Biology modelling

geant4-dna.org

From DNA strand breaks to repair models

Konstantinos Chatzipapas
Delft University of Technology, Delft, Netherlands
k.chatzipapas@tudelft.nl

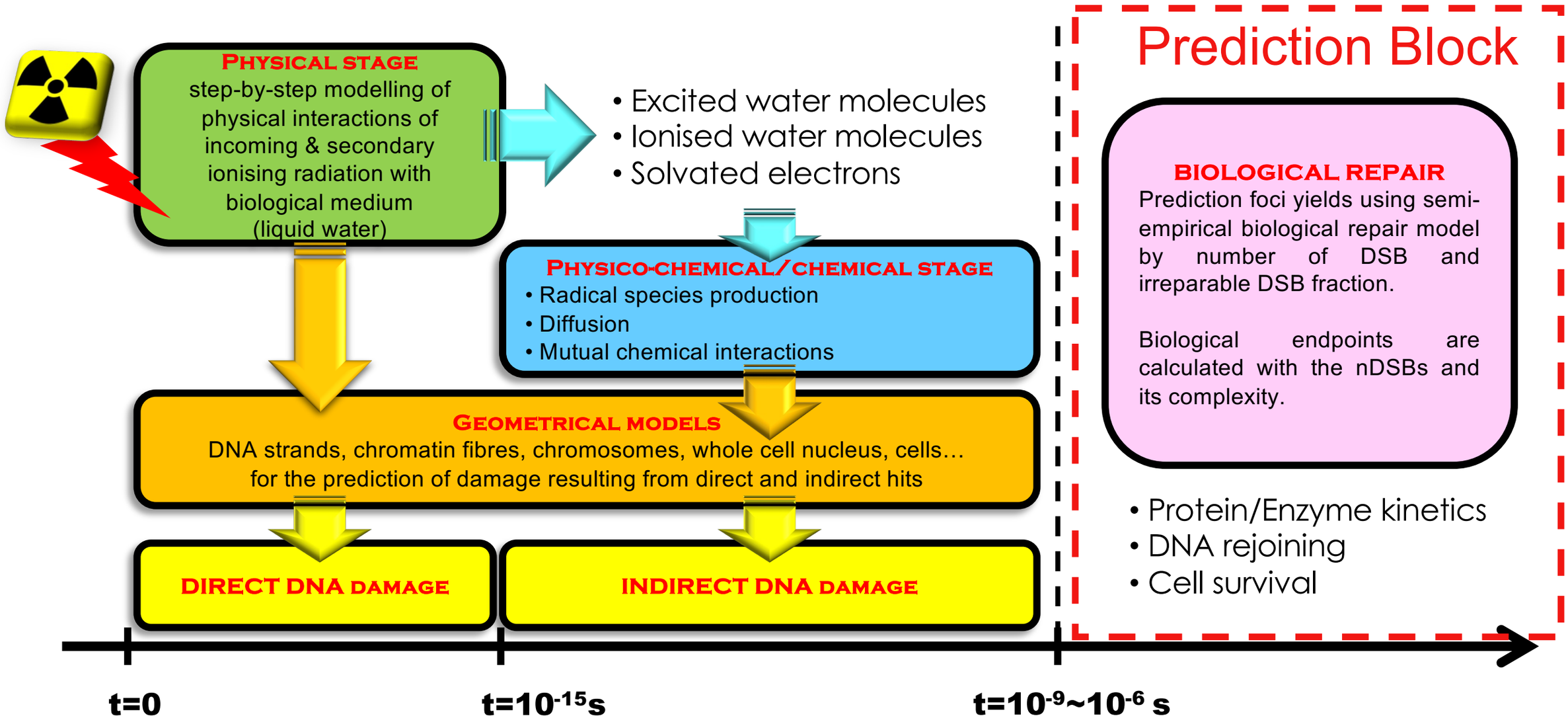
On behalf of the Geant4-DNA collaboration

2026 Geant4-DNA International Tutorial
Princess Srisavangavadhana Faculty of Medicine,
Bangkok, Thailand

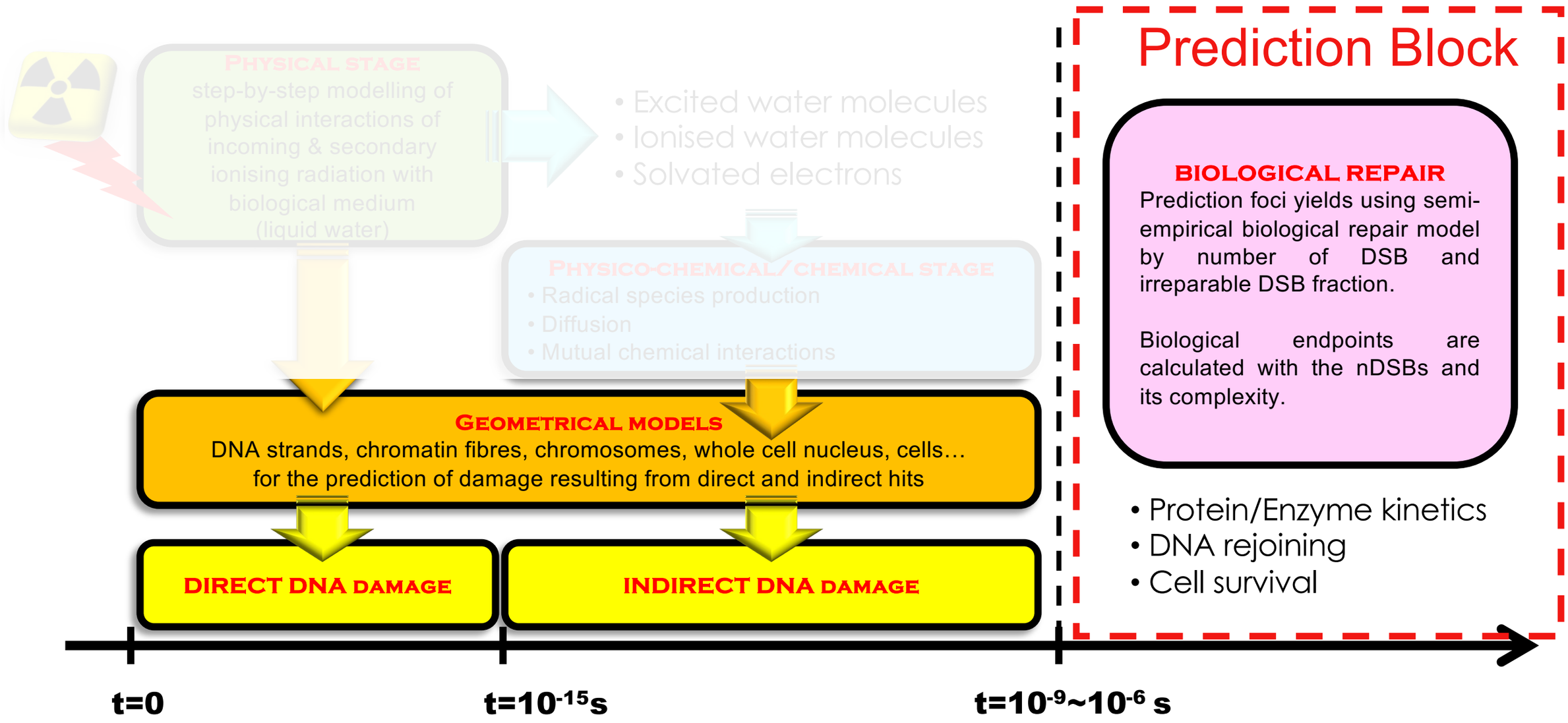
18-20/03/2026

Geant4 version 11.2
Released in December 2023

Geant4-DNA implementation



Geant4-DNA implementation



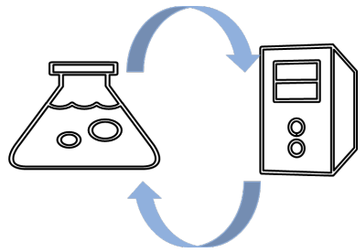
Contents of this talk

- Why biology modelling?
- Geometrical models
- Damage calculation and classification
- Biological models
- Geant4-DNA examples
- In conclusion

Contents of this talk

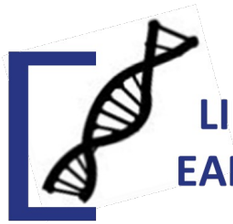
- Why biology modelling?
- Geometrical models
- Damage calculation and classification
- Biological models
- Geant4-DNA examples
- In conclusion

Understanding radiation-induced effects



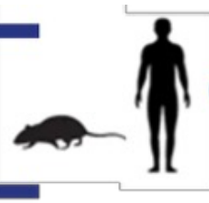
IRRADIATION

PARTICLE
ENERGY
DOSE
DOSE RATE
FRACTIONATION
ENVIRONMENT



LINK PHYSICS/
EARLY DAMAGE

MOLECULAR
MECHANISMS



CONTROL/
RISK

TCP/NTCP

WEIGHT
SURVIVAL

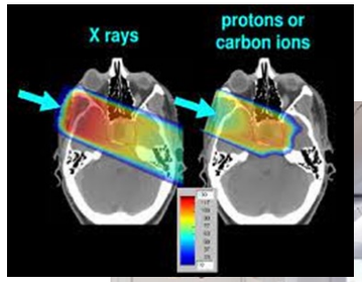
HISTOLOGY
ANATOMO PATHOLOGY
EARLY AND LATE INJURIES

Why simulation in radiobiology?

- Correlating dosimetric quantities with radiation induced effects
  - Understand radiation-induced biological effects from a mechanistic point of view
  - Using proven methods and tools to answer emerging questions

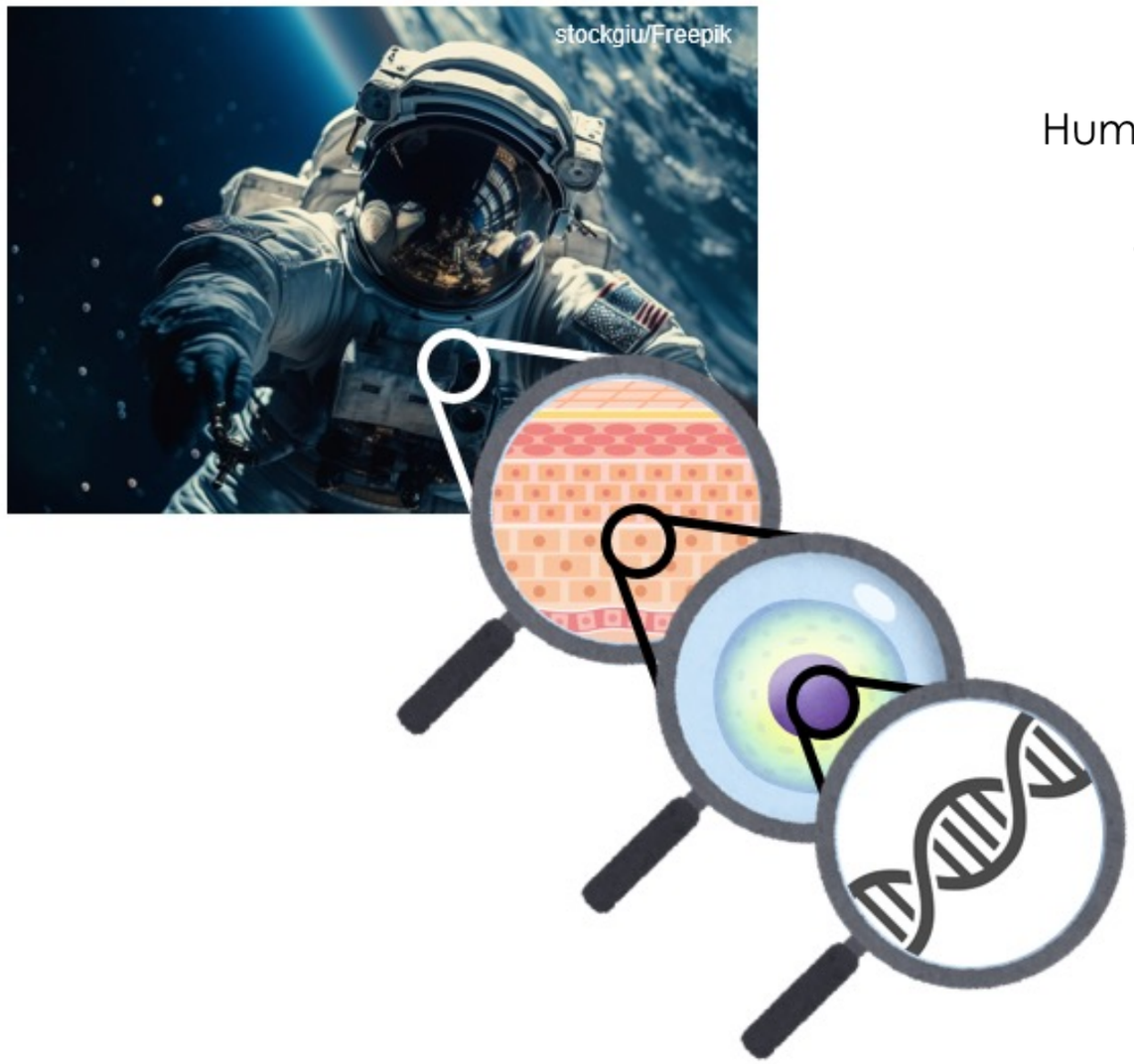
- Medical field
  - Identify the mechanisms leading to tolerance of healthy tissues or disease control
  - Develop predictive models to optimize treatments

- Space domain
  - Identifying the effects of cosmic radiation: risk models for long-duration manned flights



Hadrontherapy Caen
Caen, France, 2018

A multi-scale approach



Human: ~ 1cm - 100 cm

Radiation Sickness (Organ Level Effect)

