Evaluation of ionizing radiation induced DNA damage on a cell by integrated Monte Carlo simulations using Geant4-DNA

Dousatsu Sakata for the Geant4-DNA Collaboration

National Institutes for Quantum and Radiological Science and Technology

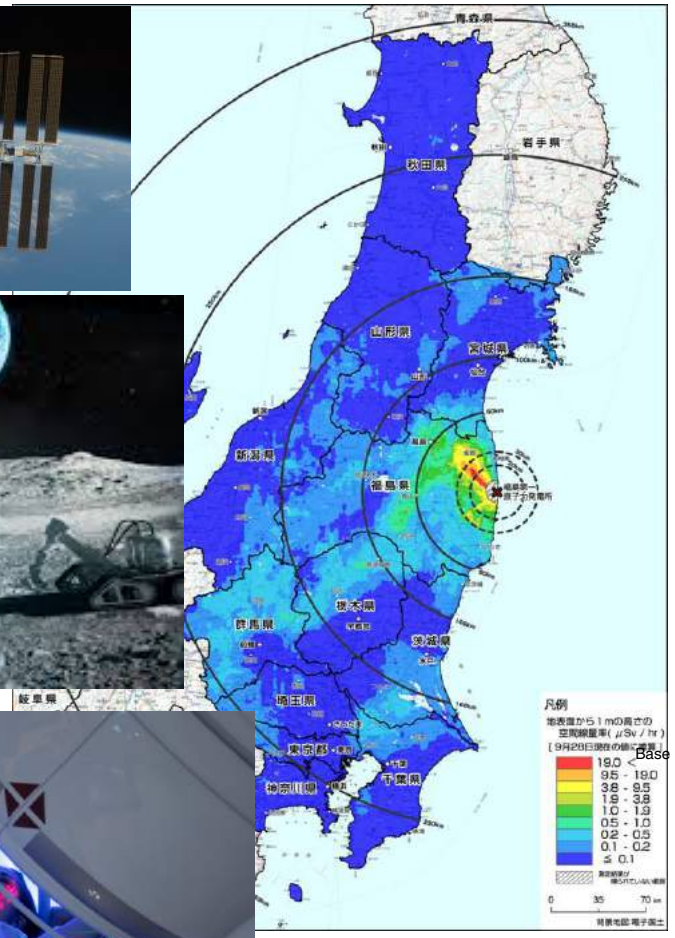
National Institute of Radiological Science

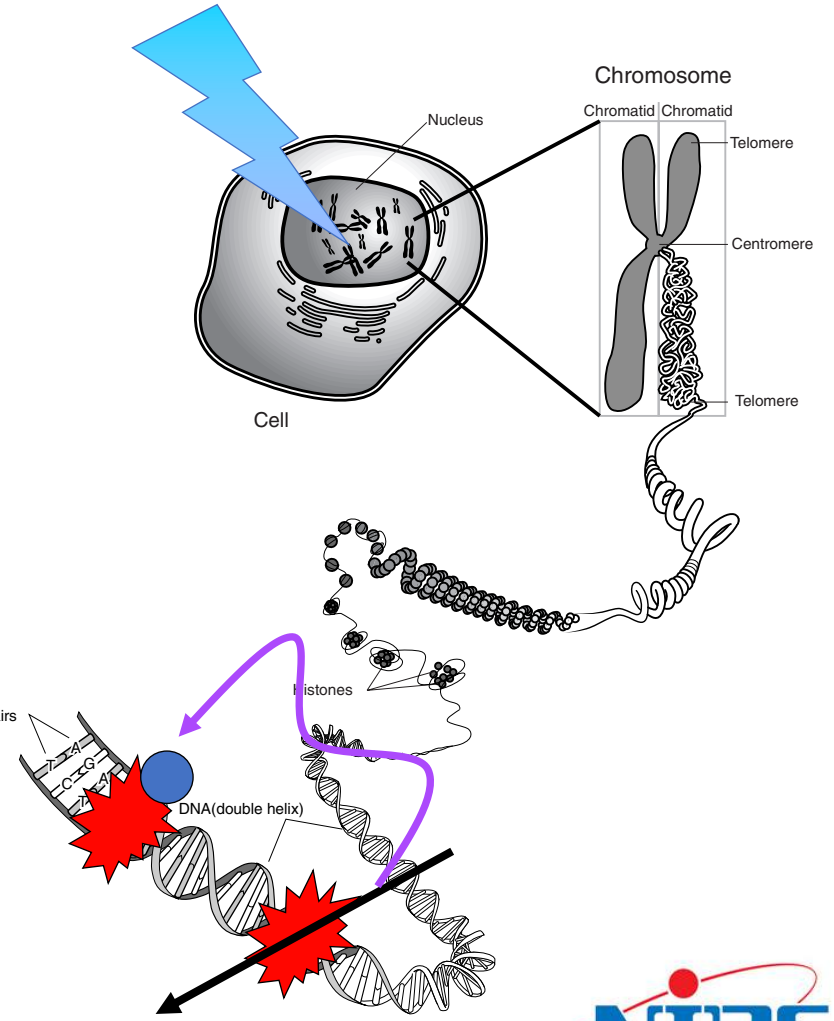
Outlook

- Introduction
- Cell nucleus Geometry
- Direct/Indirect damage
- Simulation Configuration
- Results
- Conclusion

Introduction

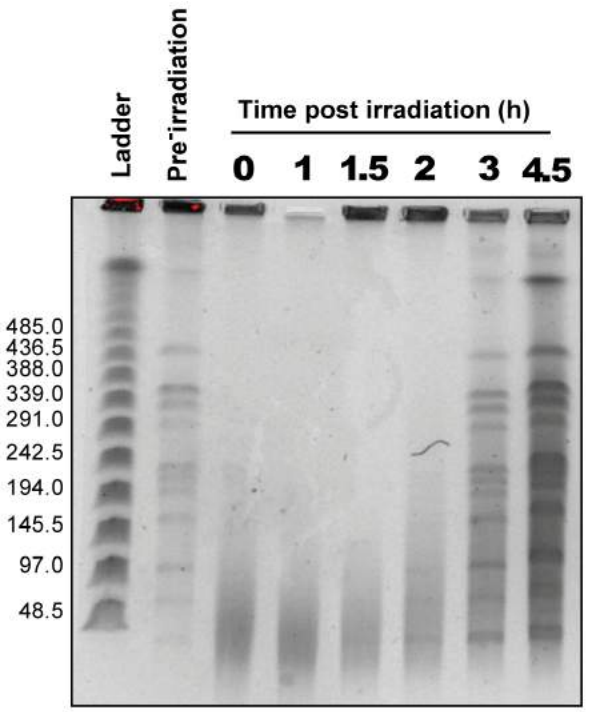
Modeling of radiation induced DNA damage



