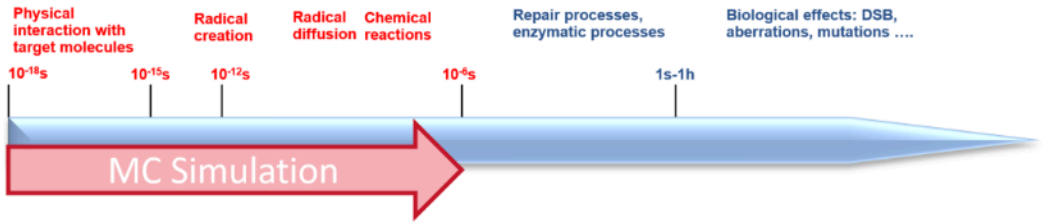
→ Radical spurs from different tracks overlap

→ **Enhanced recombination — fewer radicals reach DNA**

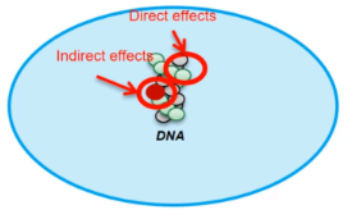
GEANT4-DNA: MONTE CARLO TRACK STRUCTURE SIMULATION TOOLKIT

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

- **FULLY INTEGRATES :**
  - → Physicalstage (fs) : ionizations, excitations, elastic scatterings
  - → Chemical stage (ps to µs) : 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**

- Electron, ions
- Ionizations / Excitations
- Sub-picoseconds

- OH^+, $e^-_{aq,}$ etc...
- Diffusion, reactions
- Picosecond to microseconds

- DNA Damage and repair
- Seconds to hours

GEANT4-DNA
A SIMULATION TOOLKIT

DNA DAMAGE SIMULATION CODES IN GEANT4-DNA

DSBANDREPAIR

- Monte Carlo simulation framework developed by Idri based on Geant4-DNA and released as an advanced example
- Designed to study DNA single-strand and double-strand break (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 :

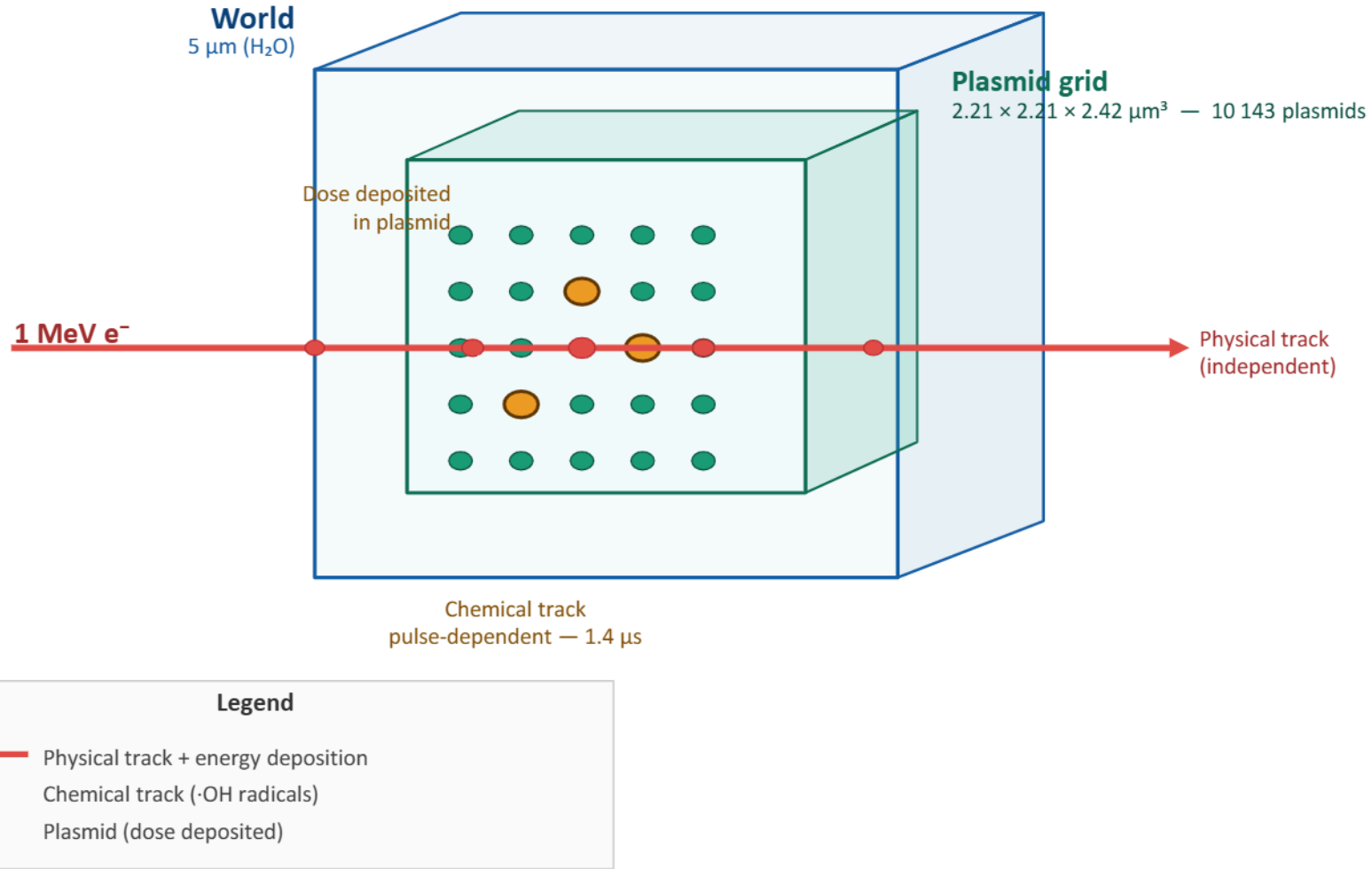
- Accurate modeling requires realistic chromatin structures
- FractalDNA geometries are procedurally generated and may lack nucleosome/fiber-level detail
- DNAFabric provides explicit DNA, nucleosome, and fiber structures