Tissue: ~ 1 mm - 10 mm

Radiation Injury

Cell: ~ 1 µm - 10 µm

Cell death

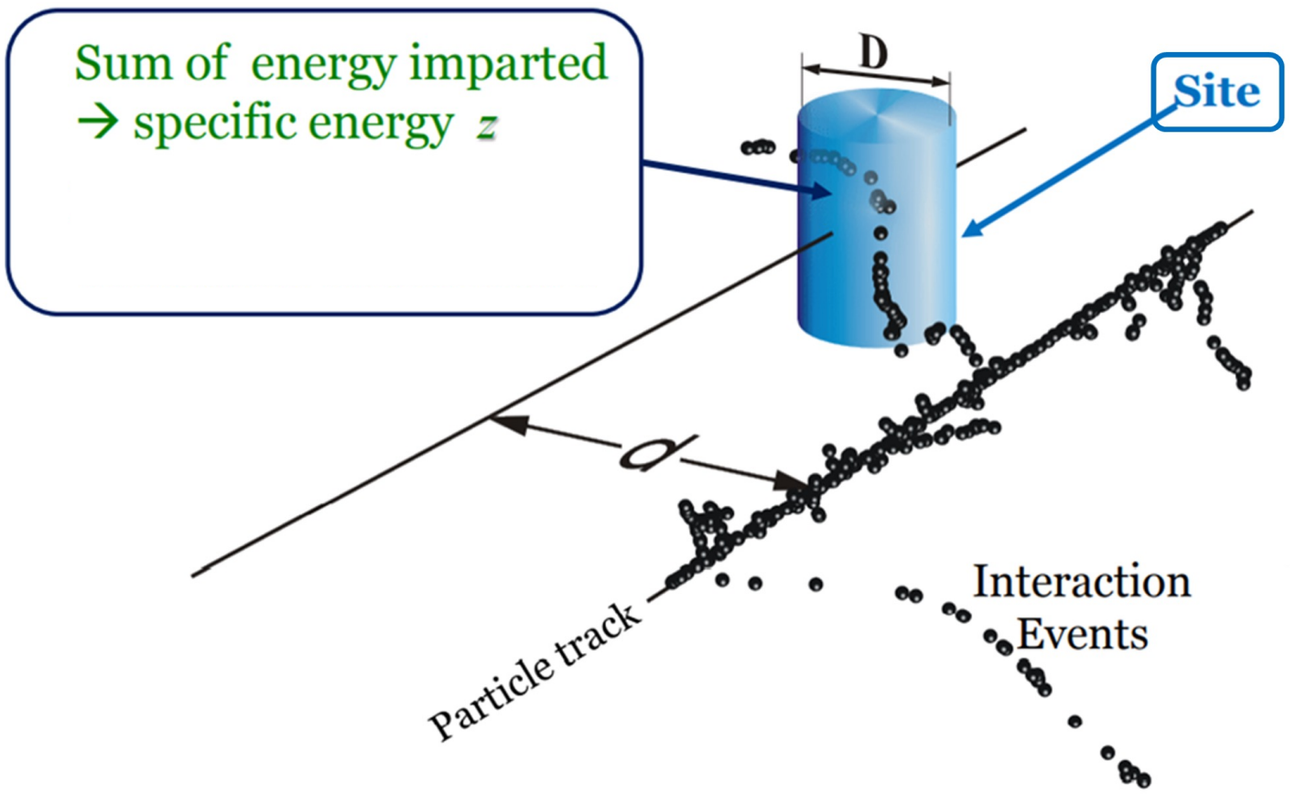
DNA: ~ 1 nm - 10 nm

DNA damage, mutation, …

You must use a dosimetry formalism adapted to your situation

Formalisms to get dose effect relationship

- Microdosimetry

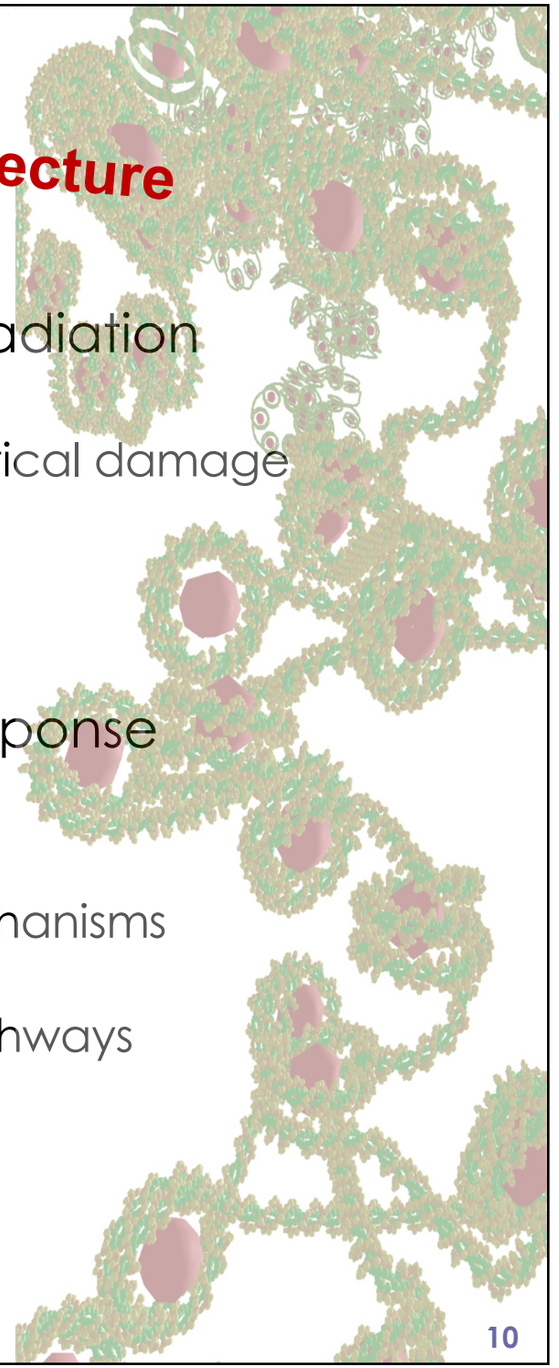


From Hans Rabus, KHYS Course "Monte Carlo Simulations for Micro- and Nanodosimetry", KIT, Karlsruhe, 25-26 October 2011

- Always ask yourself the question of choosing the "Site", i.e. the critical target volume for observing the desired biological effect
- MCTS codes are required at cellular scale due to their high resolution

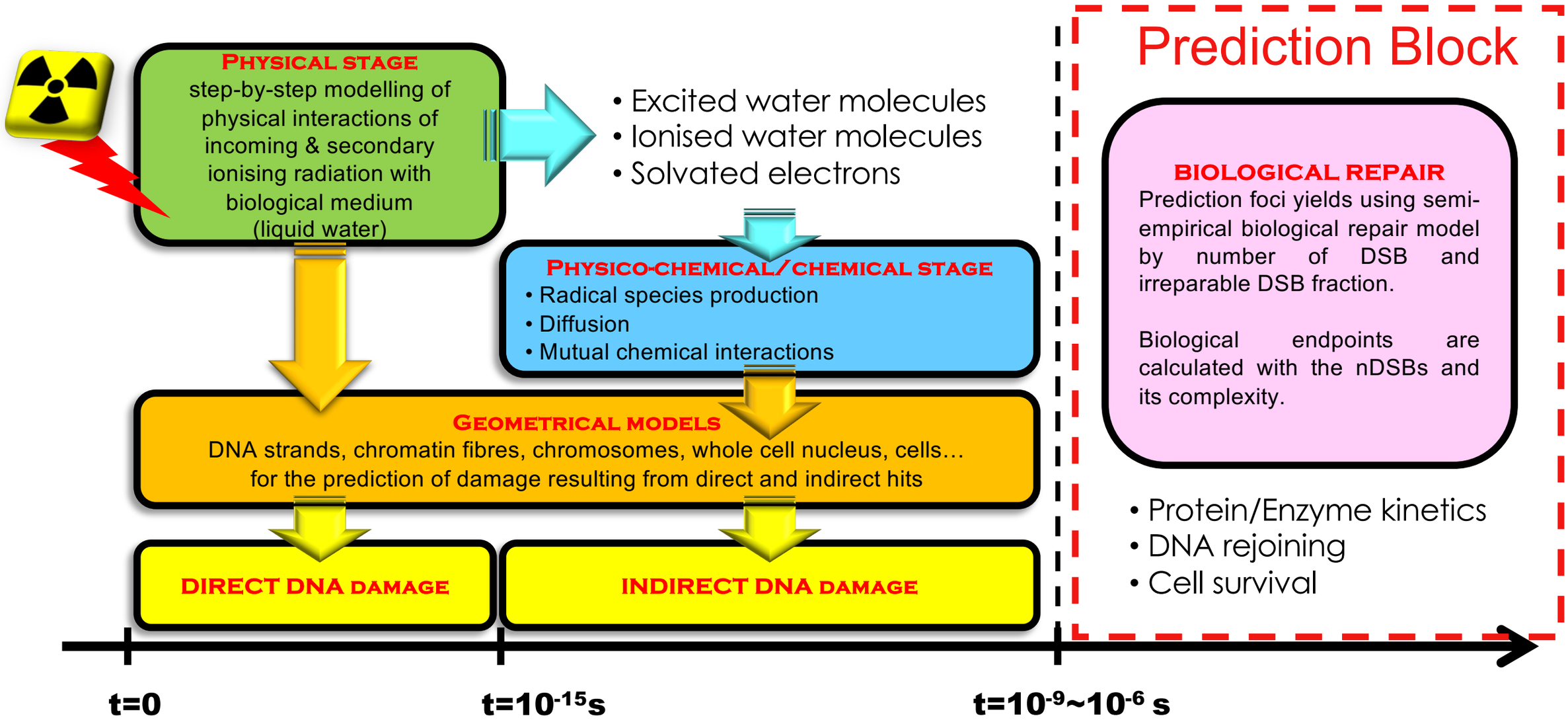
Example of the DNA target

Focus of this lecture



- DNA damage considered as a key initiating event leading to radiation induced effects
  - Complex Double Strand Breaks (DSBs) are recognized as the most critical damage
  - A multitude of chemical and enzymatic reactions is activated
  - DSBs misrepair can lead to genetic aberrations and cell death, mutation or genomic instability
- To predict cell's fate, mathematical models calculate cell's response to the induced damage, based on different repair pathways
  - Modelling in radiobiology began in the 1920s
  - The evolution of the models over time reflects our knowledge of mechanisms involved in damage repair
  - Repair models tend to integrate the action of the different repair pathways that are identified

Geant4-DNA implementation

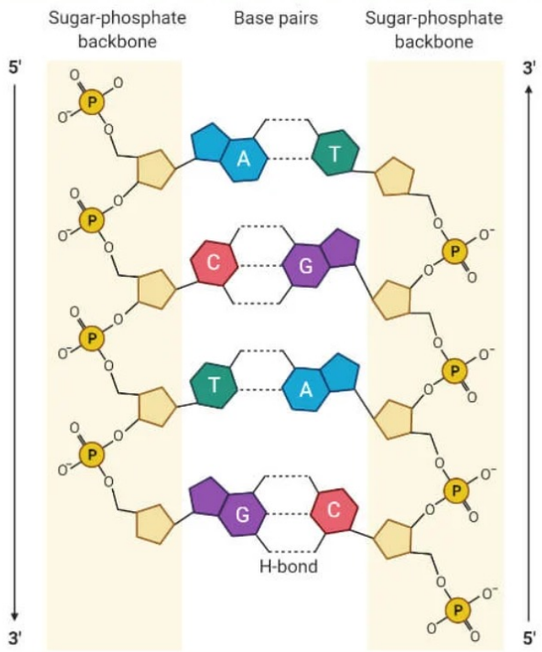


Contents of this talk

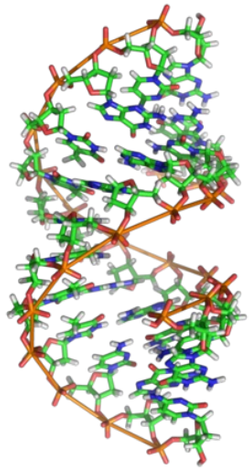
- Why biology modelling?
- Geometrical models
- Damage calculation and classification
- Biological models
- Geant4-DNA examples
- In conclusion

The DNA molecule

Molecular structure



DNA forms

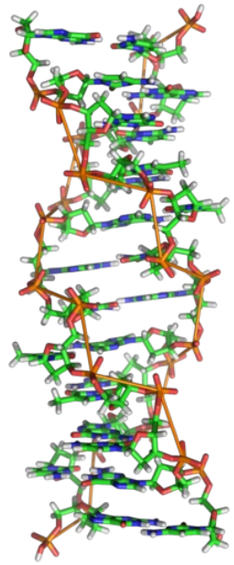


A-DNA

under dehydrating conditions, rare

B-DNA

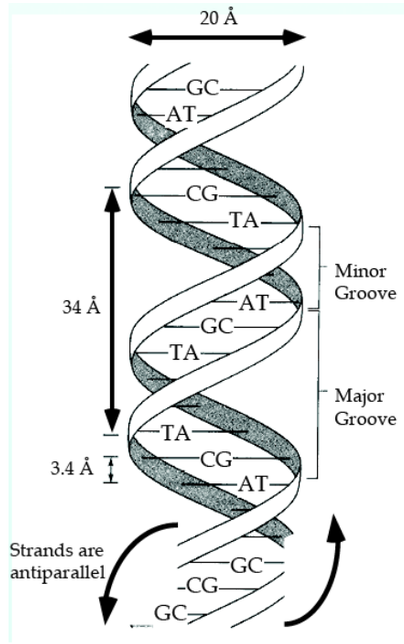
the most common form, discovered by Watson and Crick