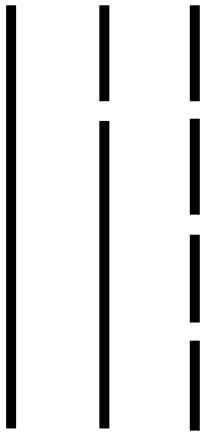


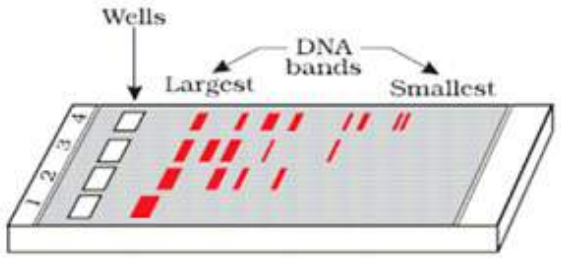
Radiobiological Experiments

Electrophoresis

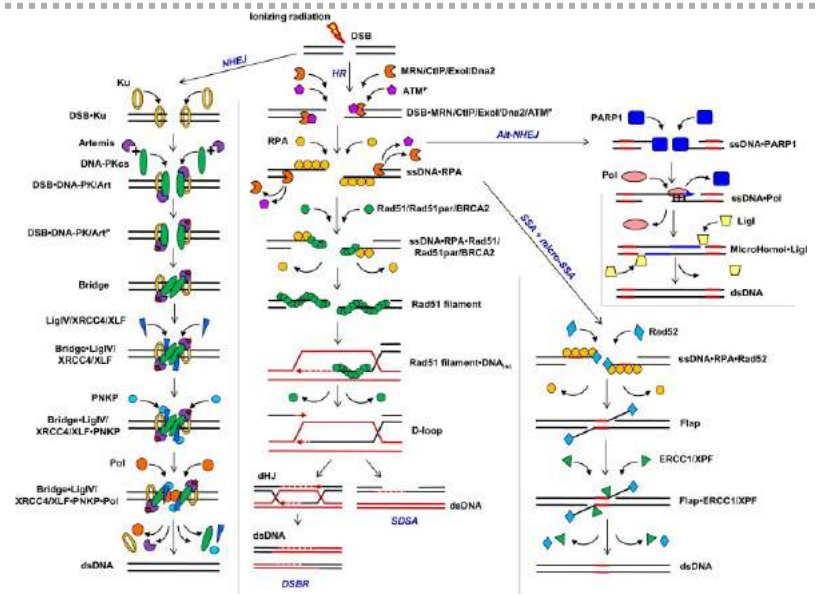


PLoS Genet 6(1): e1000799.

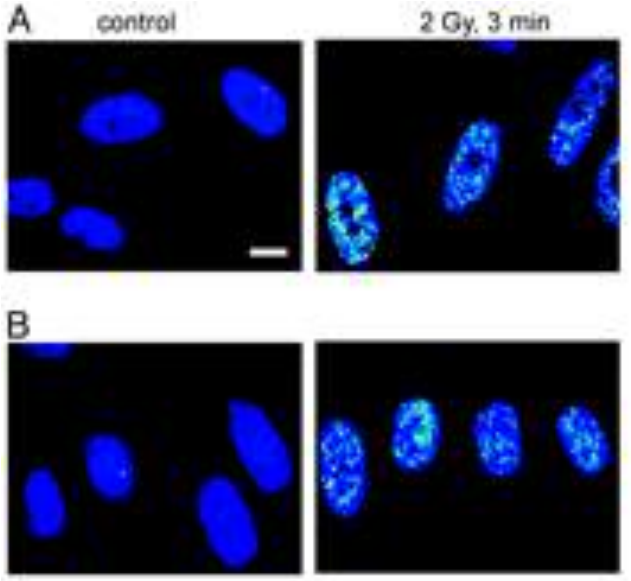




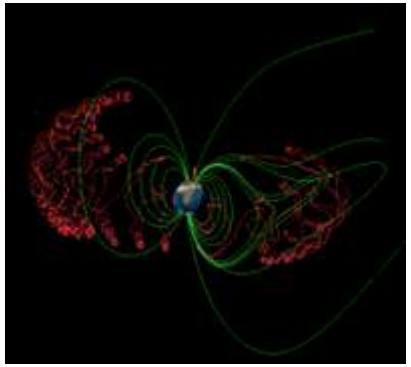
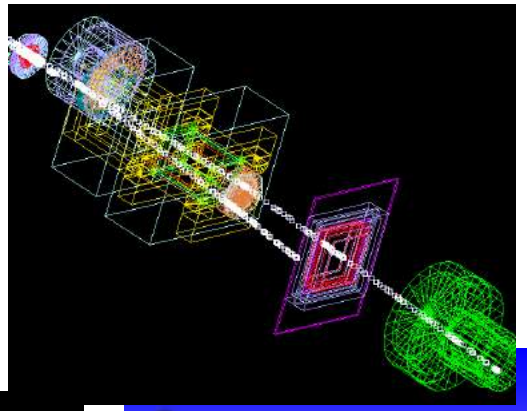
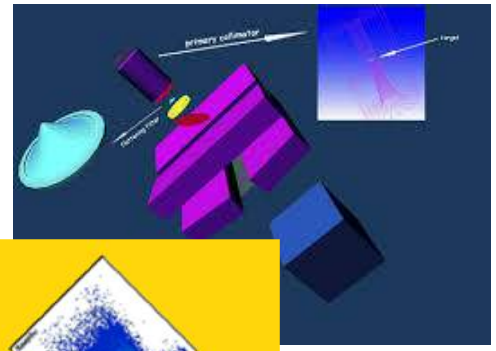
NCERT Class XII Biology Chapter 11 :
Biotechnology Principles and Processes



Foci (γ H2AX)