Method / Implementation :

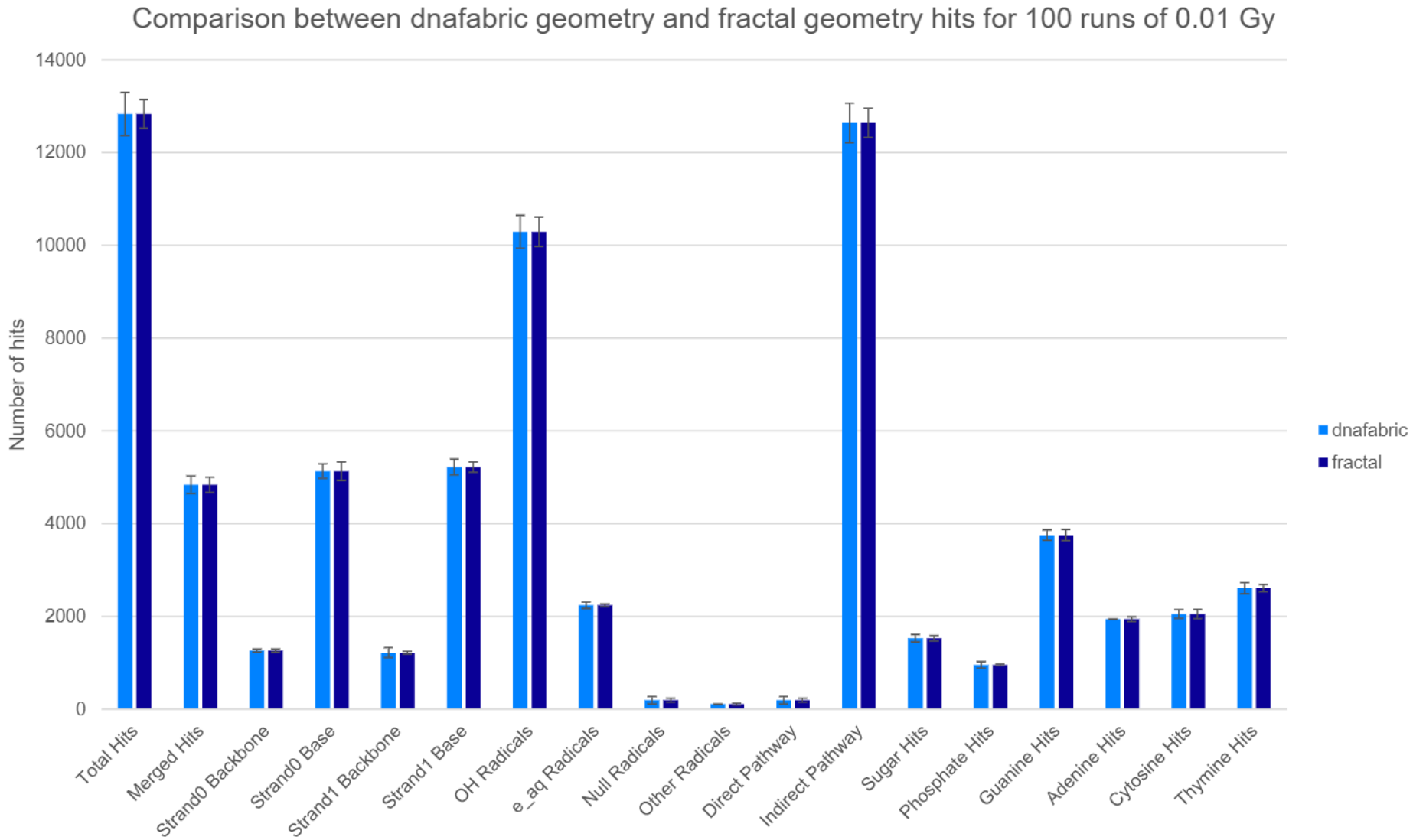
- MolecularDNA code adapted to read DNAFabric files directly
- Preserves strand topology, base-pair organization, and nucleosome/fiber structure