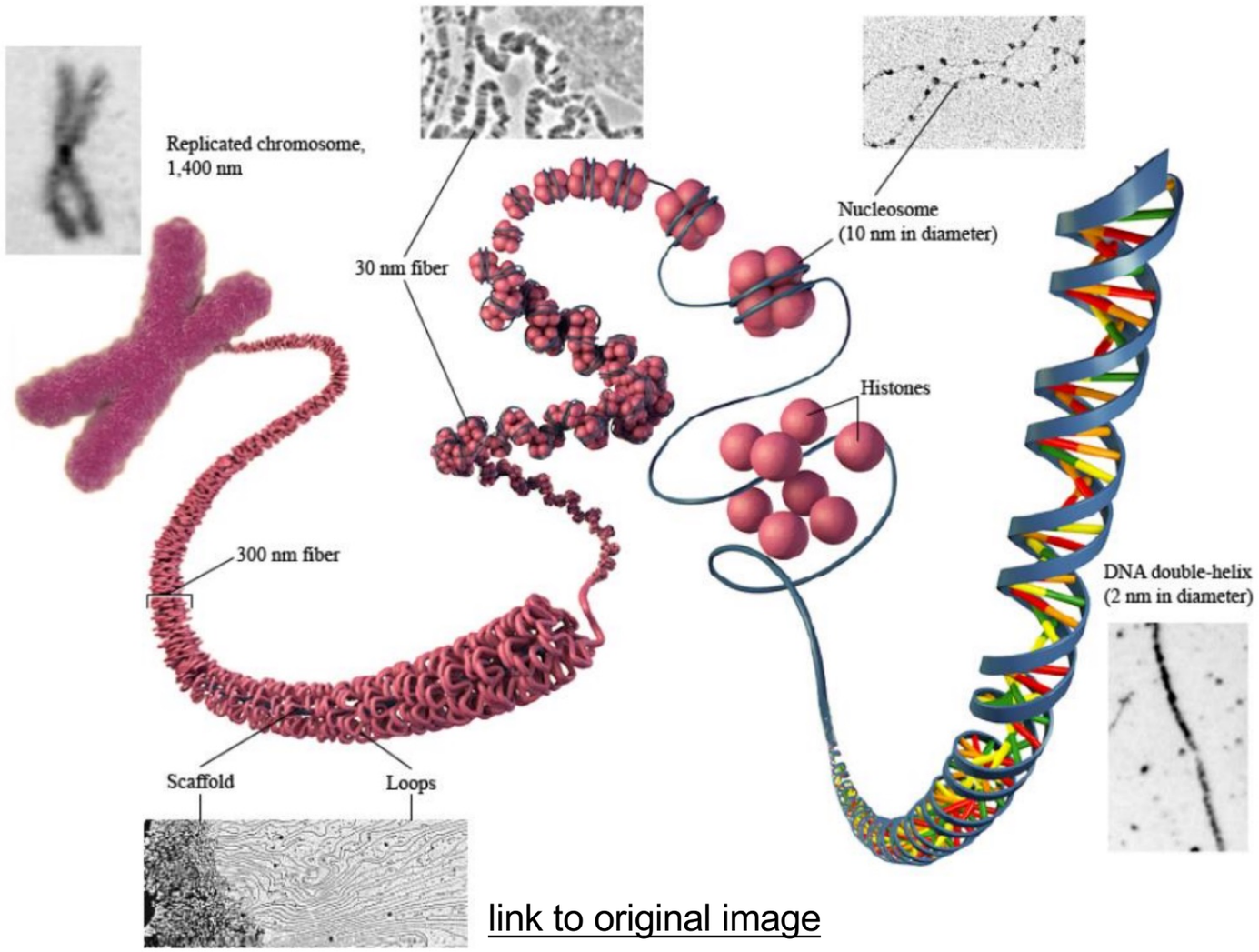
Z-DNA

role in the regulation of gene expression

B-DNA



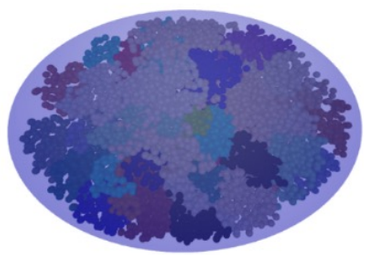
DNA molecule compaction



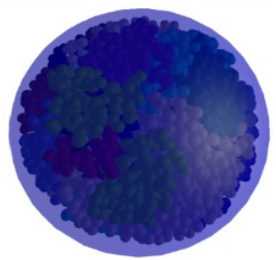
link to original image

Examples of cell nucleus models

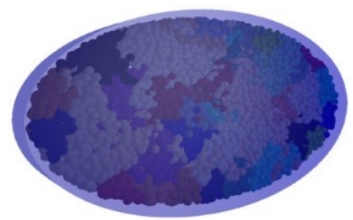
Characteristics	Fibroblast	Lymphocyte	Endothelial
Shape	Ellipsoid	Sphere	Elliptical cylinder
Mean dimensions	Semi-major: 9.85 µm Semi-minor$_1$: 7.1 µm Semi-minor$_2$: 2.5 µm	Radius: 5 µm	Semi-major: 9.5 µm Semi-minor: 5.1 µm Height: 2 µm
Volume (µm^3)	732.4	523.6	304.4
$\bar{l}$ parallel irradiation (µm)	3.66	7.02	2.00
$\bar{l}$ isotropic irradiation (µm)	5.81	6.67	3.05
E to obtain 1 Gy (MeV)	4.58	3.27	1.90
n (Gbp)	6	6	6
DNA density (Mbp/µm^3)	8.19	11.5	19.71



Fibroblast



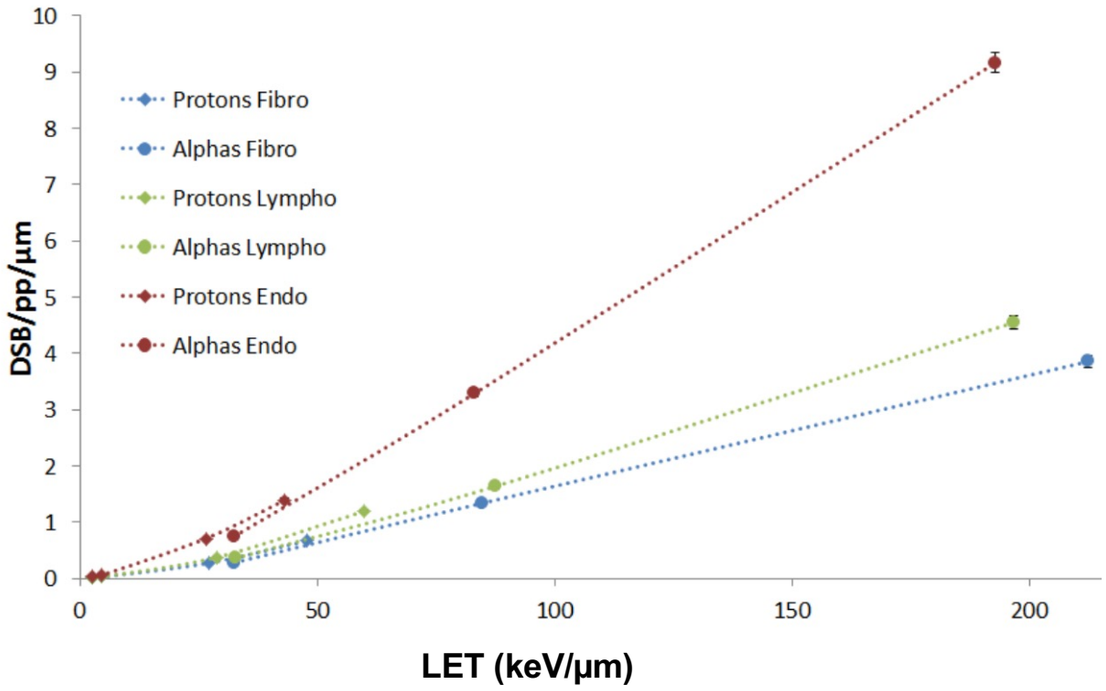
Lymphocyte

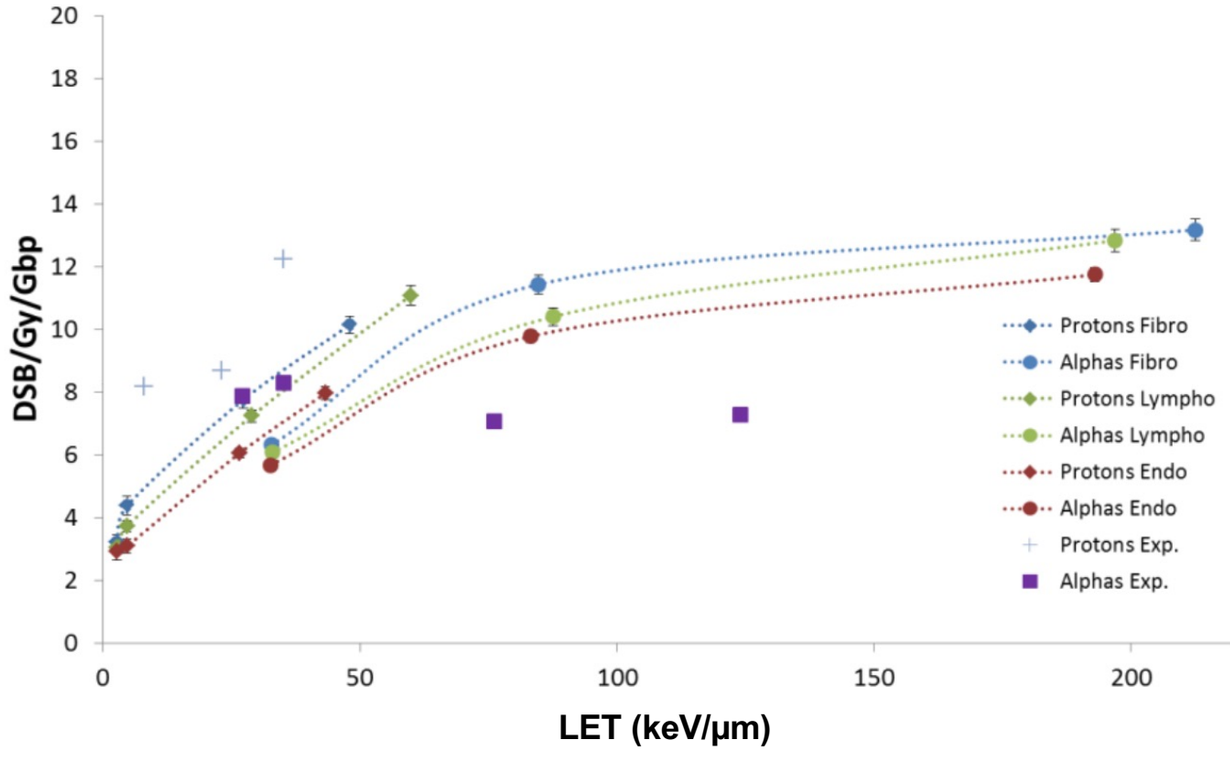


Endothelial

Impact of cell nucleus models

- DNA density (shape, volume, genome content of the cell nucleus) has an impact on DSB yield

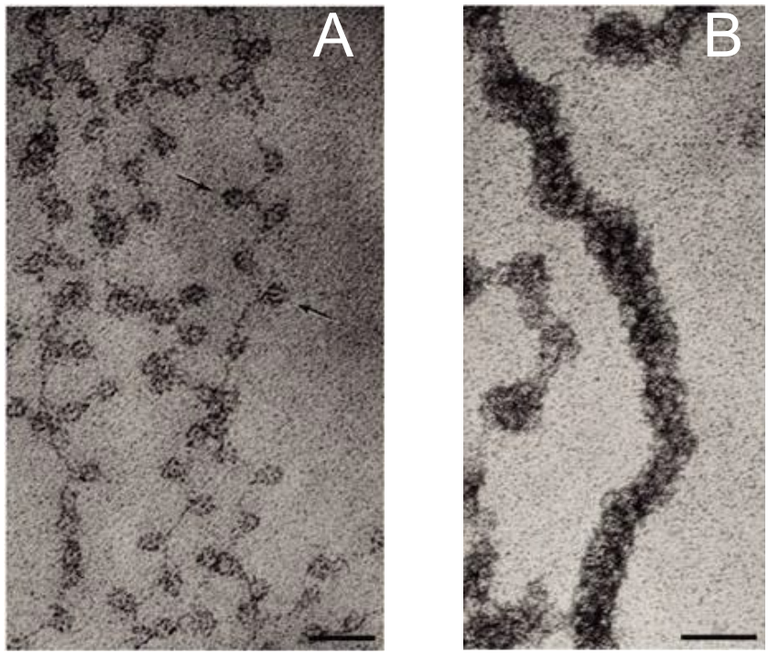




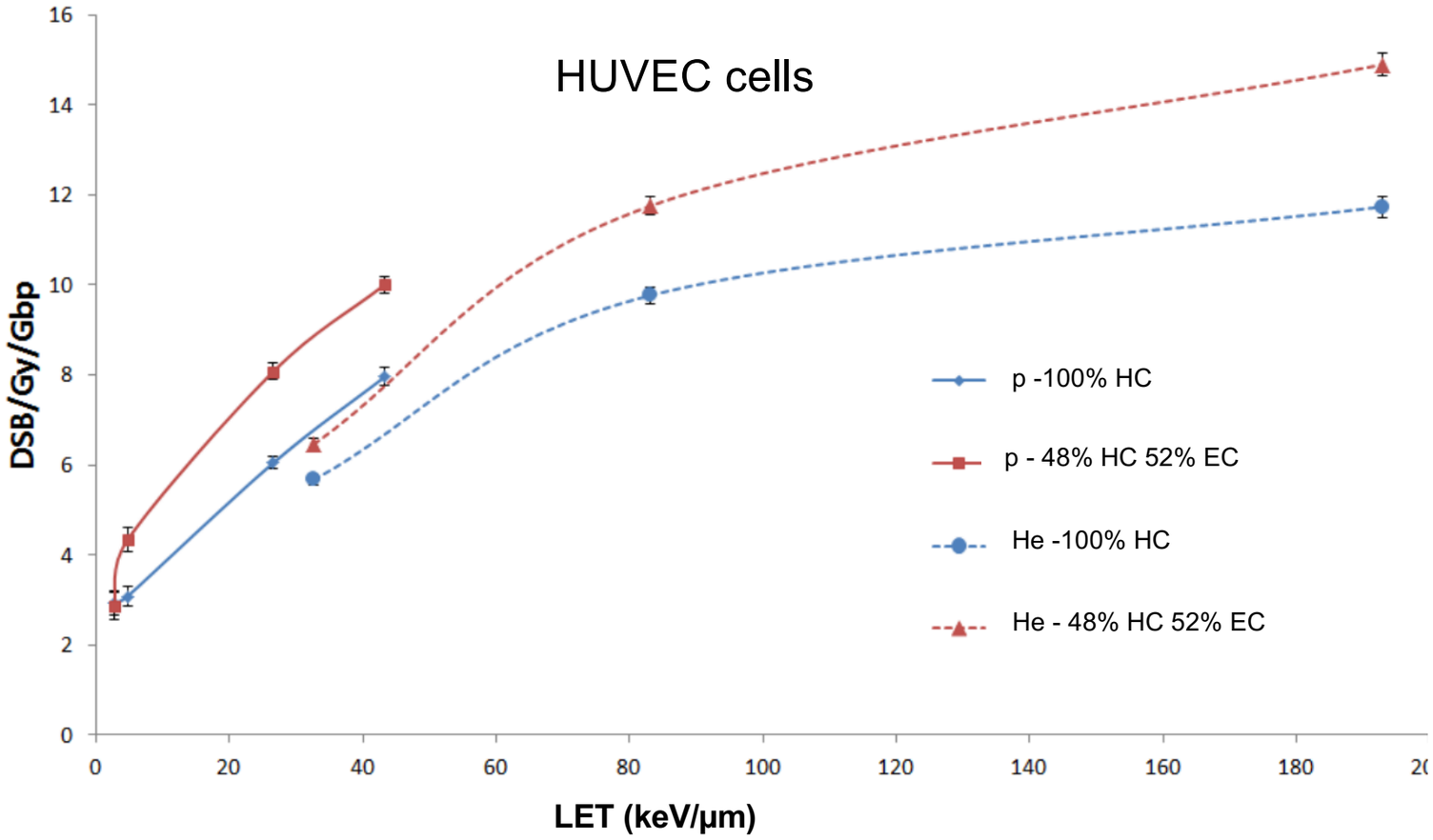
Tang, PhD Thesis 2019

Impact of DNA compaction

- DNA compaction has also an impact on DSB yield



Chromatin, G0/G1 phase [Olins et Olins, 2003]
A : Euchromatin (EC)
B : Heterochromatin (HC)

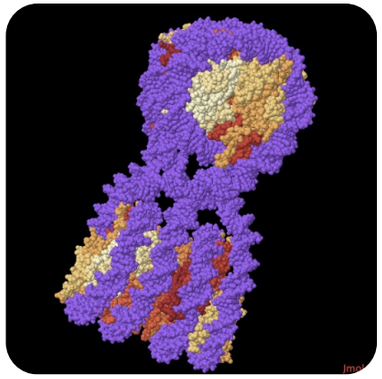


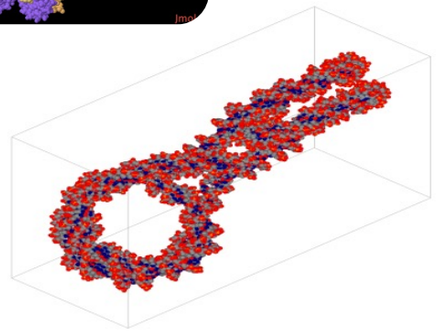
Tang, PhD Thesis 2019
Tang, Med. Phys. 2019