Proc Natl Acad Sci U. S. A. 2003 29;100(9):5057-62.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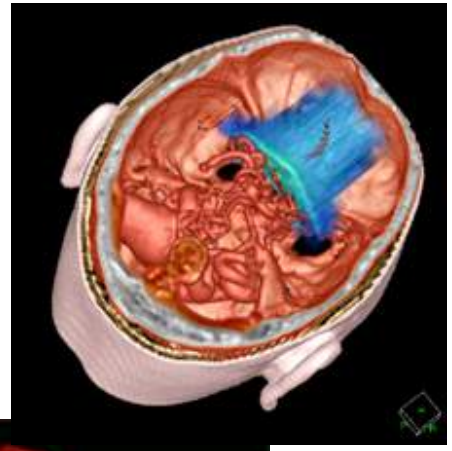
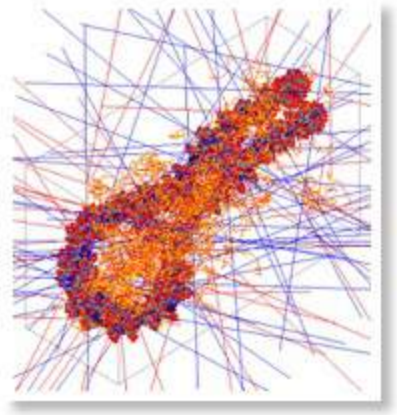
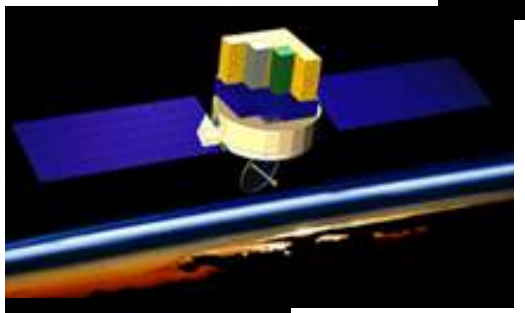
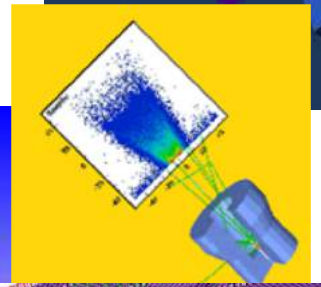
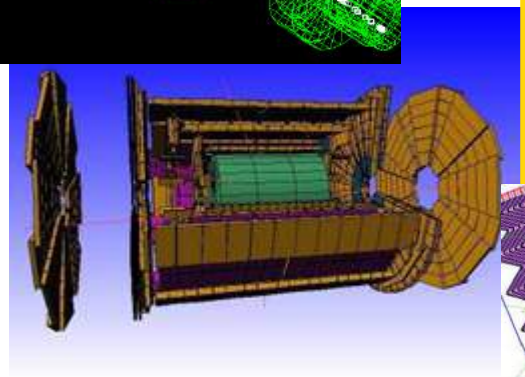
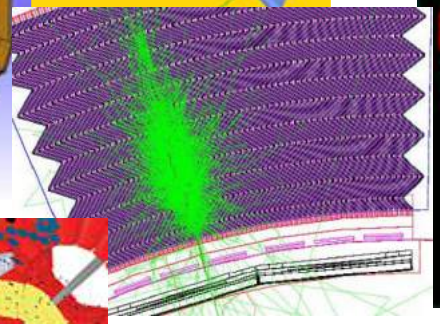
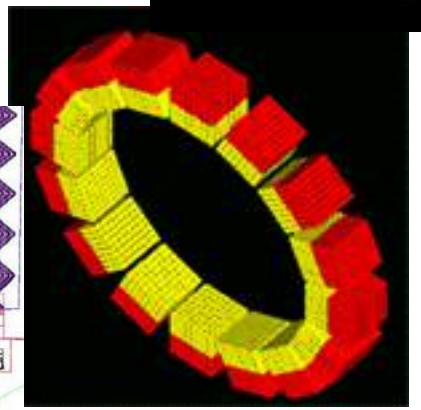
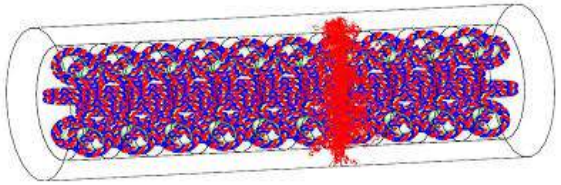
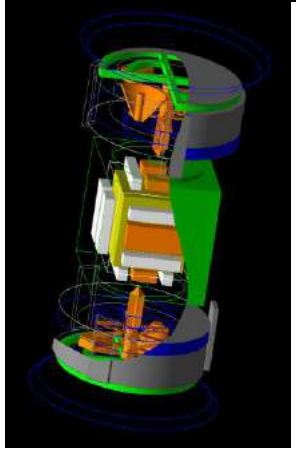
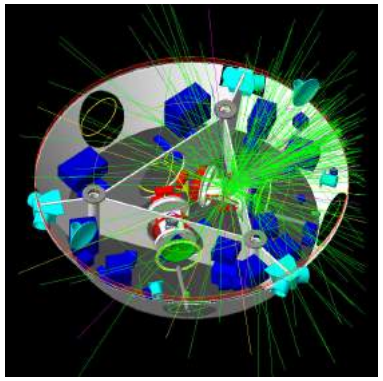
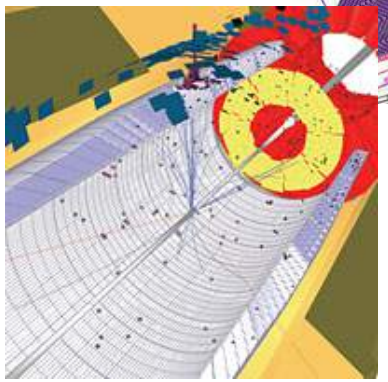
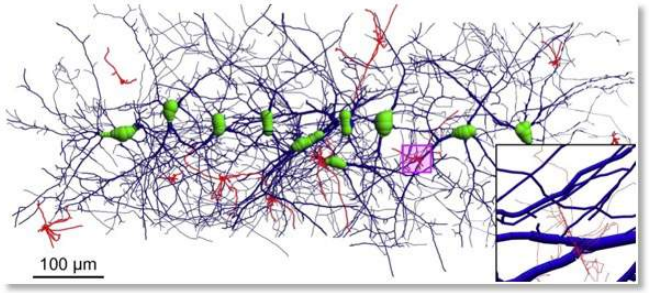
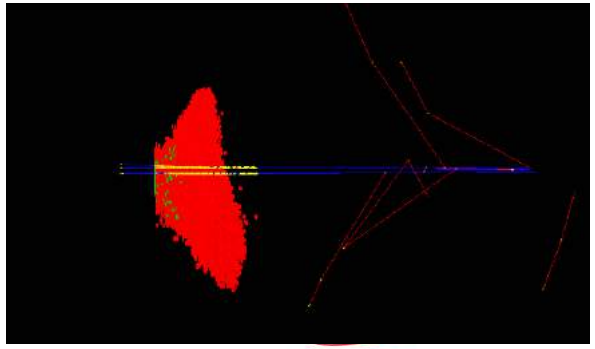
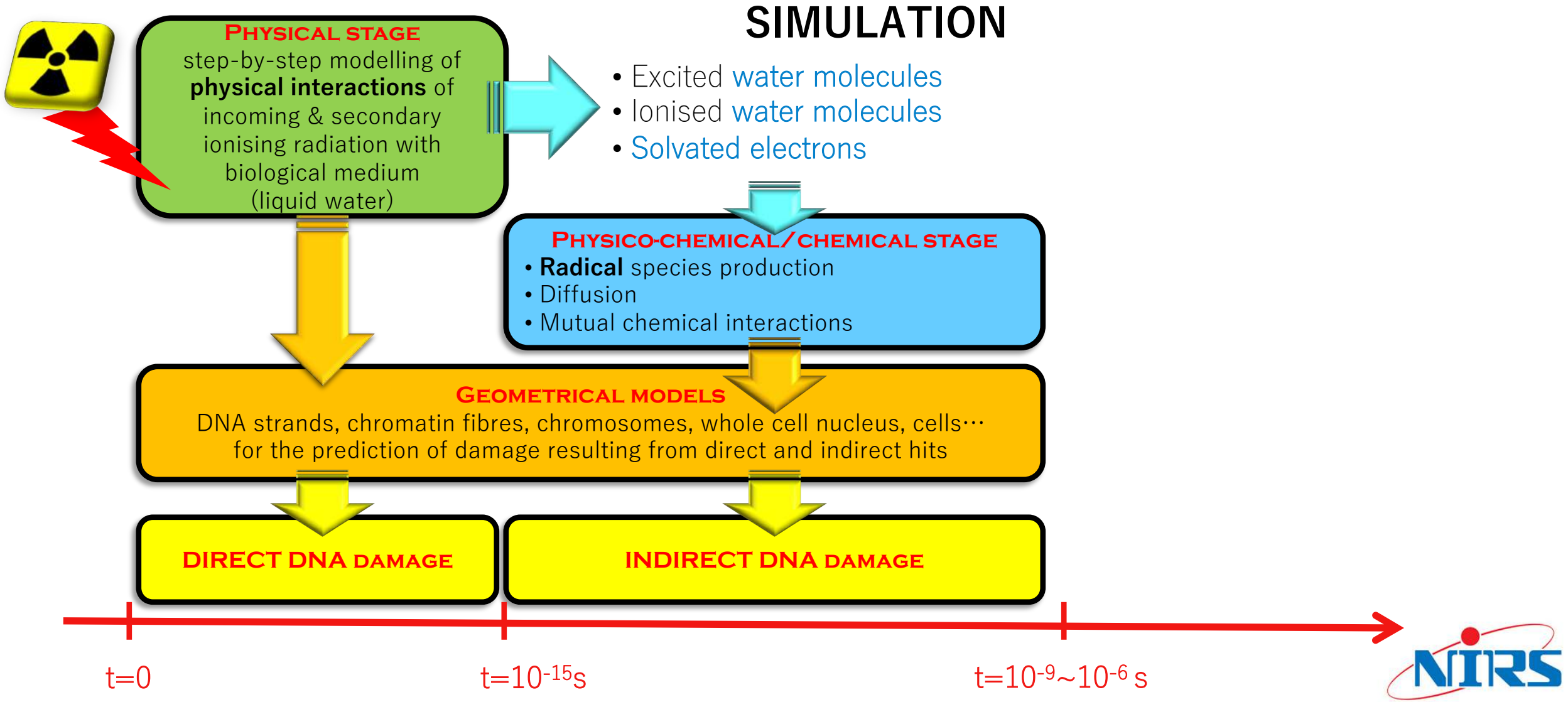
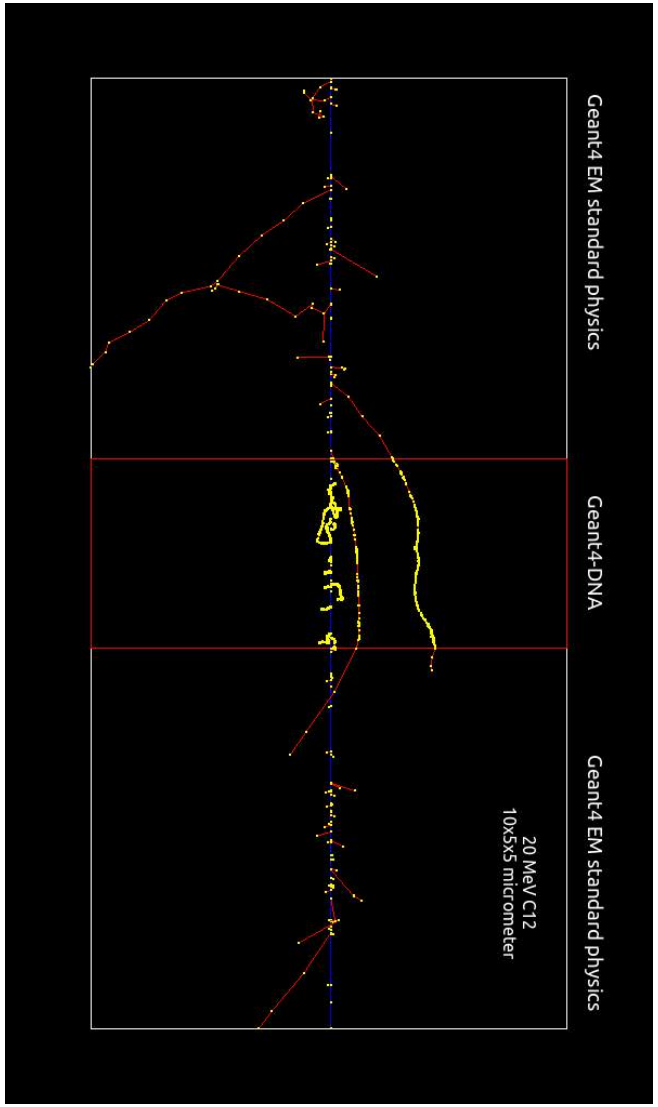