GEOMETRY OVERVIEW

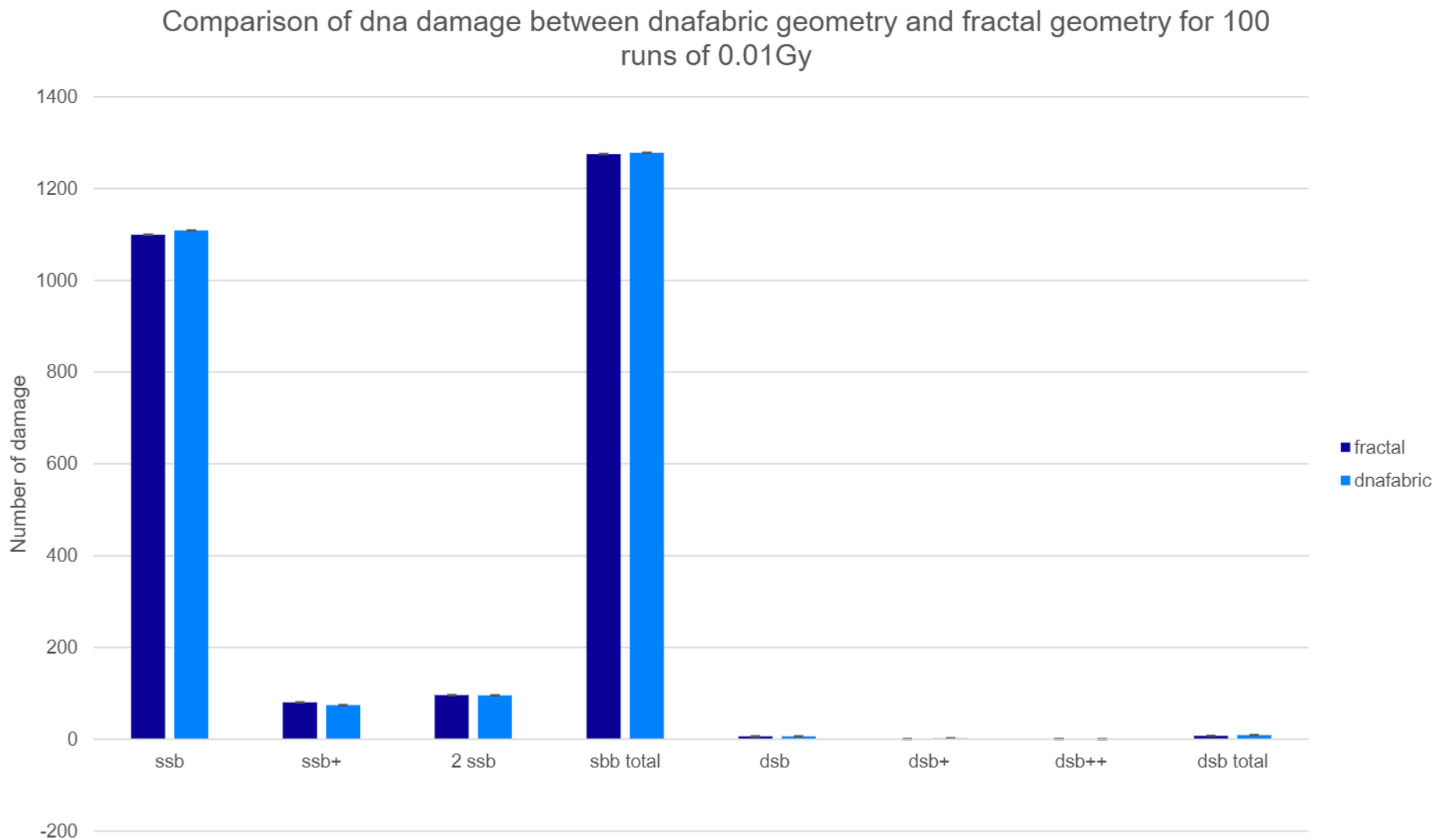
- World volume: 5 µm side
- DNA geometry: 10143 plasmids pBR322 arranged in a 4.42 × 4.42 × 4.84 µm³ cube
- Primary particles: 100 runs of 1 MeV electrons
- Dose per run: 0.01 Gy
- Total dose : 1 Gy
- Pulse duration: 1.4 µs
- Dose rate ~8000 Gy/min
- Physics list: Geant4-DNA Option 2
- Chemistry list: Geant4-DNA Option 3