Geant4-DNA Geometry models

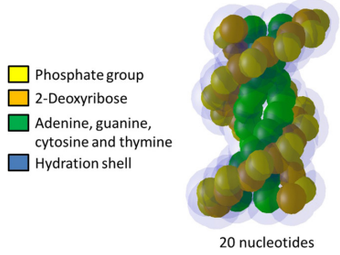
10^{-10} 10^{-9} 10^{-6} [m]

- **Atomic Scale**
  - **pdb4dna**

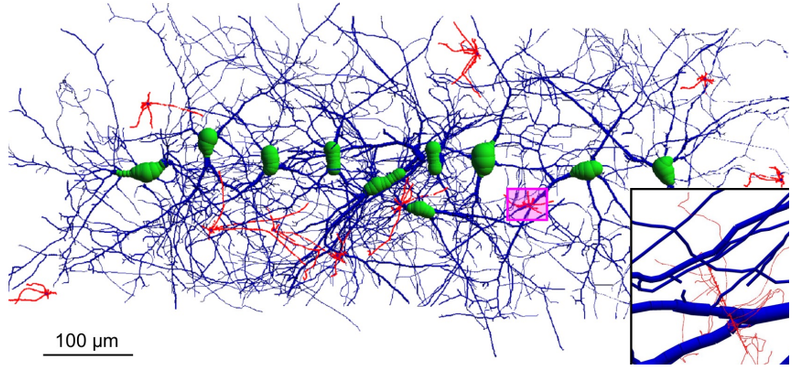


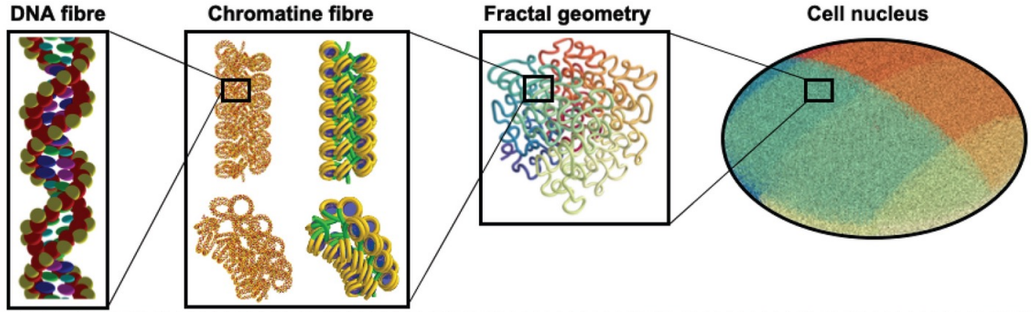


- **Molecular Scale**
  - **wholeNuclearDNA**
  - **danamage1, dsbandrepair**
  - **molecularDNA**



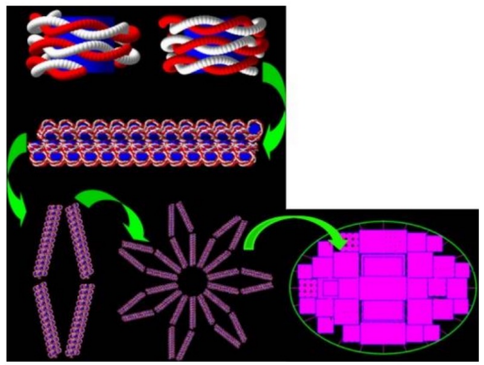
- **Cellular Scale or Larger**
  - **microbeam**
  - **neuron**





Geant4-DNA Geometry models of full cell nuclei

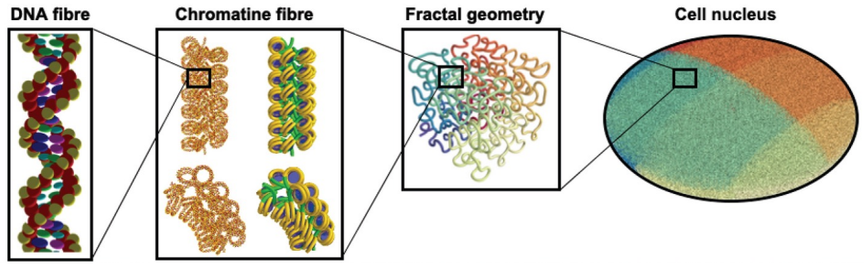
wholeNuclearDNA



Five compaction levels:
- double helix,
- nucleosome,
- chromatin fiber,
- simple chromatin fiber loop,
- complex chromatin fiber loops

Only direct SB

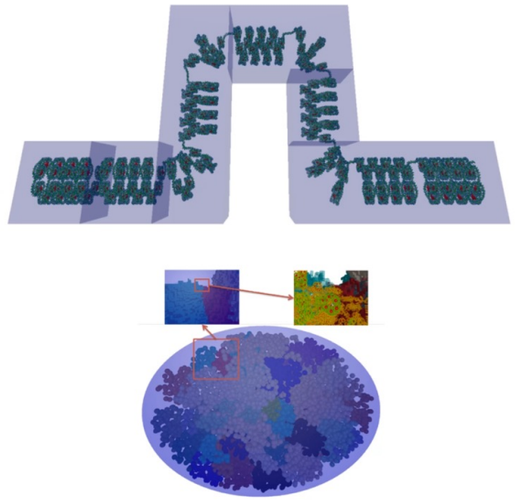
molecularDNA



A fractal Hilbert Curve is used to seed the continuous curve of the DNA
Each section making up the curve is then replaced with chromatin

Direct and indirect SB

dsbandrepair



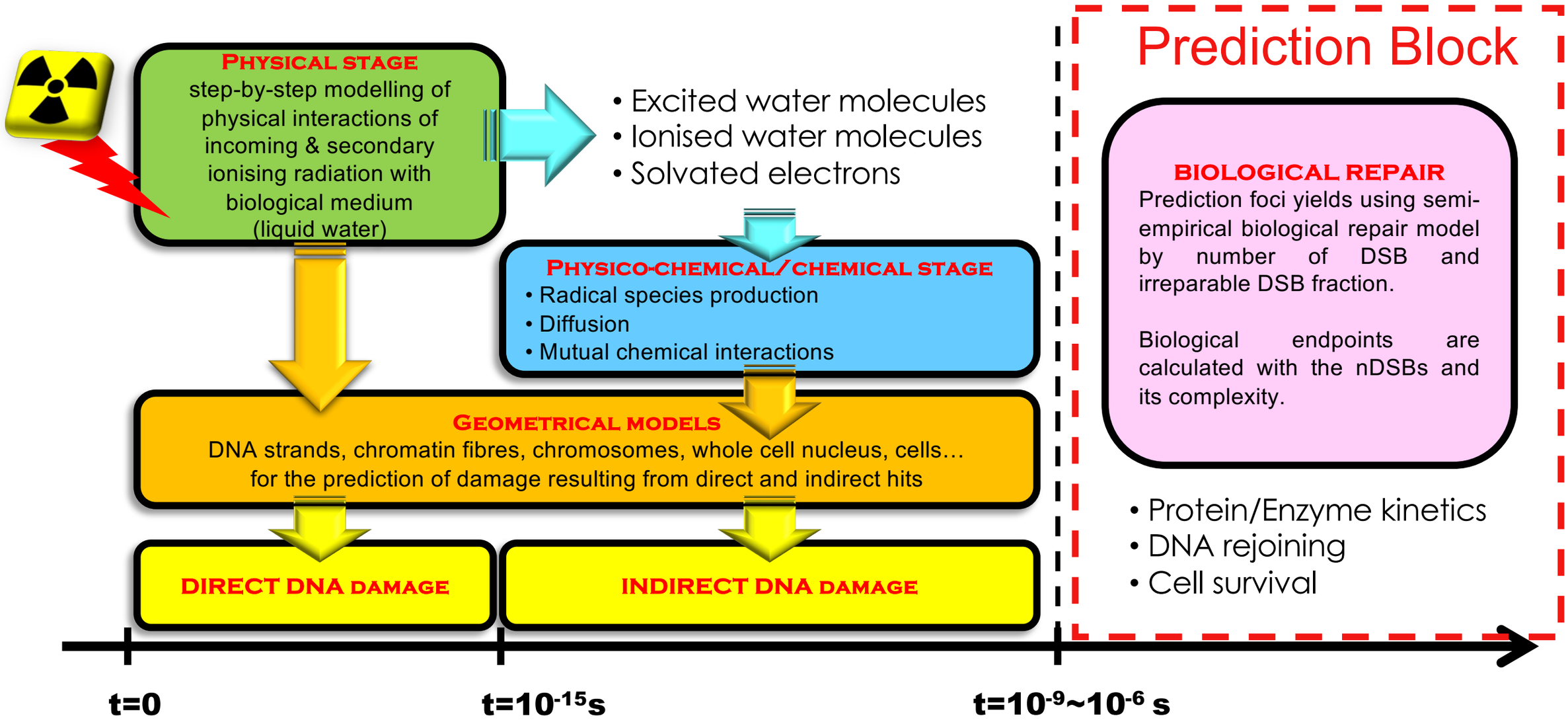
Elementary voxels are assembled to form a continuous chromatin fiber loops in 1 Mbp domains
Heterochromatin and euchromatin compaction is modelled

Direct and indirect SB

Contents of this talk

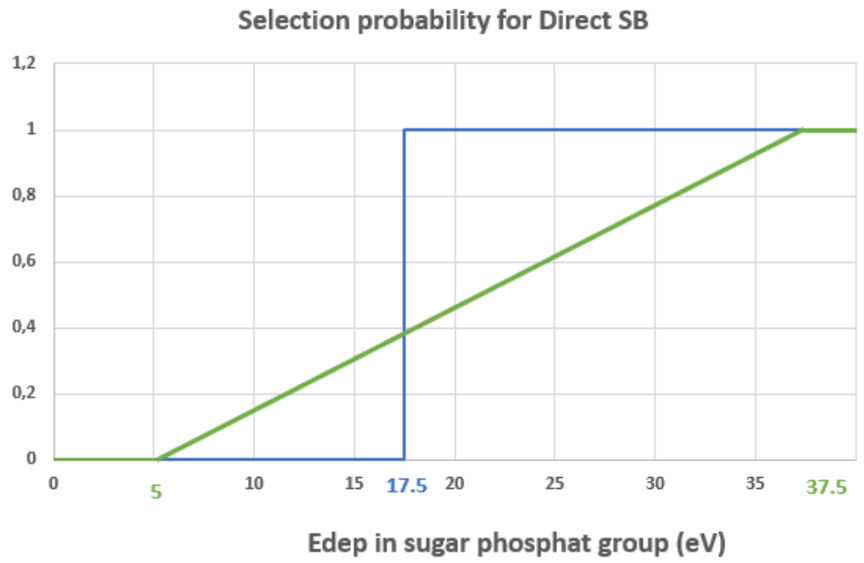
- Why biology modelling?
- Geometrical models
- Damage calculation and classification
- Biological models
- Geant4-DNA examples
- In conclusion

Geant4-DNA implementation

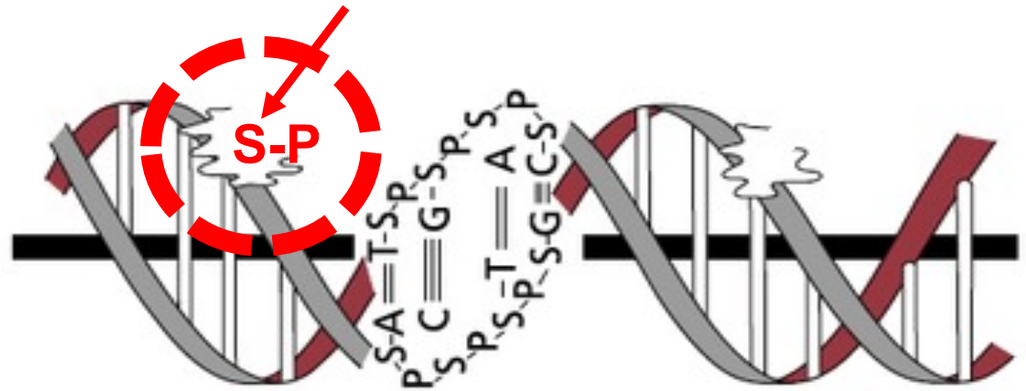


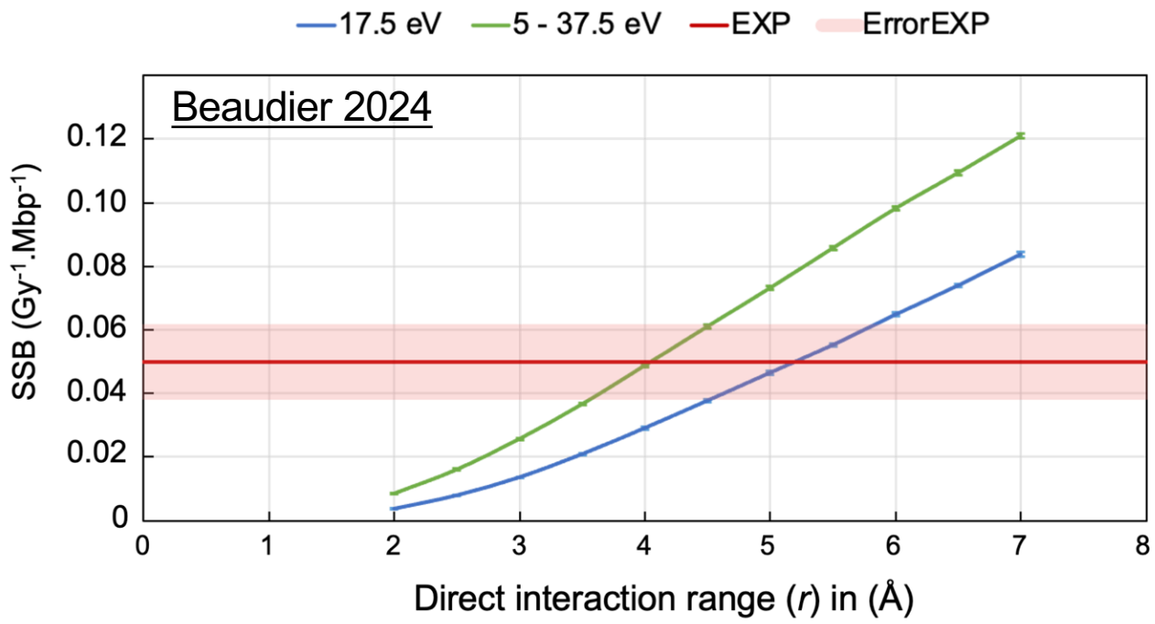
Direct Strand Breaks

SB occurs when sufficient energy deposit in proximity of sugar-phosphate group:
- $R_{phosphat}$ or R_{sugar} for moleculardna
- Hydration shell for dsbandrepair



Inelastic collisions

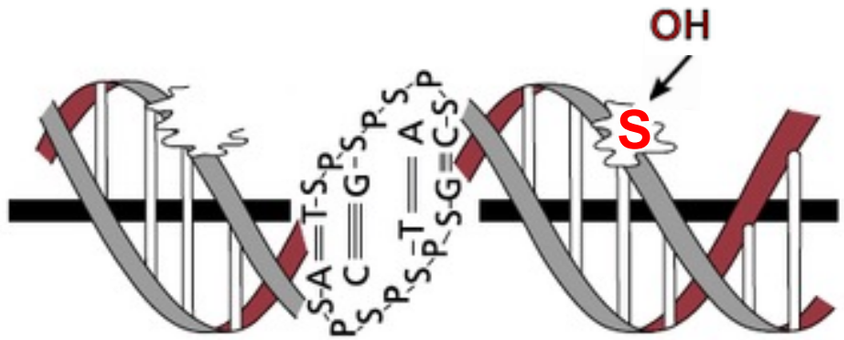




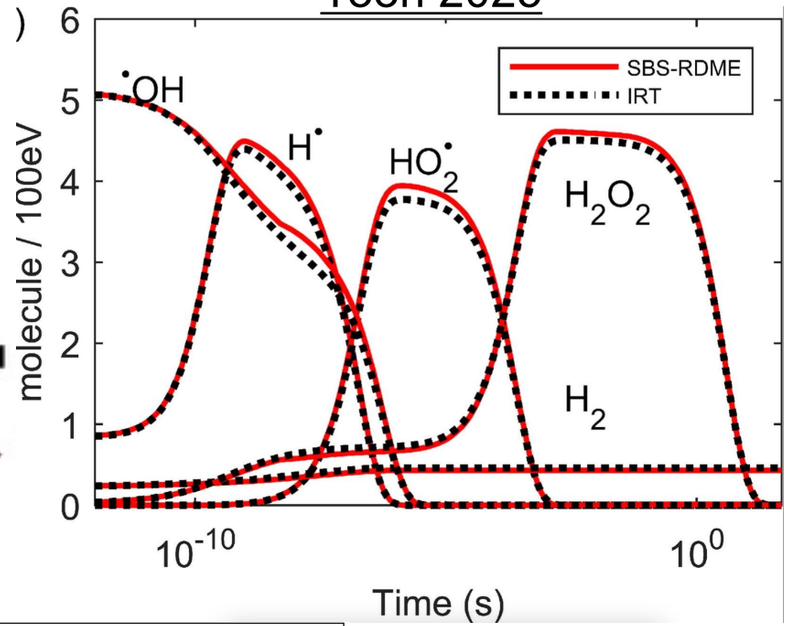
Indirect Strand Breaks

SB occurs when OH radical reaction occurs with sugar.