100 µm


Simulation Overview

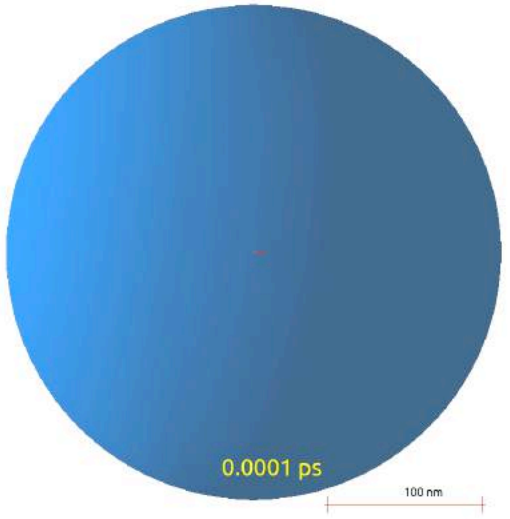


Physics and Chemistry

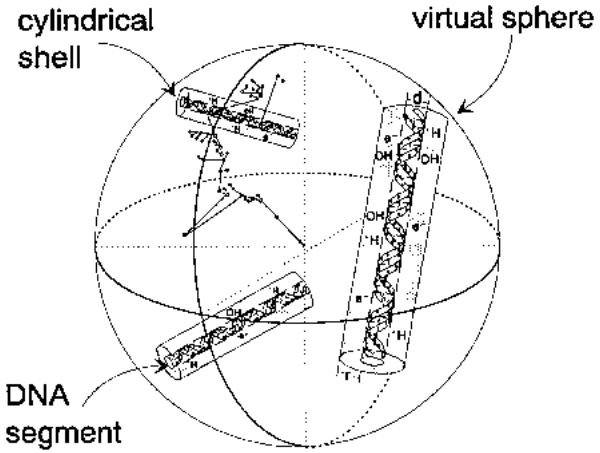


Electronic state	Decay Channel	Fraction (%)
All ionization states	$H_3O^+ + \bullet OH$	100
Excitation state A1B1: (1b1) → (4a1/3s)	$\bullet OH + H\bullet$	65
	$H_2O + \Delta E$	35
Excitation state B1A1: (3a1) → (4a1/3s)	$H_3O^+ + \bullet OH + e^-_{aq}$	55
	$\bullet OH + \bullet OH + H_2$	15
	$H_2O + \Delta E$	30
Excitation state: Rydberg, diffusion bands	$H_3O^+ + \bullet OH + e^-_{aq}$	50
	$H_2O + \Delta E$	50

Reaction	Reaction rate (10^{10} M^{-1} s^{-1})
$H\bullet + e^-_{aq} + H_2O \rightarrow OH^- + H_2$	2.65
$H\bullet + \bullet OH \rightarrow H_2O$	1.44
$H\bullet + H\bullet \rightarrow H_2$	1.20
$H_2 + \bullet OH \rightarrow H\bullet + H_2O$	4.17×10^{-3}
$H_2O_2 + e^-_{aq} \rightarrow OH^- + \bullet OH$	1.41
$H_3O^{\mp} + e^-_{aq} \rightarrow H\bullet + H_2O$	2.11
$H_3O^{\mp} + OH^- \rightarrow 2\ H_2O$	14.3
$\bullet OH + e^-_{aq} \rightarrow OH^-$	2.95
$\bullet OH + \bullet OH \rightarrow H_2O_2$	0.44
$e^-_{aq} + e^-_{aq} + 2\ H_2O \rightarrow 2\ OH^- + H_2$	0.50