VALIDATION OF THE GEOMETRY IMPLEMENTATION (1)



VALIDATION OF THE GEOMETRY IMPLEMENTATION (2)



WORK IN PROGRESS – SCAVENGER HANDLING

Towards **realistic biological environments** and **experimental validation**

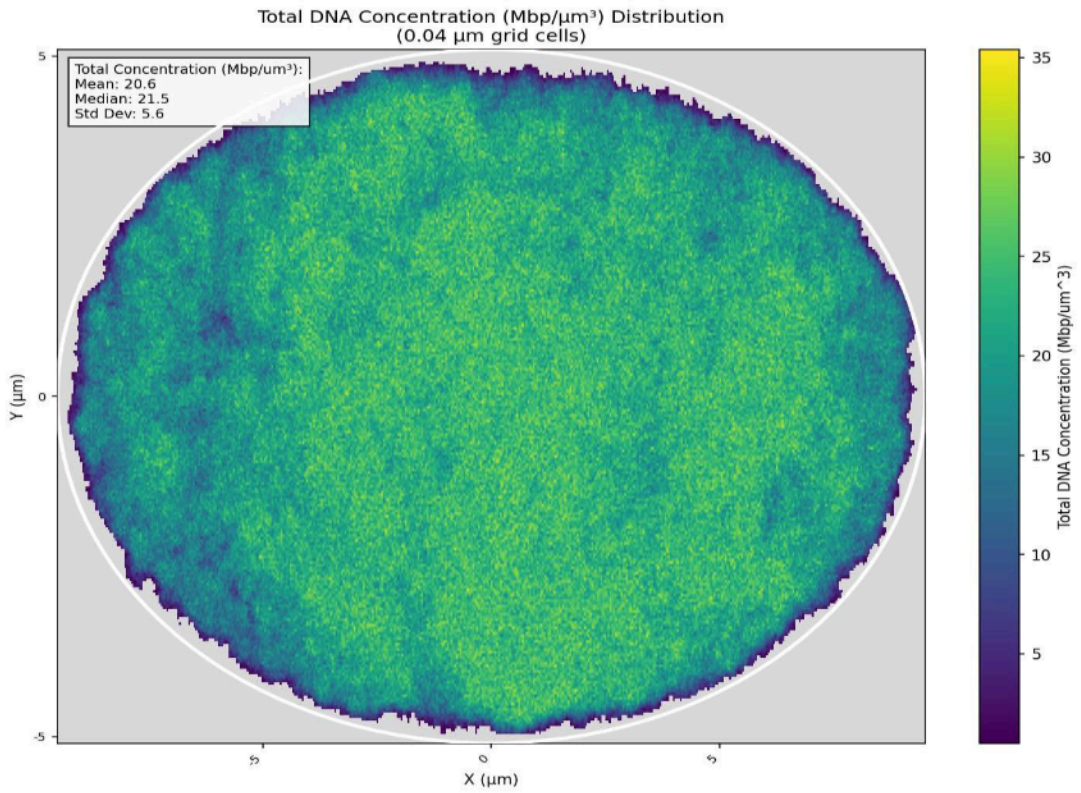
Introduce **O_2, $H3O^+/OH^-$ (pH of the medium) and other scavengers**