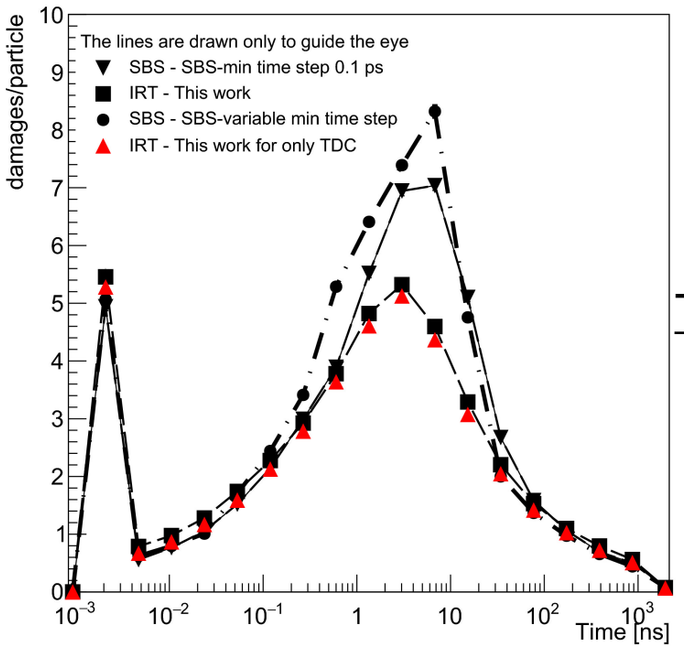
Not all reactions leads to SB: use an activation probability



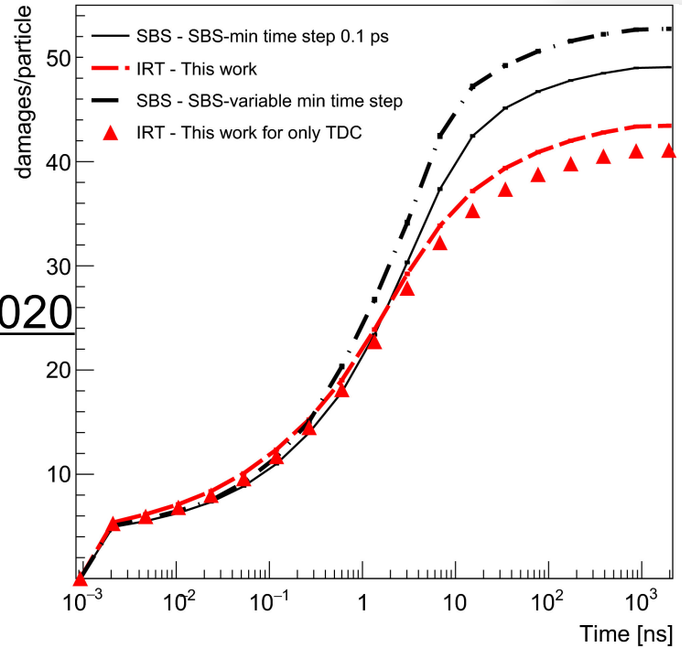
Yoon 2025



DNA damage yields including direct (plotted at 2 ps) and indirect damage including DNA backbone and bases (second part of the curve starting from 4 ps) as a function of virtual time

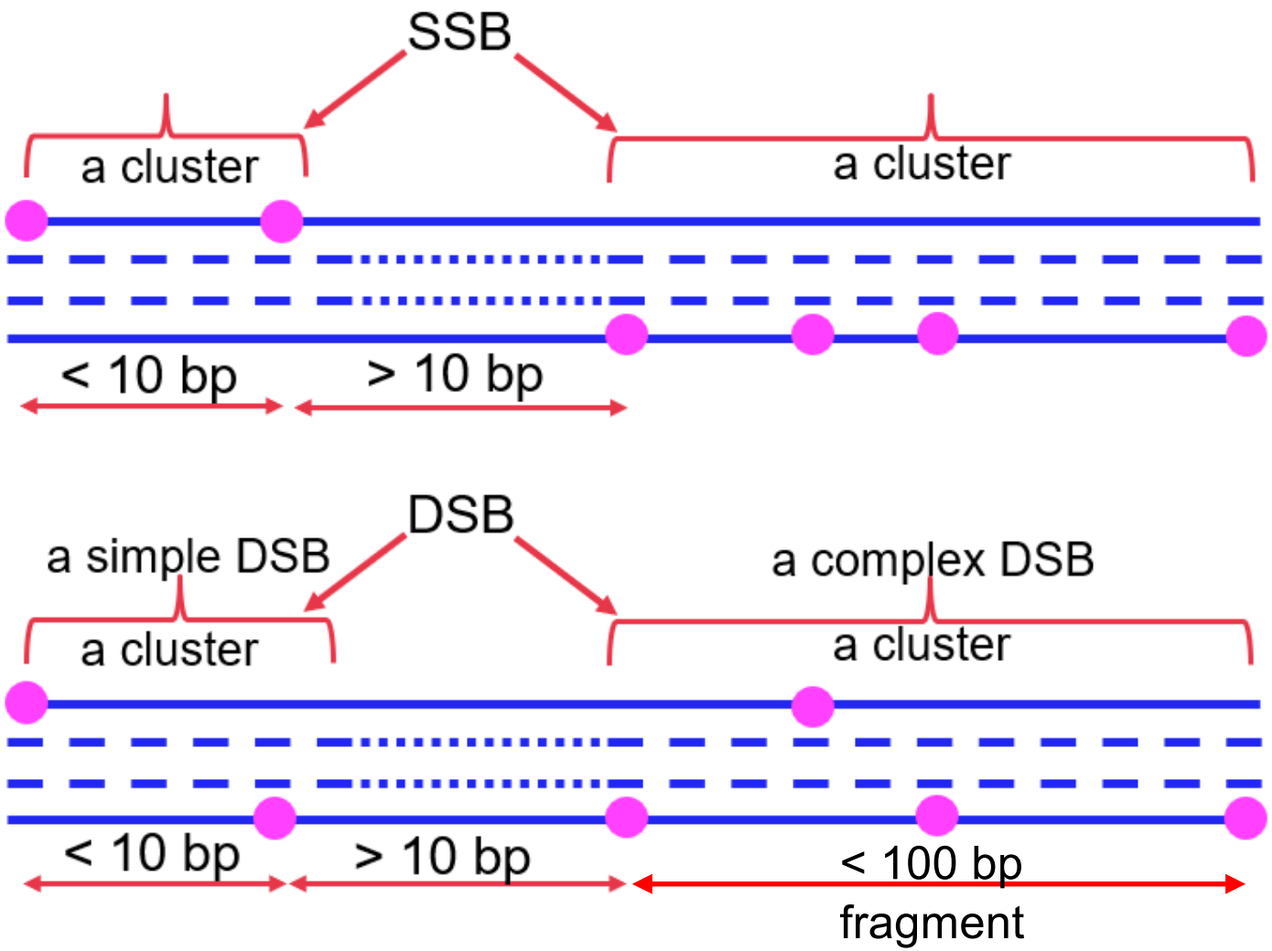


Tran 2020



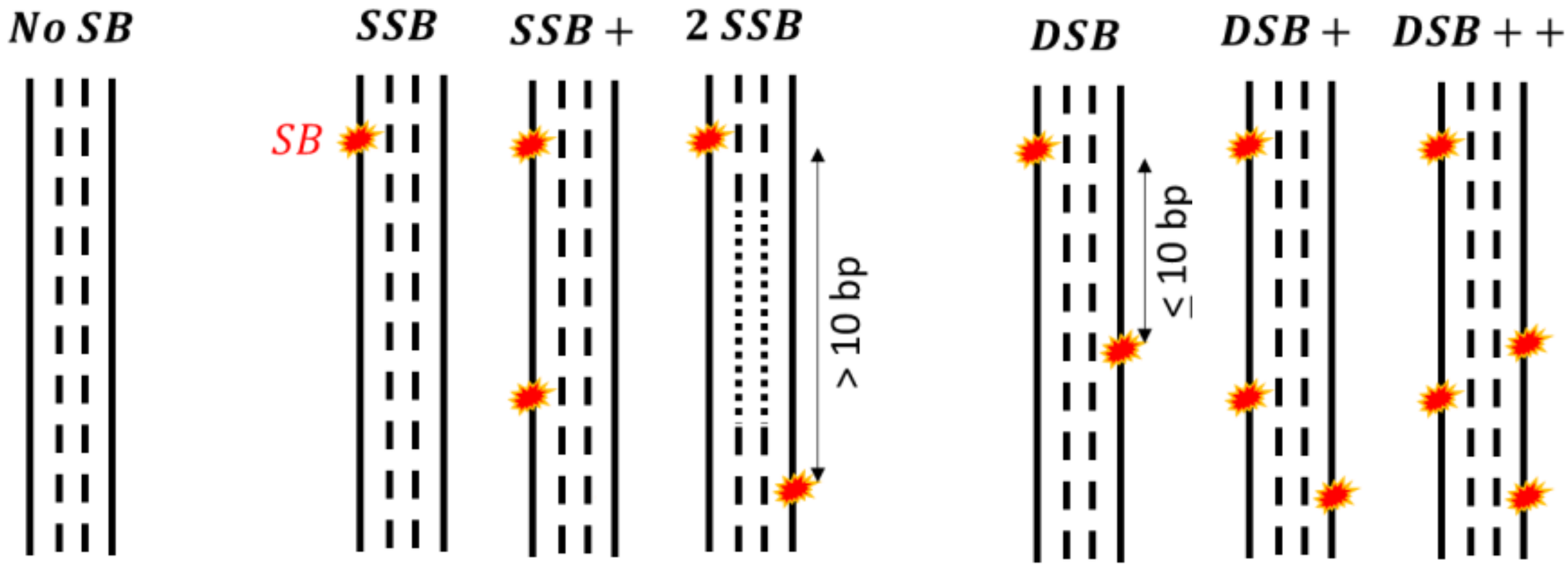
Cumulative damage yield as a function of virtual time corresponding to the results.

Clustering algorithm and classification

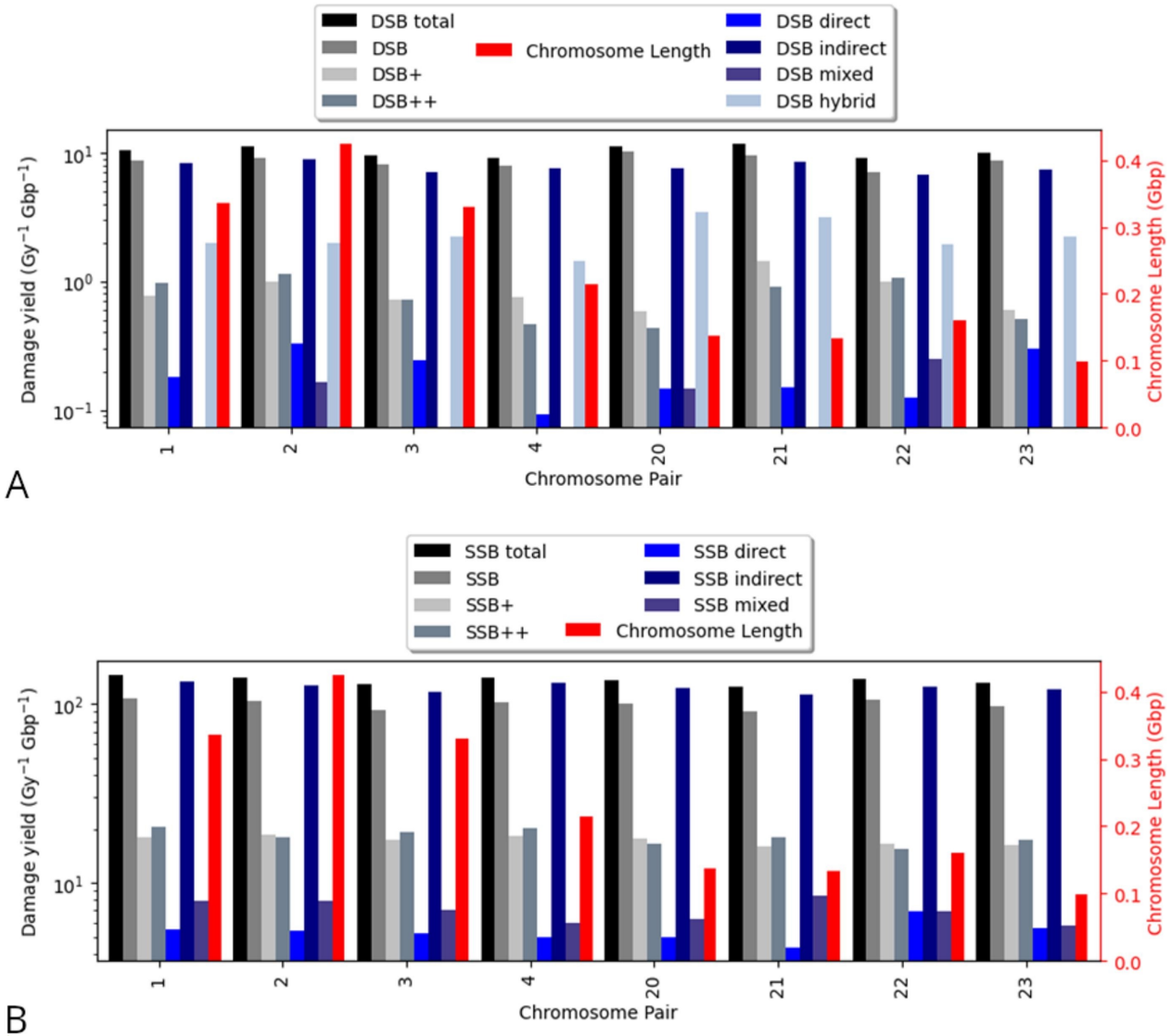


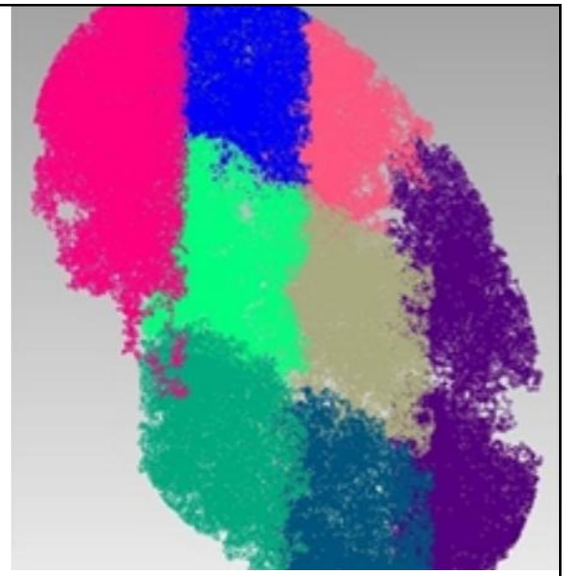
Clustering algorithm and classification

Classification by complexity (adapted from Nikjoo et al. IJRB 1997)



DNA Damage quantification





MC simulations and Geant4-DNA provide us with tools to accurately quantify and classify radiation induced damage.