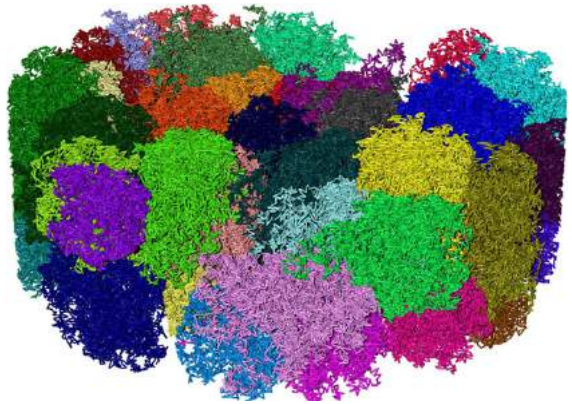


Geometry in Previous Simulations

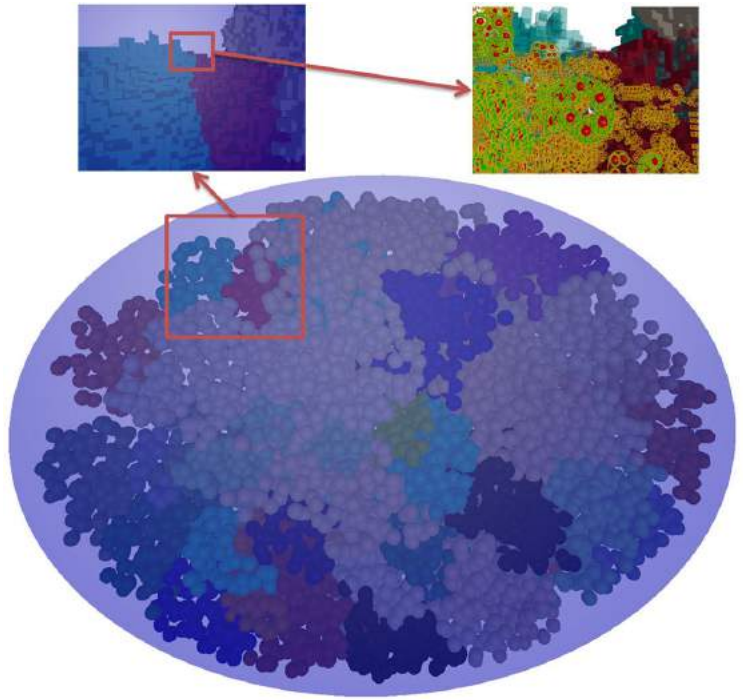


I. J. Rad. Bio.
66:5, 453-457 (1994)
KURBUC

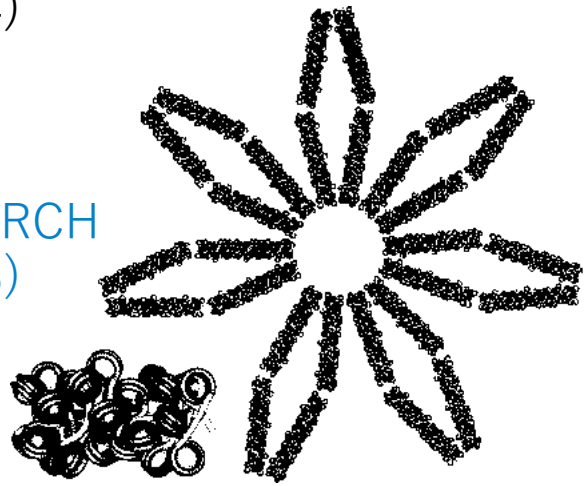
PARTRAC
Mut. Res. 711, 28–40 (2011)

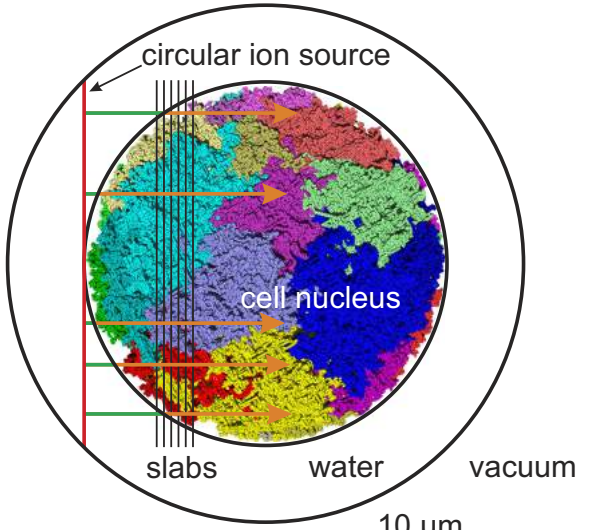


Geant4-DNA
Sci. Rep., 7: 11923. (2017)



RADIATION RESEARCH
159, 401–410 (2003)
PARTRAC

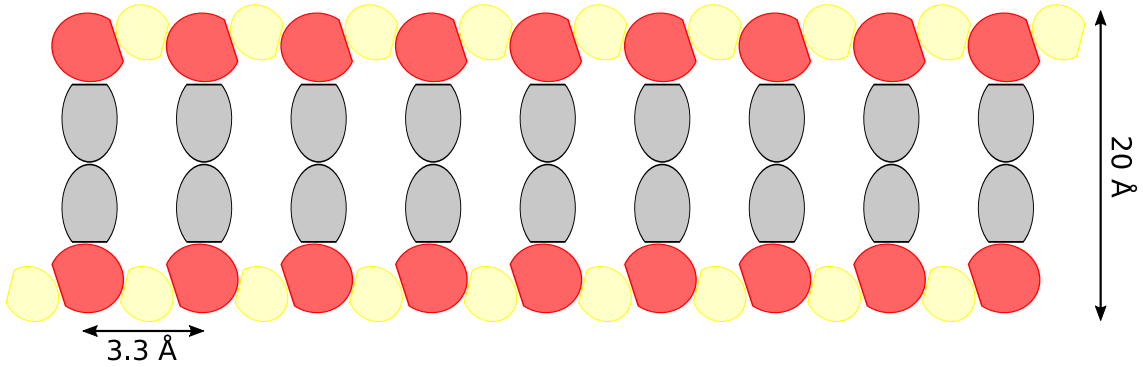




PARTRAC
Sci. Rep.,
7: 45161. 2017

Cell Nucleus Geometry

DNA Geometry



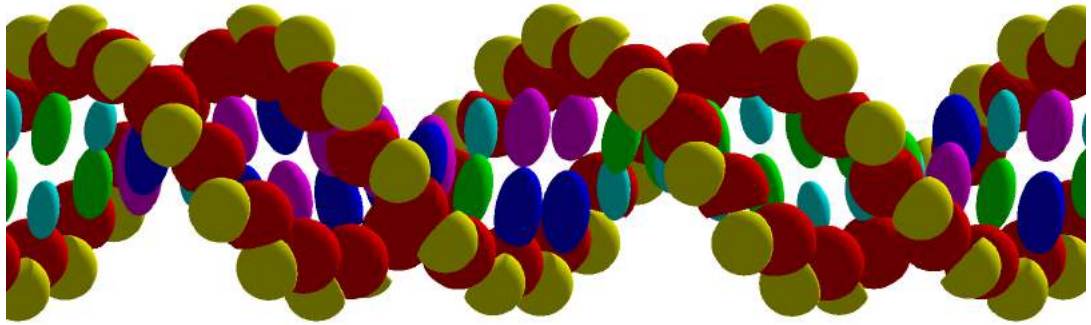
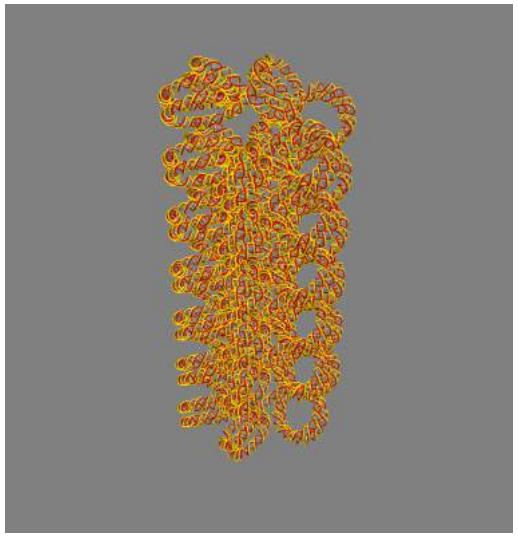


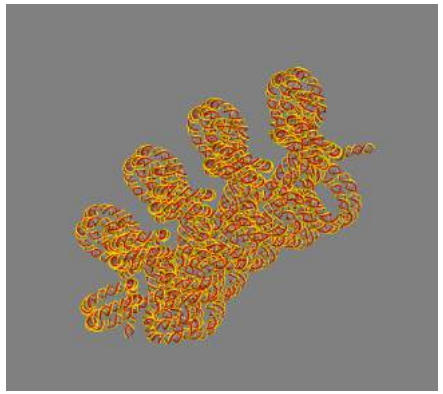
TABLE I. The minimum allocation molecule geometries

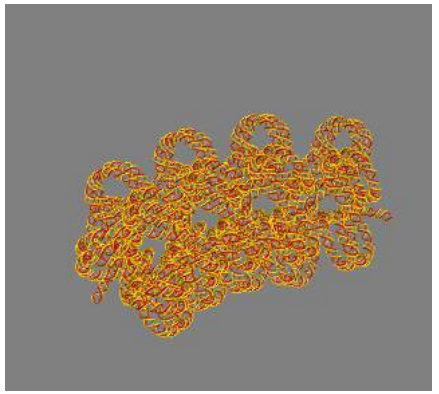
Name	Chemical formula	Volume shape	Radius (X) [Å]	Radius (Y) [Å]	Radius (Z) [Å]
Phosphate	H_3PO_4	Sphere	2.28	2.28	2.28
Deoxyribose	$C_5H_{10}O_4$	Sphere	2.63	2.63	2.63
Guanine	$C_5H_5N_5O$	Ellipsoid	3.63	3.80	1.89
Adenine	$C_5H_5N_5$	Ellipsoid	3.43	3.74	1.93
Cytosine	$C_4H_5N_3O$	Ellipsoid	3.60	3.07	1.77
Thymine	$C_5H_6N_2O_2$	Ellipsoid	4.21	3.04	2.00