Handle **concentration, diffusion, and reaction rates**

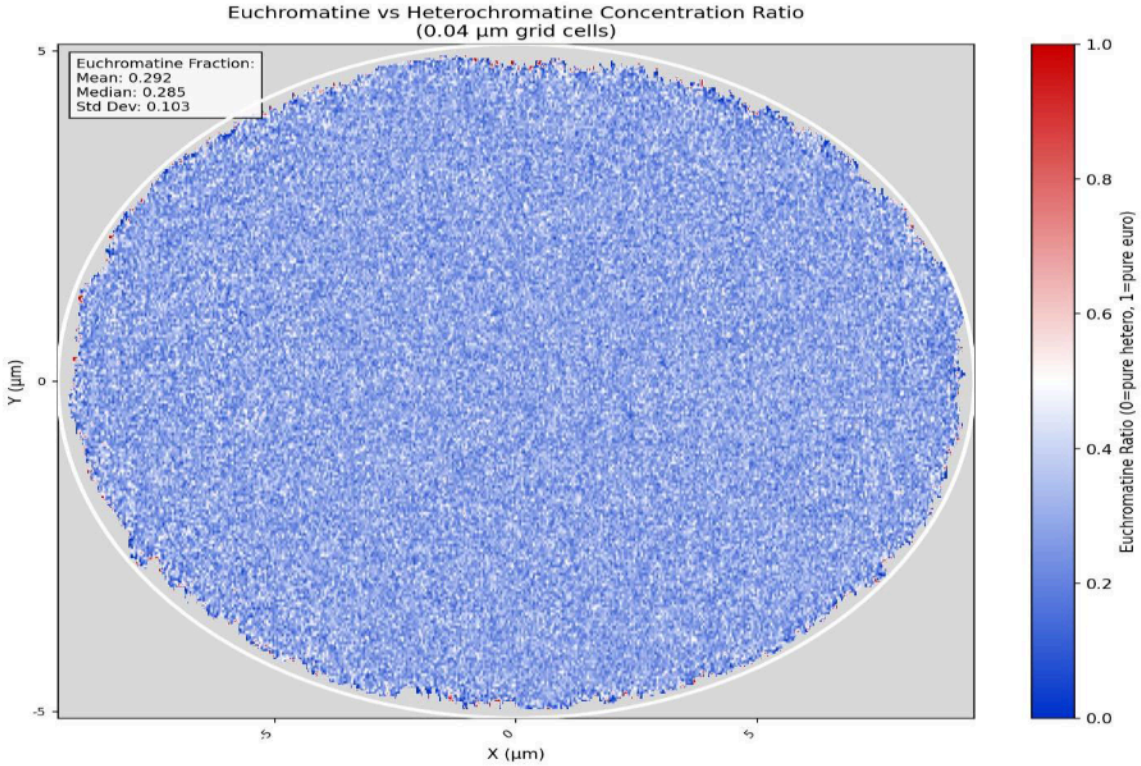
Extend chemistry **aqueous solution**

Mapping chromatin organisation and DNA concentration across the entire endothelial nucleus