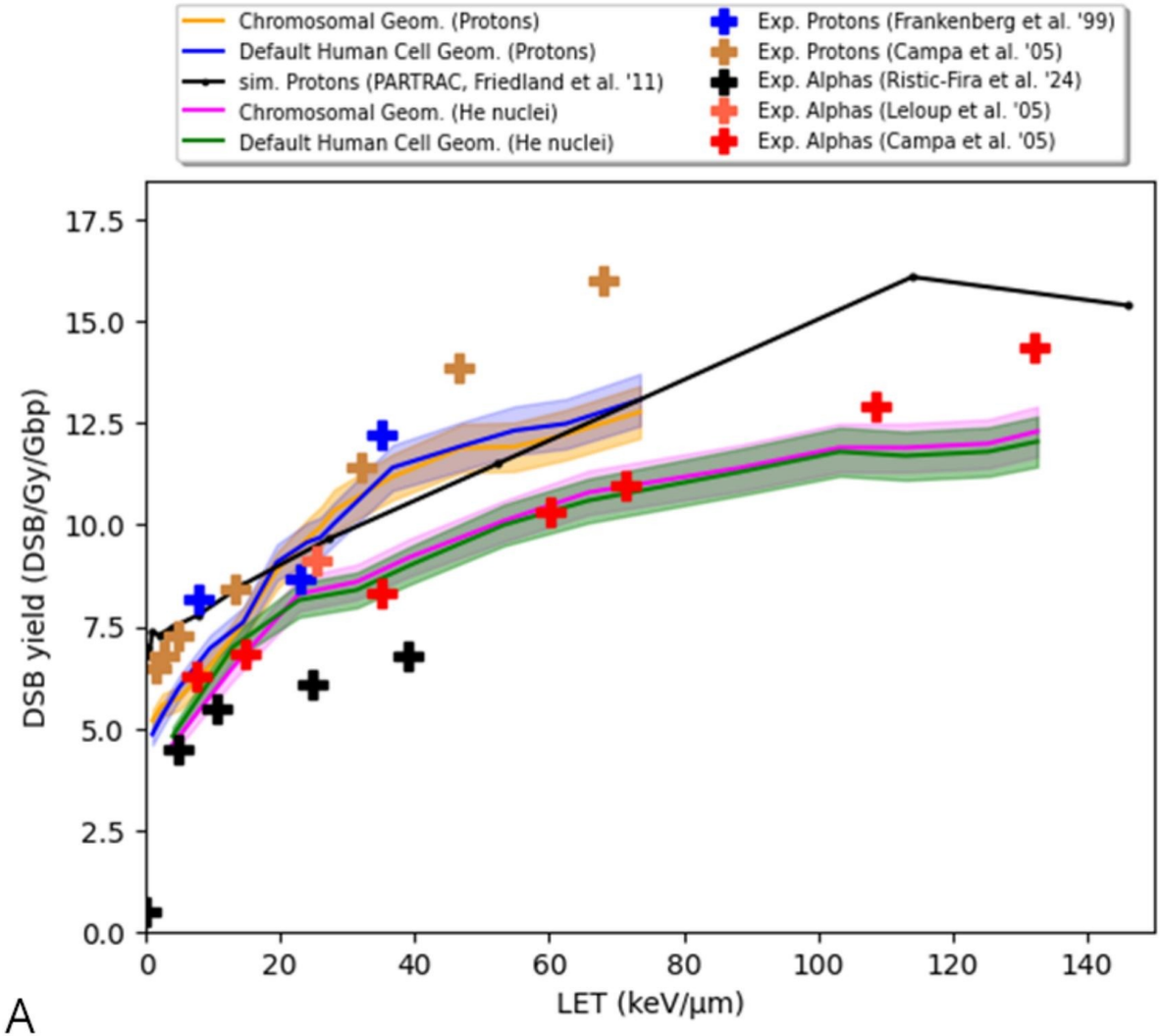
- Per classification type
- Per DNA fragment (e.g. chromosomes)

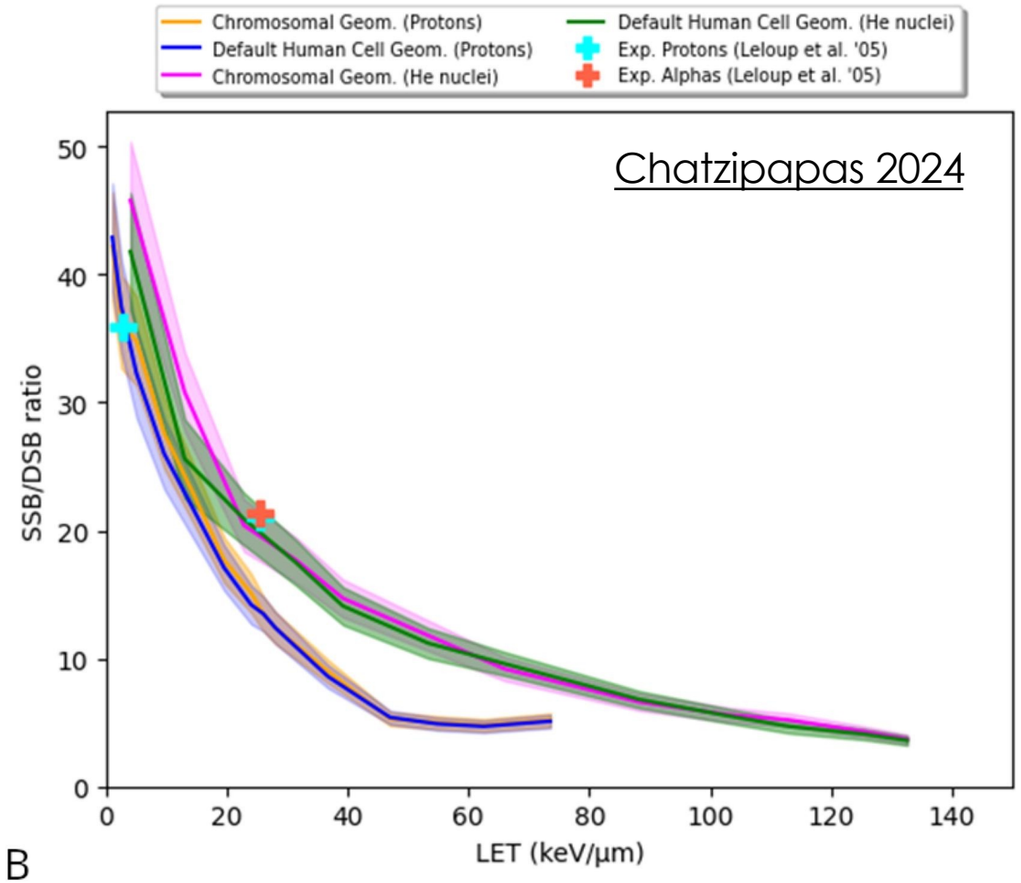
Chatzipapas 2024

DNA Damage yield

DSB and SSB yield for different types of radiation (e.g. alphas vs protons)

Sparse experimental data



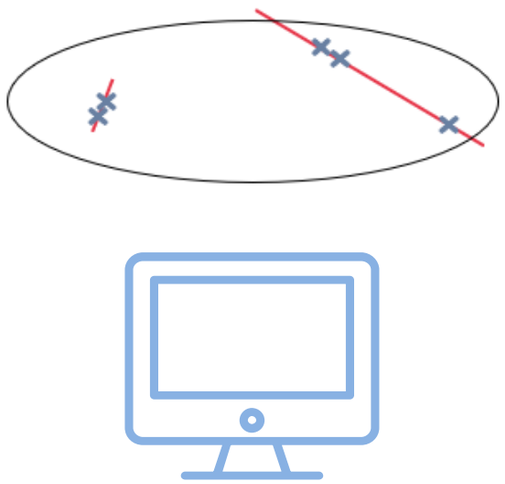


Be careful when comparing DSBs with experimental data

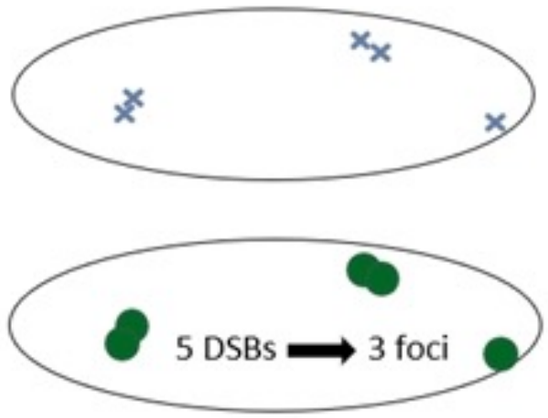
Direct comparison of simulated DSBs to experimental is not always possible

Experimental data measure foci formed by DNA repair factors that accumulate specifically at damaged sites, and are detected as distinct spots

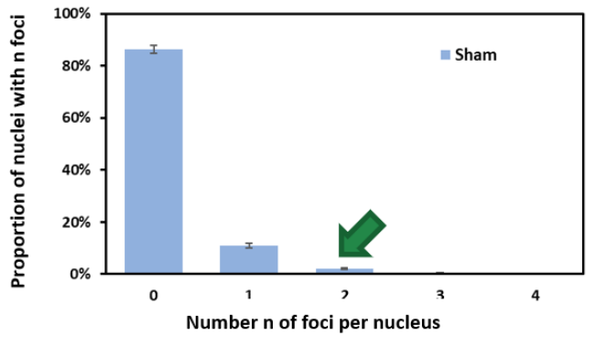
DSBs
(accessible via simulation)

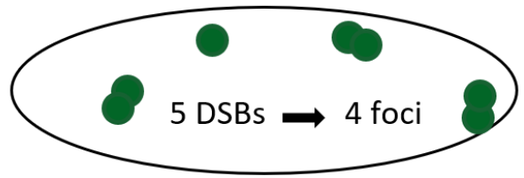


Detection threshold



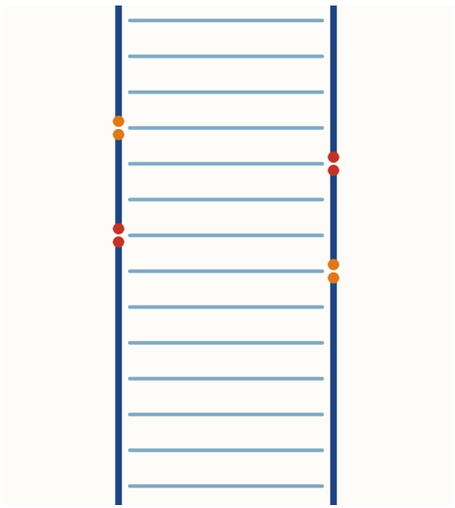
Background

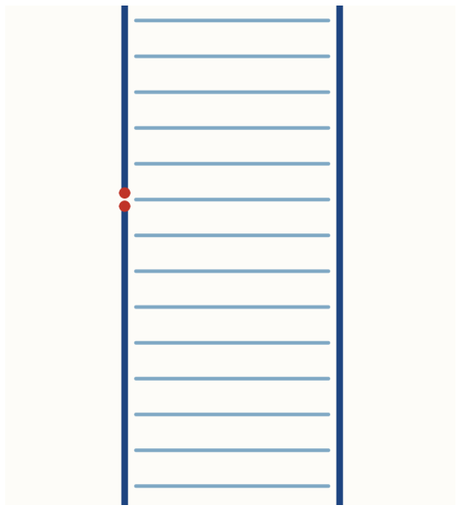


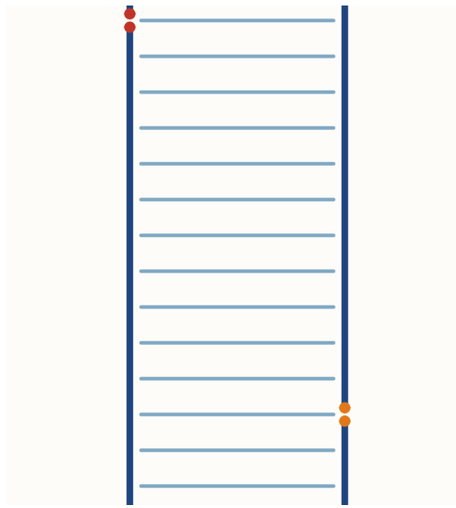


Quiz

Classify the DNA damage



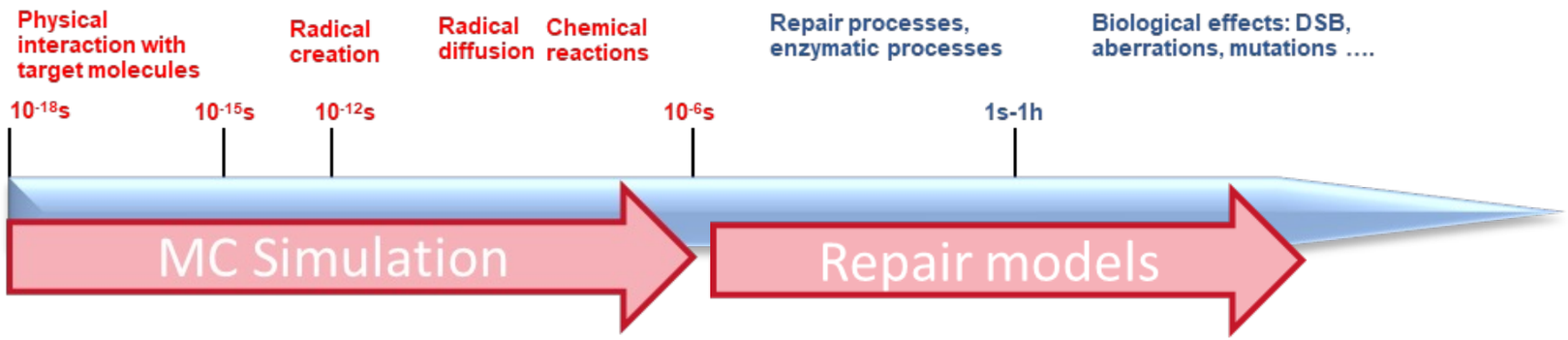


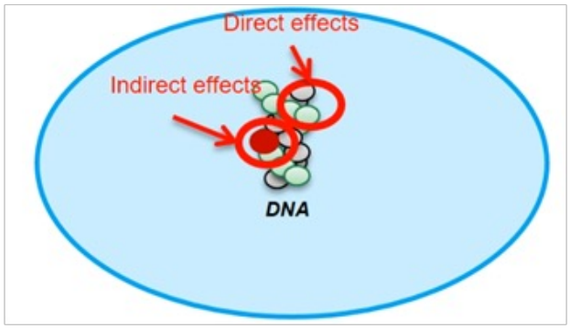


Contents of this talk

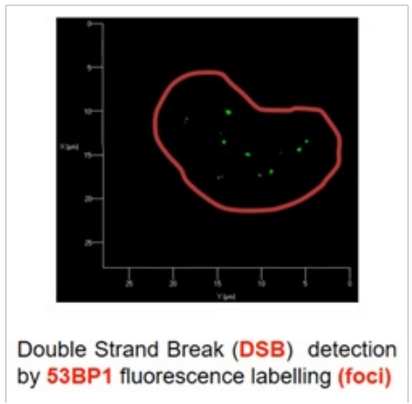
- Why biology modelling?
- Geometrical models
- Damage calculation and classification
- Biological models
- Geant4-DNA examples
- In conclusion