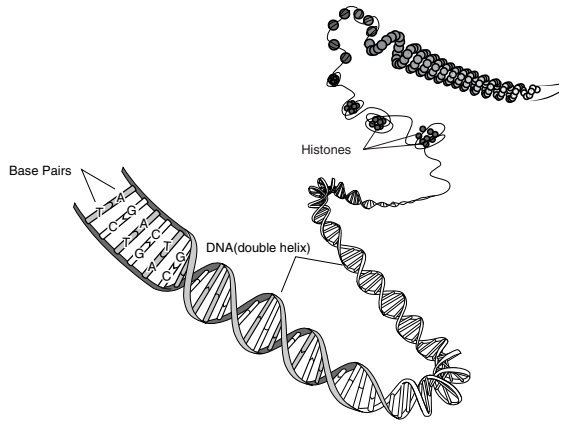
N. Lampe et al, Phys. Med. 2018; 48:135-145

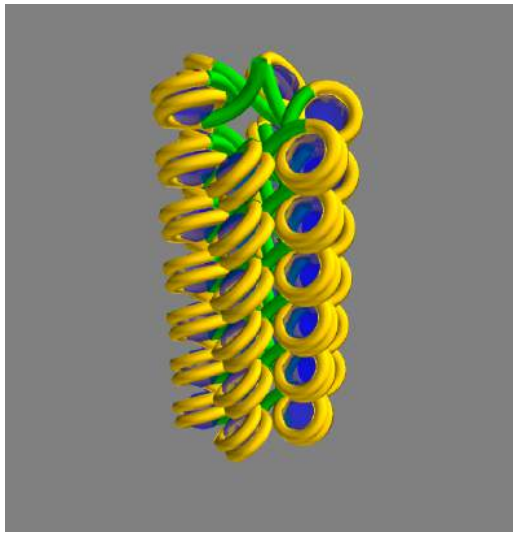
DNA Voxel Chromatin Fiber Geometry

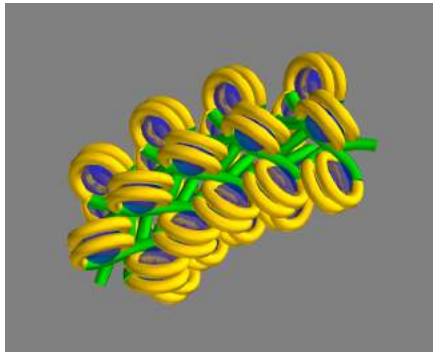


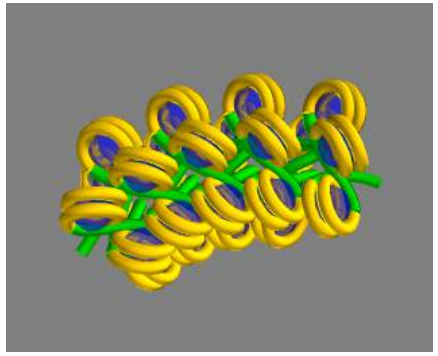








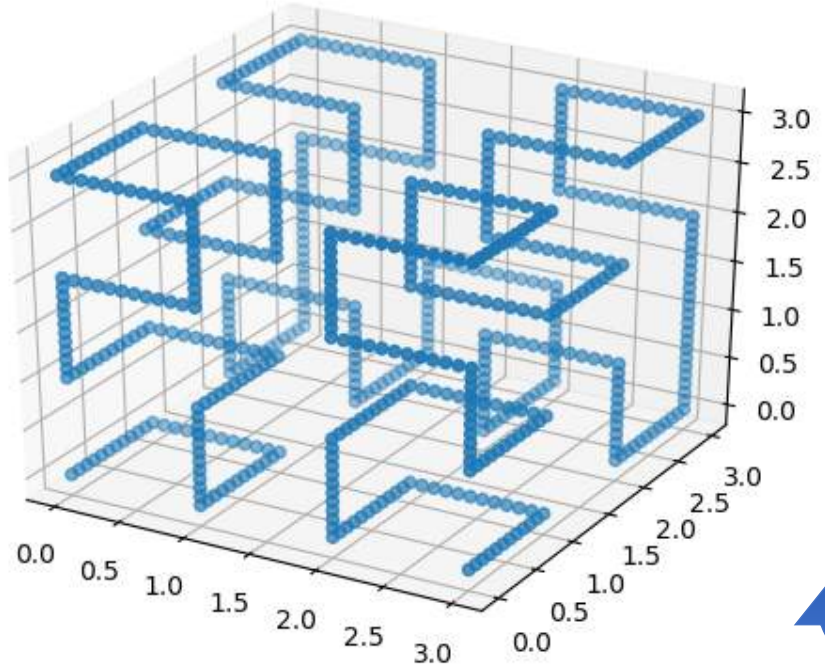


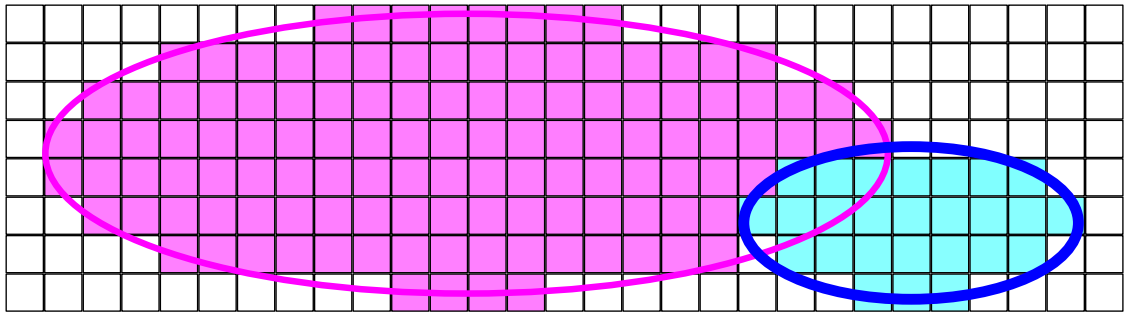


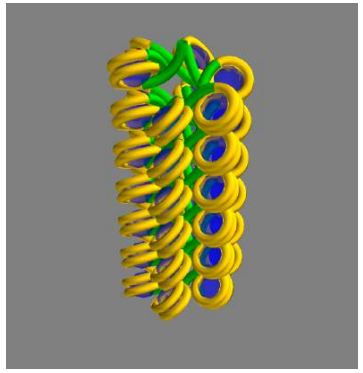
Type of Unit Geometry
- Straight
- Turn
- Turn-Twisted