Total DNA Concentration · 40 nm grid



Euchromatin / Heterochromatin Ratio · 40 nm



2 574 583 Voxel

6.06805 Gbp

20.6 Mbp/µm³
mean DNA conc.

29.2%
euchromatin fraction

0.04 µm
grid resolution

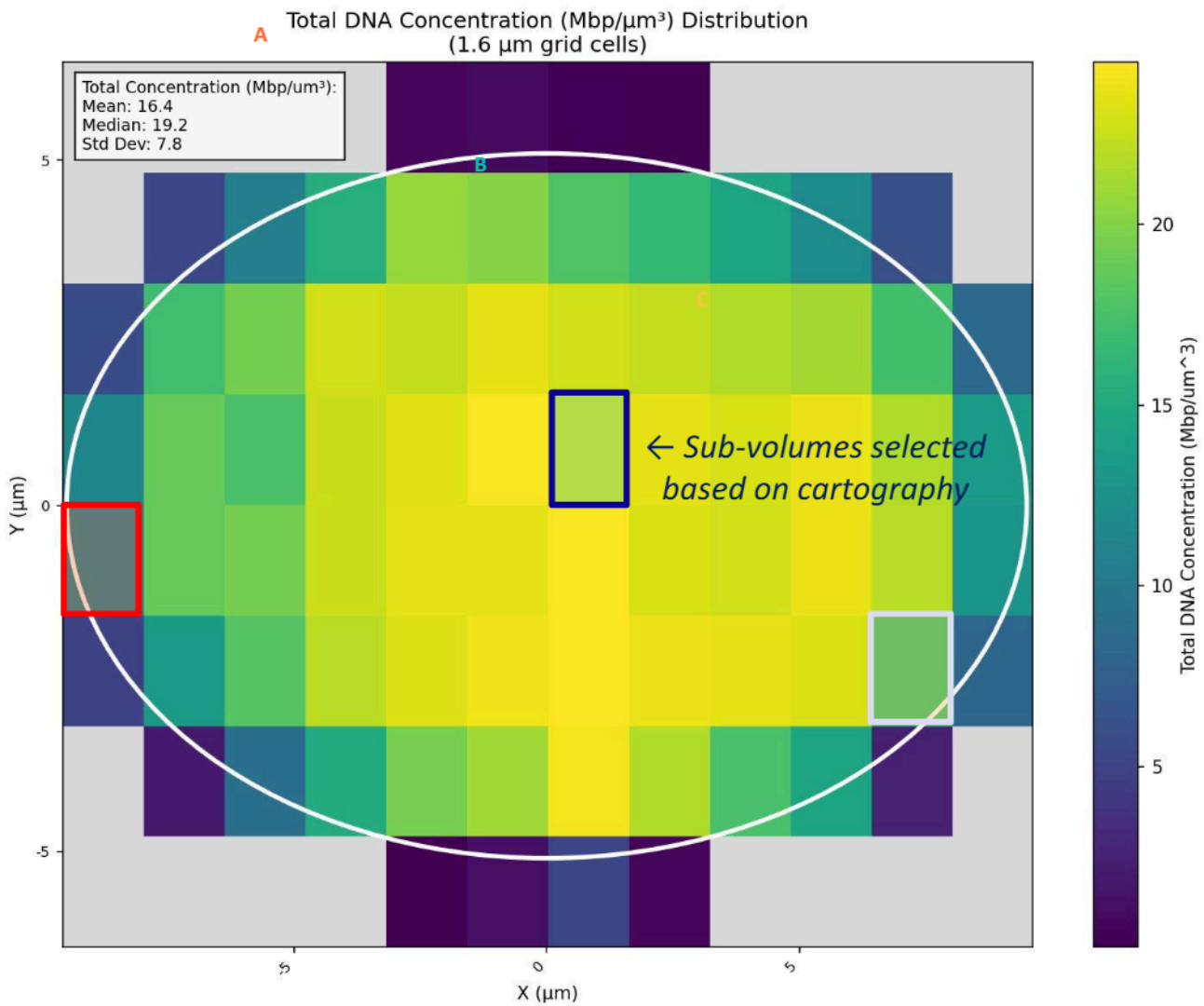
What this cartography tells us

- 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

→ 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 & 1.6µm 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