Simulation the prediction of cell fate

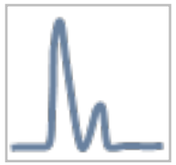




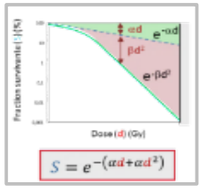
Goal



Double Strand Break (DSB) detection by 53BP1 fluorescence labelling (foci)



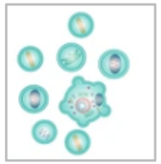
cell cycle



survival

senescence

molecular interactions



apoptosis

chromosome aberrations

Evolution of repair models

- Historical models derived from the target theory (Crowther 1924) calculate the link between an irradiation and cell survival. Limitations:
  - survival is linked to whether a cell is hit
  - DNA damage repair not considered
- Phenomenoligical models
  - RBE modelling is made on microdosimetric or nanodosimetric simulations and simplistic assumptions about cellular fate
  - For example: Microdosimetric Kinetic Model (Hawkins 1996),
    Two Lesion Kinetic Model (Stewart 2001),
    Local Effect Model (Elsasser 2008)
- Mechanistic models
  - Describe in detail the kinetics of the enzymatic processes associated with repair
  - Cucinotta 2008, Friedland 2013, Taleei 2013, Belov 2015

non-exhaustive

- Parameters need be optimized for each different implementation

Geant4-DNA and repair models

- Some repair models have been applied to output data from Geant4-DNA simulations: Tang 2019 for LEM and TLK (Ph.D. thesis in French), Sakata 2020 for TLK and Belov's model
- The BioRad3 project (ESA funding), led by the Geant4-DNA collaboration, enabled to continue the investigation on repair models

Model	Endpoint	Reference	Input Data	Validation Experimental Data from Literature
Local Effect Model IV	Non rejoined DSB	Tommasino et al (2013) *Rad. Res. 180, 524-538*	Simple and complex DSBs in 2 Mbp chromatin loops	- Stenerlow (2000): Fibroblast, α 40 keV/µm - Lobrich (1998): Fibroblast, α 70 keV/µm and 120 keV/µm
Two Lesion Kinetic Model	Surviving fraction	Stewart (2001) *Rad. Res. 156, 365-378*	Simple and complex DSBs	- Belli (2000): Fibroblast, p 7.7 keV/µm - Hamada (2000): Fibroblast, α 16.2 keV/µm - Netti (2004): Fibroblast, α 132 keV/µm
Belov model	DSB repair	*Belov et al. (2015) J. Theo. Biol. 366, 115-130*	Distant simple and complex DSBs	- Antonelli (2015): Fibroblast, p 28.5 keV/µm

Local Effect Model

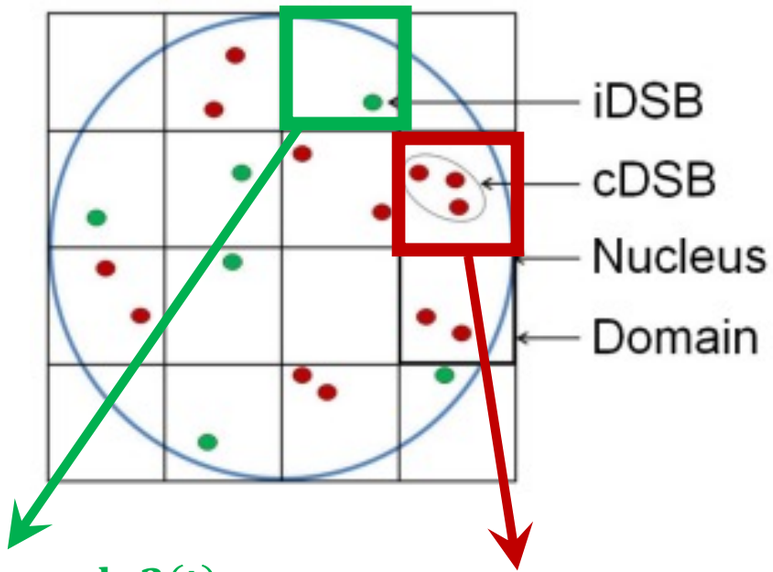
LEM principles

- LEM was initiated in the 1990s at GSI in Darmstadt in the context of heavy ion radiotherapy
  - RBE prediction for a variety of ions and LET
  - LEM used as an input for heavy ion treatment plans
  - Assumption: similar distribution of DNA damage should lead to equivalent biological damage regardless of the quality of the radiation that causes it
  - More recent versions of the LEM have moved to explicitly consider break repair and misrepair probabilities (Friedrich 2012)

- LEM IV:
  - Based on the spatial distribution of DSBs within the cell nucleus
  - It looks at the number of DSBs present in 2 Mbp of chromatin loops called "Giant loops" or domains representing sensitive DNA structures
  - The fast and slow components of rejoining observed in the experiments can be related to the processing of simple and complex DSBs

LEM IV principles

DSB calculation



Analysis in 2 Mbp segments

$$n_{DSB} = n_i + n_c \lambda_c$$

n_i : num. domains with iDSB
n_c : num. domains with cDSB
λ_c : mean number of DSB in cDSB

$$\mathbf{U(t) = F_{fast_{(iDSB)}} * e^{-\frac{ln2(t)}{\tau_{fast}}} + (F_{slow(cDSB)} - F_{unrej}) * e^{-\frac{ln2(t)}{\tau_{slow}}} + F_{unrej}}$$

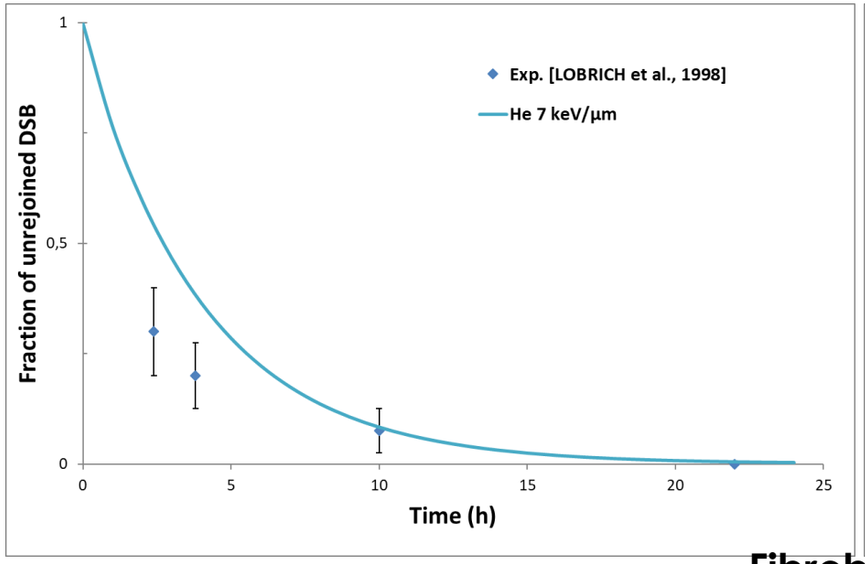
$F_{fast} = n_i/(n_i + n_c \lambda_c)$
τ_{fast} = 0.24 h (fibroblast)

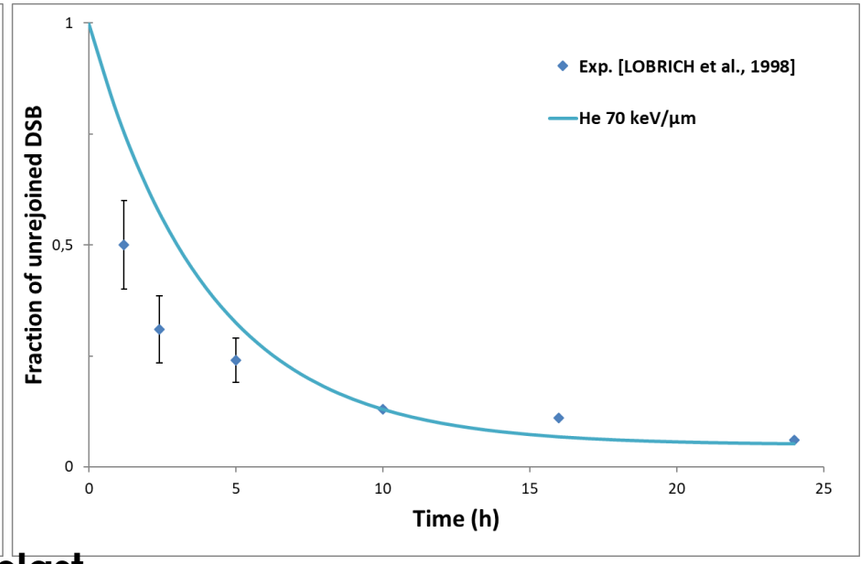
$F_{slow} = n_c \lambda_c/(n_i + n_c \lambda_c)$
τ_{slow} = 2.81 h (fibroblast)

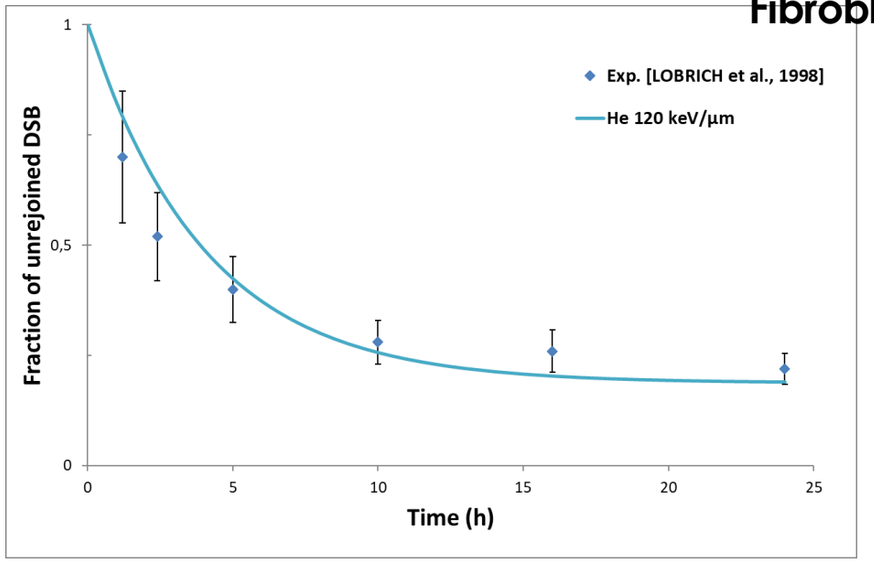
Particle	LET (keV/µm)	F_{unrej}
He	7	0.0008
He	70	0.050
He	120	0.188
N	97	0.096
Fe	150	0.107

Parameters for fibroblast from Tommasino 2015 who fitted experimental data

Geant4-DNA and LEM IV results







Fibroblast

dsbandrepair
Le Tuan 2024

It was shown that the simulation results for ions agreed with experimental data (Le Tuan, Phys. Med., Jul 2024)

For implementation details see ***dsbandrepair*** example

Two Lesion Kinetic Model

TLK principles

- TLK was developed in 2001 by Stewart with the aim of providing a method capable of linking DSBs with cell death
- DSBs are subdivided into simple and complex DSBs
  - A single DSB (sDSB) is considered as two SBs located on each of the two DNA strands over a length of 10 to 20 bp (repairable DSB)
  - A complex DSB (cDSB) is defined as a sDSB containing additional damage (unrepairable DSB)
  - The DNA fragments associated with DSBs can interact with each other in pairs and form lethal or non-lethal chromosomal aberrations
- TLK includes non-saturable first and second order repair processes, DNA repair is performed by using first-order nonlinear differential equations
- Parameters of the model needs be defined for each implementation (cell type)

TLK principles

- Let: $L_1(t)$ num. simple DSB at time t, $L_2(t)$ num. complex DSB at time t
- The evolution of $L_1(t)$ and $L_2(t)$ follows:

$$\frac{dL_1(t)}{dt} = -\lambda_1 L_1(t) - \eta L_1(t)[L_1(t) + L_2(t)]$$

$$\frac{dL_2(t)}{dt} = -\lambda_2 L_2(t) - \eta L_2(t)[L_1(t) + L_2(t)]$$

- λ1: repair probability of sDSB
- λ2: repair probability of cDSBs
- η: probability of interaction between two DSBs to form lethal lesions