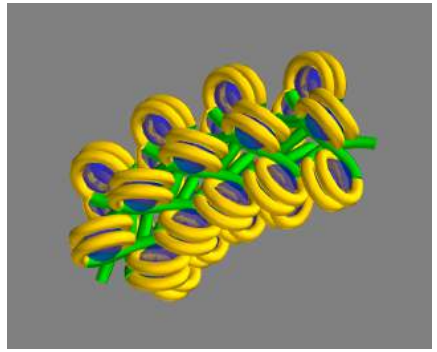
Newly developed in this work

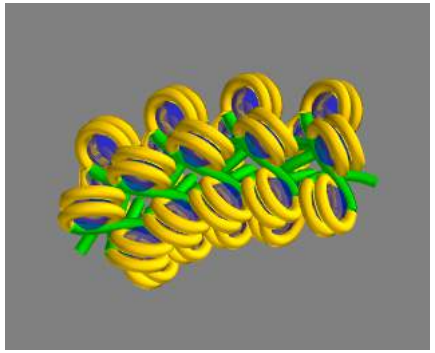
DNA Fractal Geometry





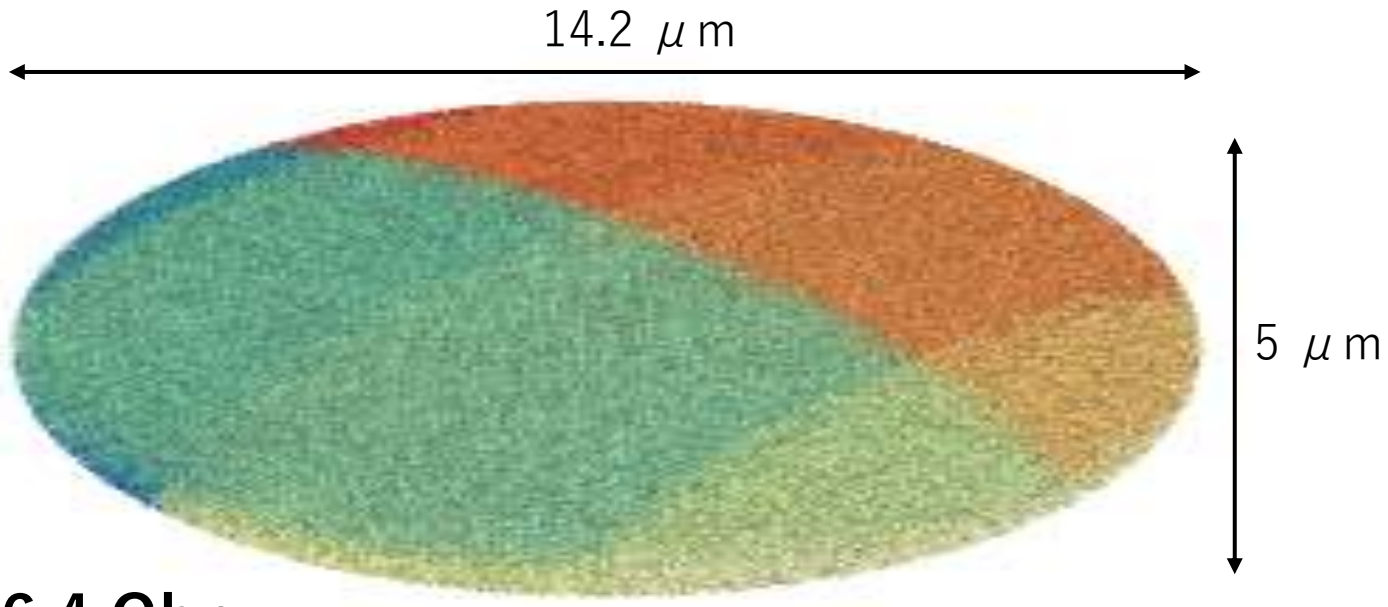




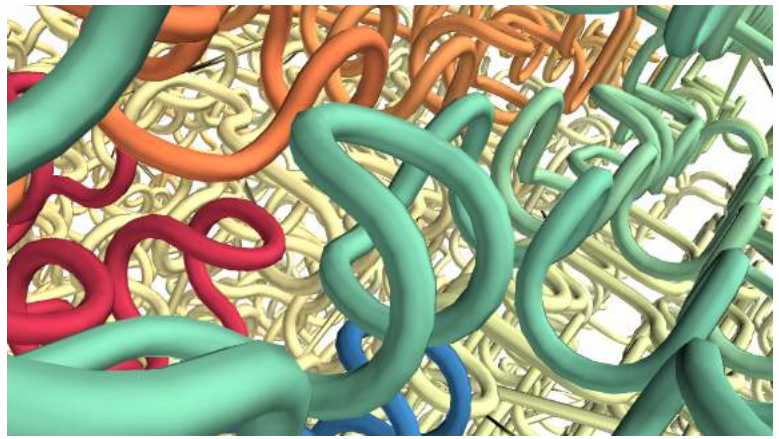


N. Lampe et al, Phys. Med. 2018; 48:146-155

A Whole Cell Nucleus



6.4 Gbp



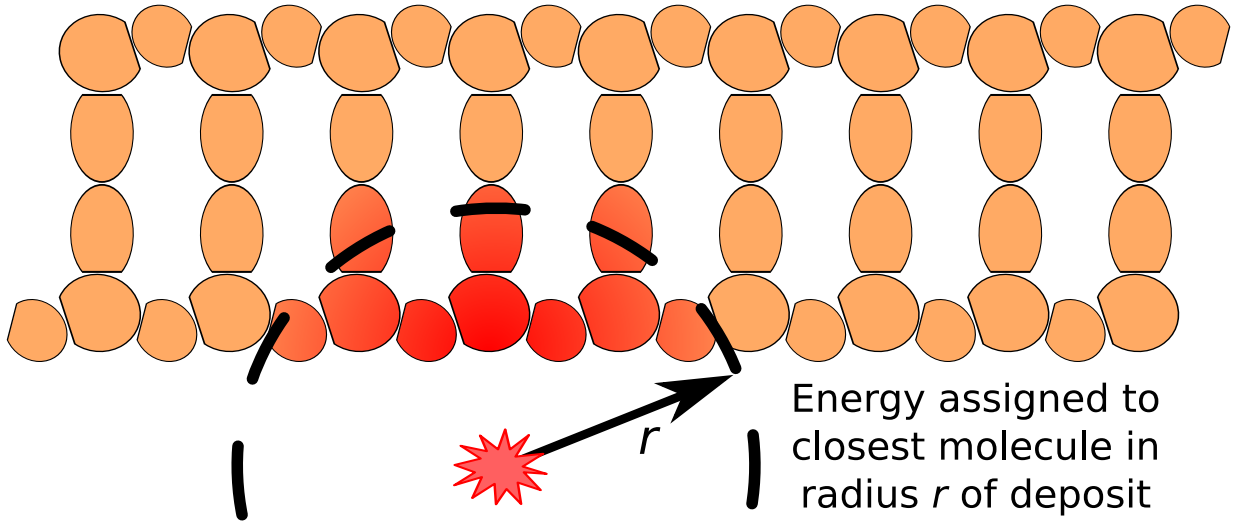
0.17 Gbp

2 μm sphere
as an example

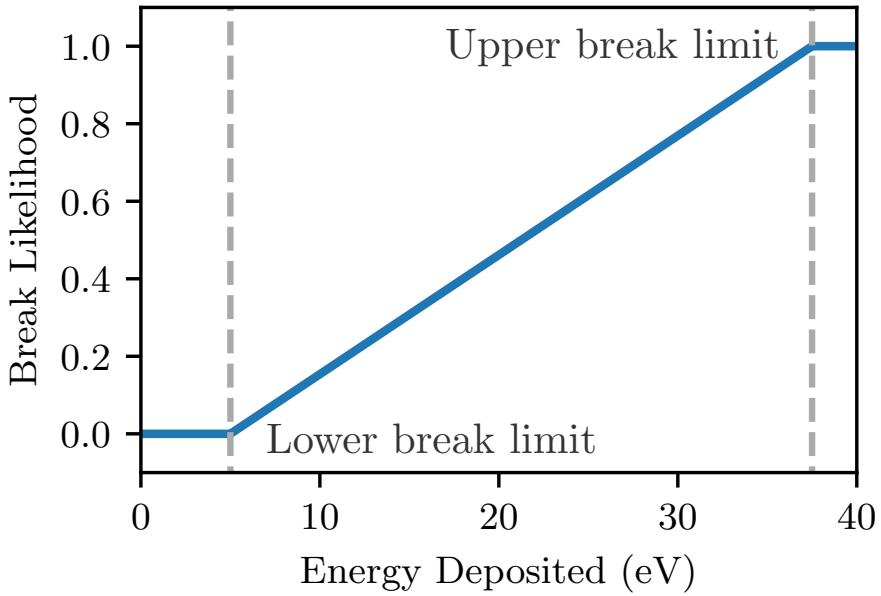
Direct/Indirect damage and repair models