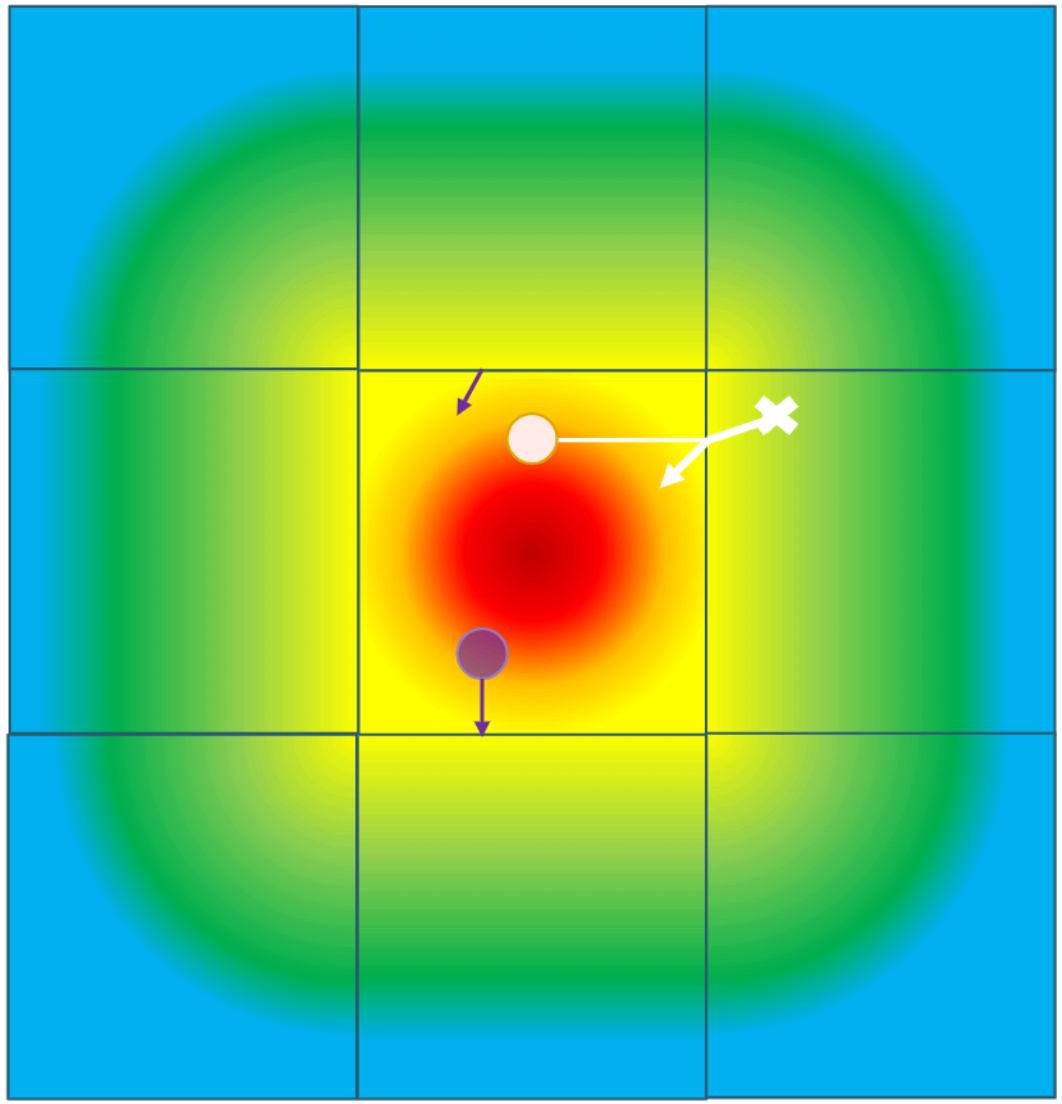
Each sub-volume is simulated separately — feasible compute time per box

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 interior are approximately translationally periodic at the scale of a sub-volume (~1.6 µm). PBC is the standard in molecular dynamics and radiation transport.

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)

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