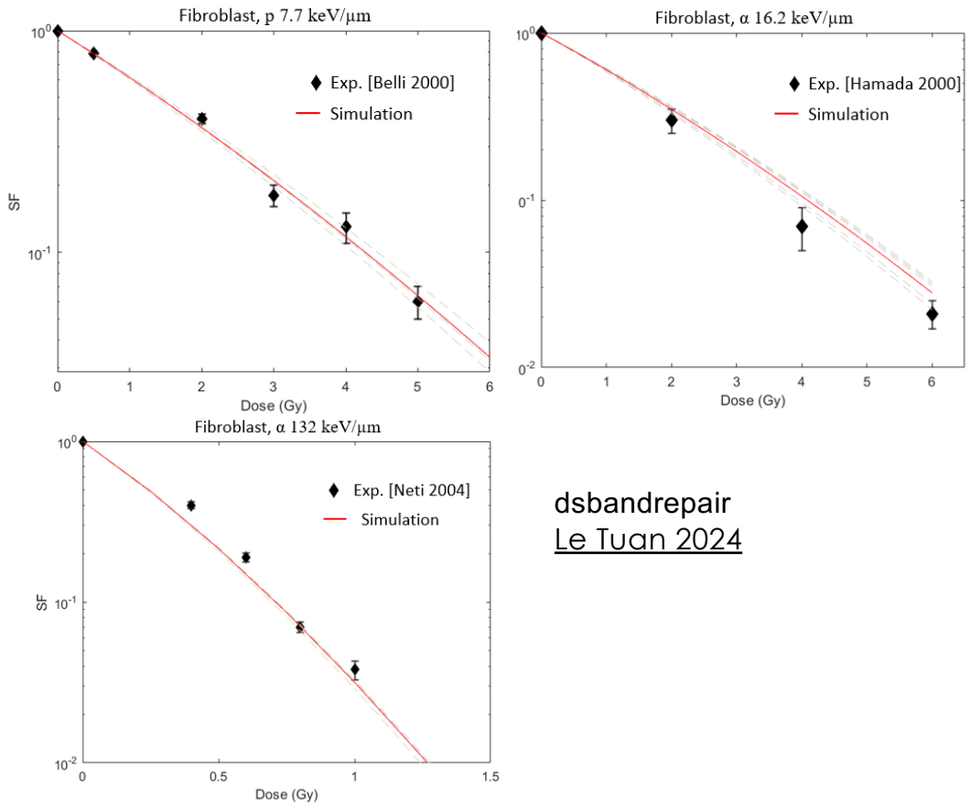
- The evolution of lethal lesion $L_{LETHAL}(t)$ is:

$$\frac{d_{LETHAL}(t)}{dt} = \beta_1 \lambda_1 L_1(t) + \beta_2 \lambda_2 L_2(t) + 0{,}25\eta[L_1(t) + L_2(t)]^2$$

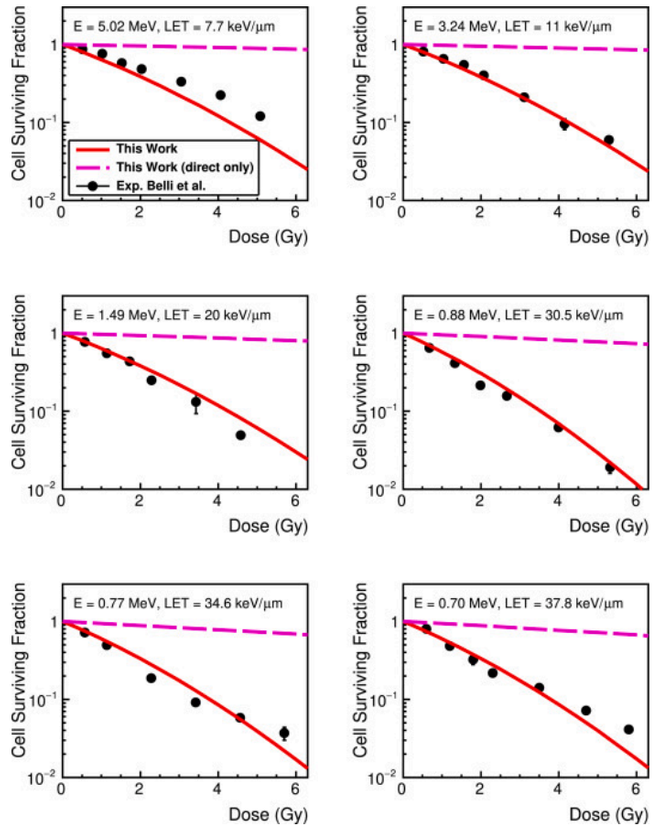
- β_1 probability of lethal misrepair for sDSBs
- β_2 probability of lethal misrepair for cDSBs

- The survival fraction S(t) is: $S(t) = e^{-L_{LETHAL}(t)}$

Geant4-DNA and TLK results



dsbandrepair
Le Tuan 2024



moleculardna
Phys. Med. 105 (2023) 102508

It was shown that the simulation results for gamma rays and ions agreed with experimental data (Sakata 2022, Le Tuan 2024)

For implementation details see ***moleculardna*** and ***dsbandrepair*** examples

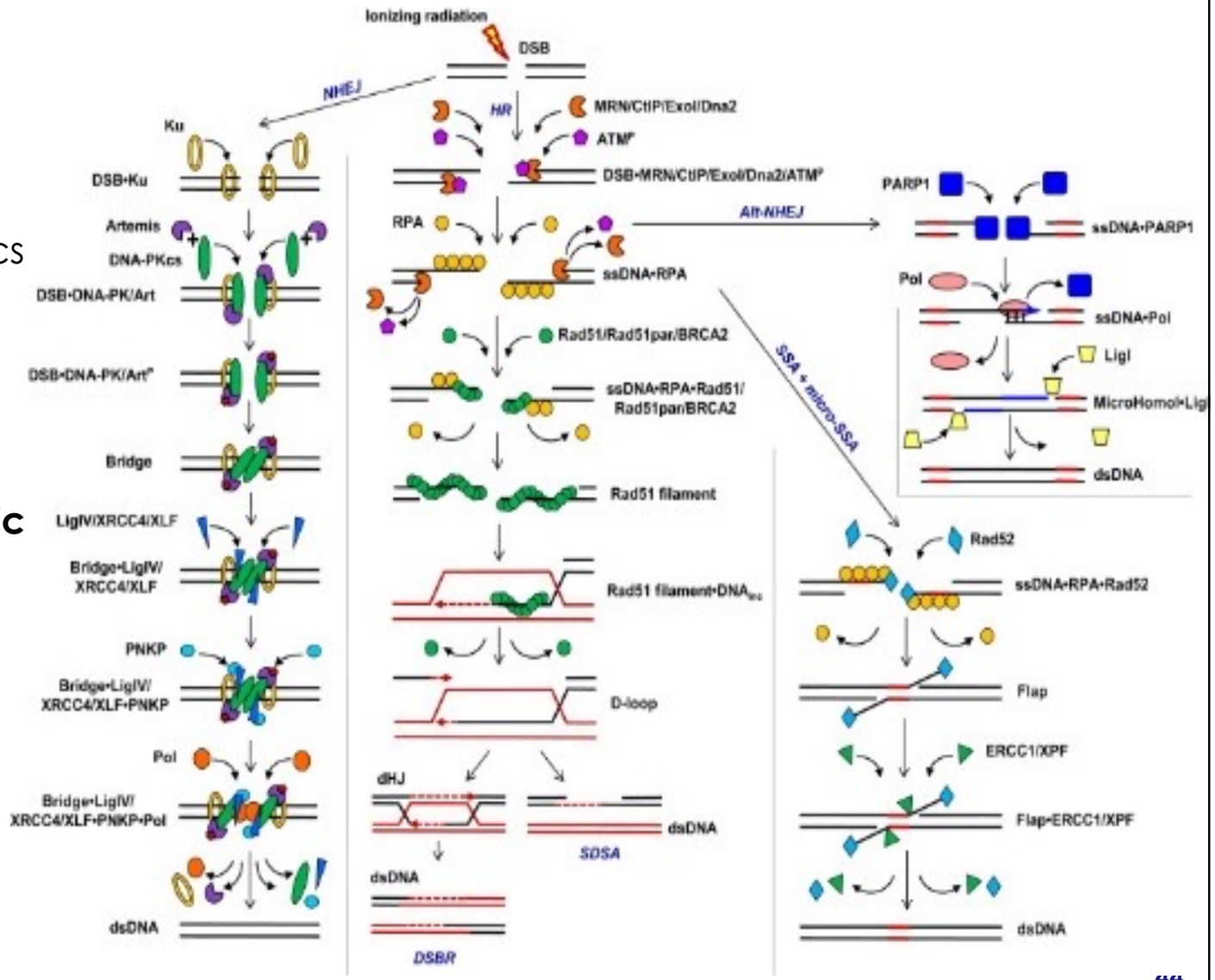
Belov's model

Belov's model principles

- Belov et al. proposed in 2015 a quantitative model for the simulation of DSB repair
- In the case of high LET irradiation, the majority of damage is complex DSBs, and several pathways may sequentially try to repair them
- Belov's model takes into account the main repair pathways in mammalian cells: non-homologous end-joining (NHEJ), homologous recombination (HR), single-strand annealing (SSA) and two alternative end-joining pathways the micro SSA and the alternative NHEJ
- The model requires the numbers of DSBs classified in two groups:
  - N_{ncDSB} : number of non-clustered DSBs i.e. two SSBs on opposite strands with a distance less than 10 bp)
  - N_{cDSB} : number of complex DSBs i.e. DSBs with additional SSBs or DSBs within 10 bp separation and with inclusion of base damage

Belov's model principles

- The repair model uses a mass-action kinetics approach to compute **the yields of accumulated proteins** for the considered pathways by means of **differential equations reflecting the dynamic change of proteins' concentration and intermediate complexes** that are involved in the repair mechanism



Belov's model principles

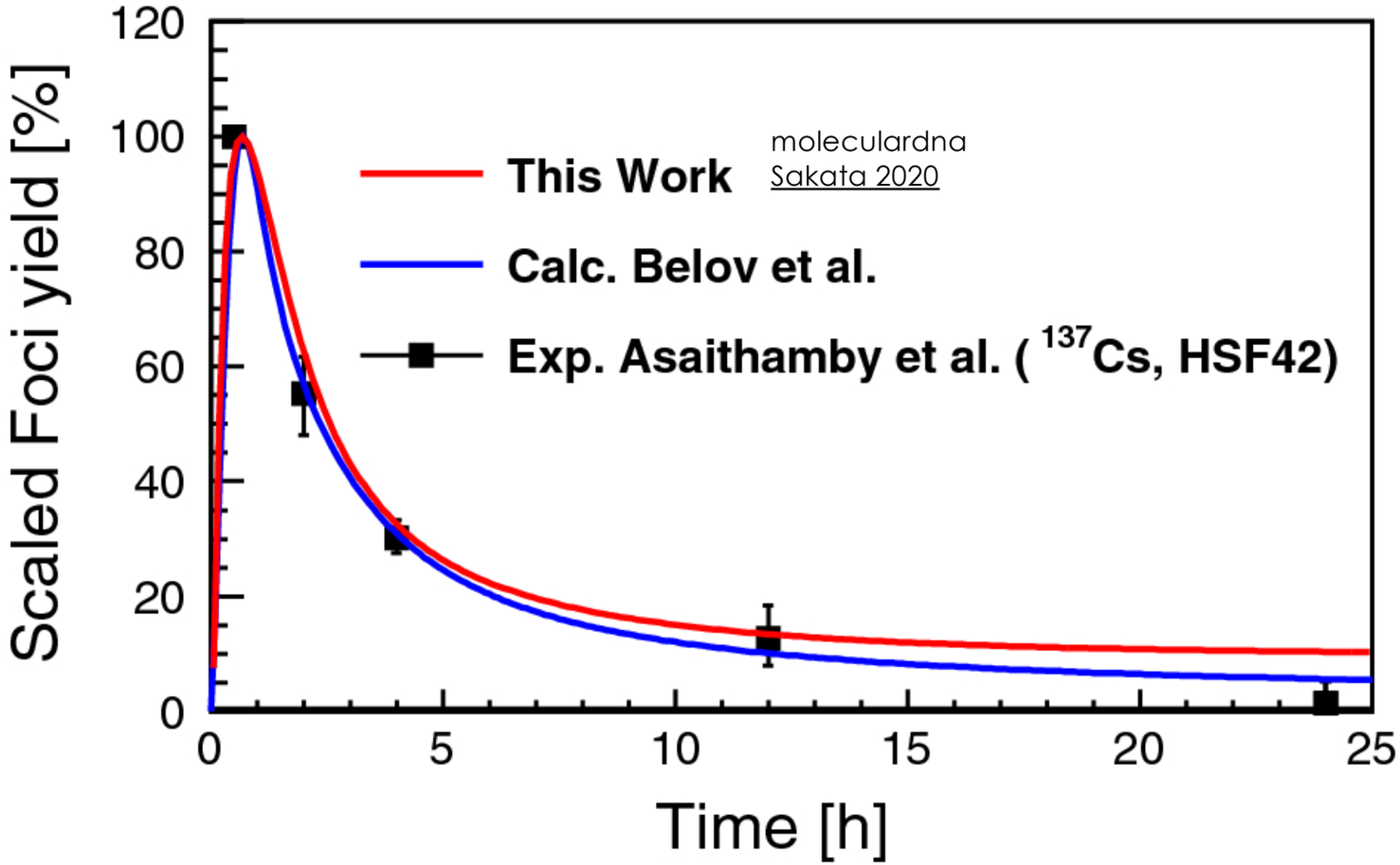
- The temporal evolution of the number of DSBs is then obtained according to the following equation

$$\frac{dN_0}{dt} = \alpha(L)\frac{dD}{dt}N_{cDSB} - V_{NHEJ} - V_{HR} - V_{SSA} - V_{microSSA} - V_{Alt-NHEJ}$$

  - $N_0 = N_{ncDSB}+N_{cDSB}$
  - V_{NHEJ}, V_{HR}, V_{SSA}, $V_{microSSA}$, $V_{Alt-NHEJ}$, the elimination term of DSBs by the different pathways related to the concentration of intermediate complexes described by the differential equations
  - D, the absorbed dose
  - a(L), DSB induction per unit dose and per cell

- The temporal evolution of proteins' concentration is also available

Geant4-DNA and Belov's model results for γ-H2AX foci



For implementation details see
moleculardna and ***dsbandrepair*** examples

Contents of this talk

- Why biology modelling?
- Geometrical models
- Damage calculation and classification
- Biological models
- Geant4-DNA examples
- In conclusion

Geant4-DNA: examples for biology damage

- **/extended/medical/dna/dnadamage1**: simulate early direct and indirect DNA damage in a cubic voxel of 40 nm side containing a piece of heterochromatin
- **/extended/medical/dna/dnadamage2**: scoring of plasmid DNA strand breaks using the IRT method
- **/advanced/dna/dsbandrepair**: simulate early direct and indirect DNA damage in various geometries
- **/advanced/dna/moleculardna**: simulate early direct and indirect DNA damage in various geometries

Also, for examples of dosimetry at the cellular scale, see:

- **/extended/medical/dna/microbeam**
- **/extended/medical/dna/neuron**
- **/advanced/dna/cellularPhantom**: simulate the irradiation of a 3D voxel phantom containing biological cells, created from confocal microscopy

Contents of this talk

- Why biology modelling?
- Geometrical models
- Damage calculation and classification
- Biological models
- Geant4-DNA examples
- In conclusion

Biology modelling with Geant4-DNA

- As a Track Structure Monte Carlo code, Geant4-DNA provides the framework to compute initial DNA damage yields
  - physics, physico-chemistry and chemistry models
  - geometry models
- Two example codes are available:
  - advanced/dna/moleculardna
  - advanced/dna/dsbandrepair
- Some repair models are available in these two codes as a demonstration of how to use the data calculated with the Geant4-DNA code
- See the hands-on and practice!