Direct Damage Model

Accumulate Eloss around molecules



Calculate probability of SSB



E_{dep} assigned to closest strand molecule → E_{dep}

R_{direct} : 3.5 angstrom

$R_{Phosphate}$ ~ 2.28 angstrom

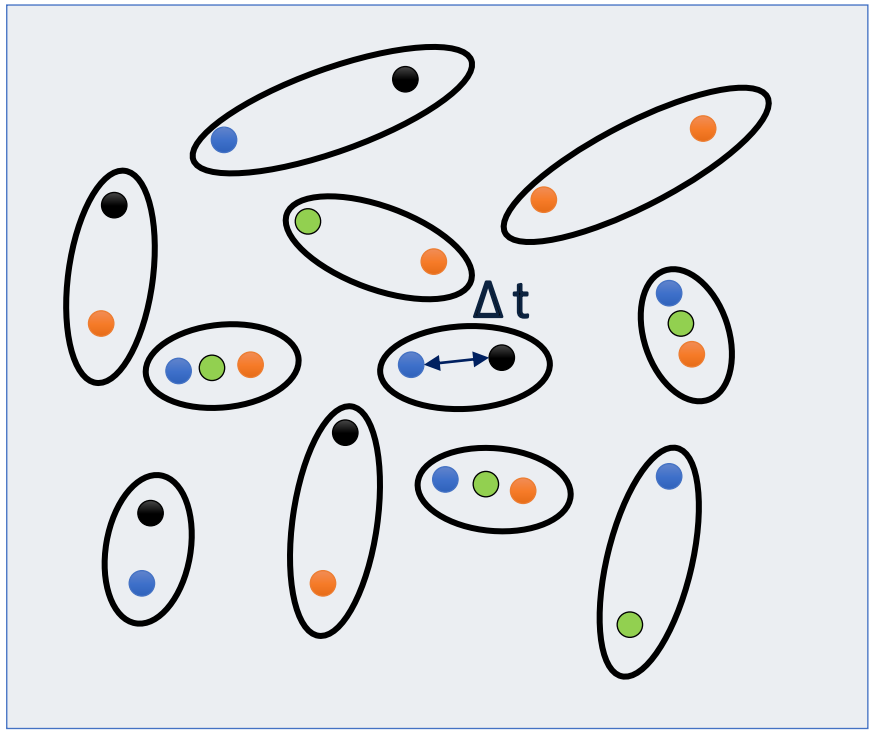
R_{Sugar} ~ 2.63 angstrom

$R_{HydShell}$ < 2 angstrom

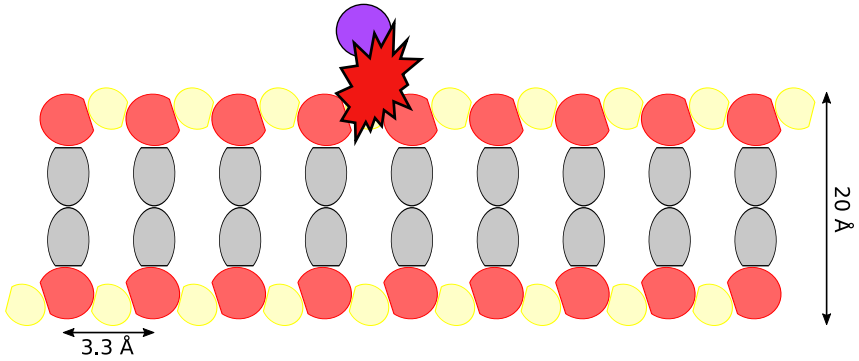
PARTRAC : 5 – 37.5 eV

KURBUC : 17.5 – 17.5 eV

Indirect Damage and Histone Scavenging



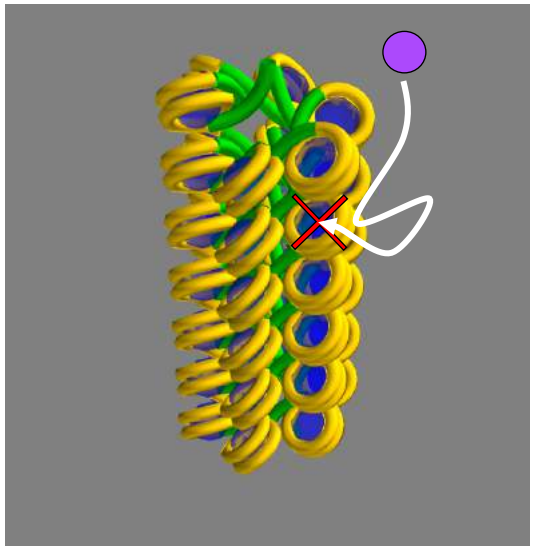
● •OH ● e^-_{aq}
● H• ● OH^-



$$DNA + {}^{\bullet}OH \rightarrow SSB$$

P_{OH} = 0.13 : KURBUC (1997)
P_{OH} = 0.13 : PARTRAC (2003)
P_{OH} = 0.4 : Lampe (2018)
P_{OH} = 0.42 : Meylan (2016)
P_{OH} = 0.7 : Kreipl (2009)

Chemistry Limits
Time duration : 5ns
Correspond Diff. Dist. : 9nm

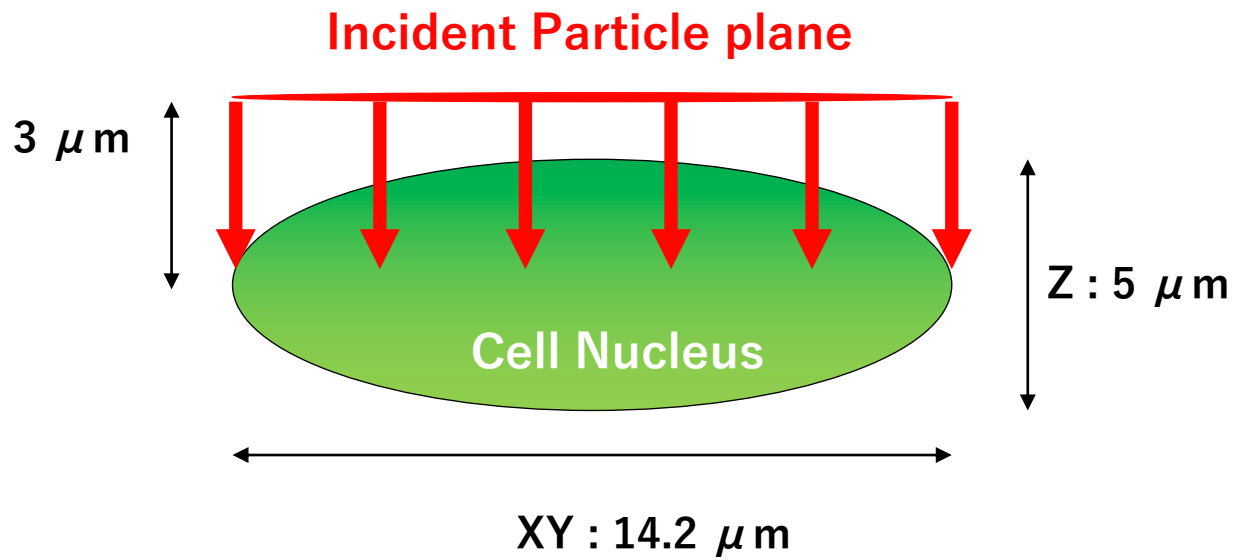


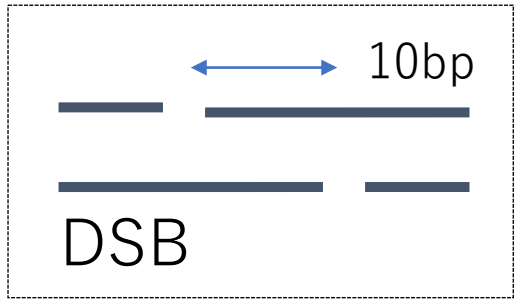
Histone Size
PARTRAC : 45 nm
This work : 25 nm

Simulation Configuration

Simulation Configuration

6.4 Gbp : 0.012 bp/nm^3

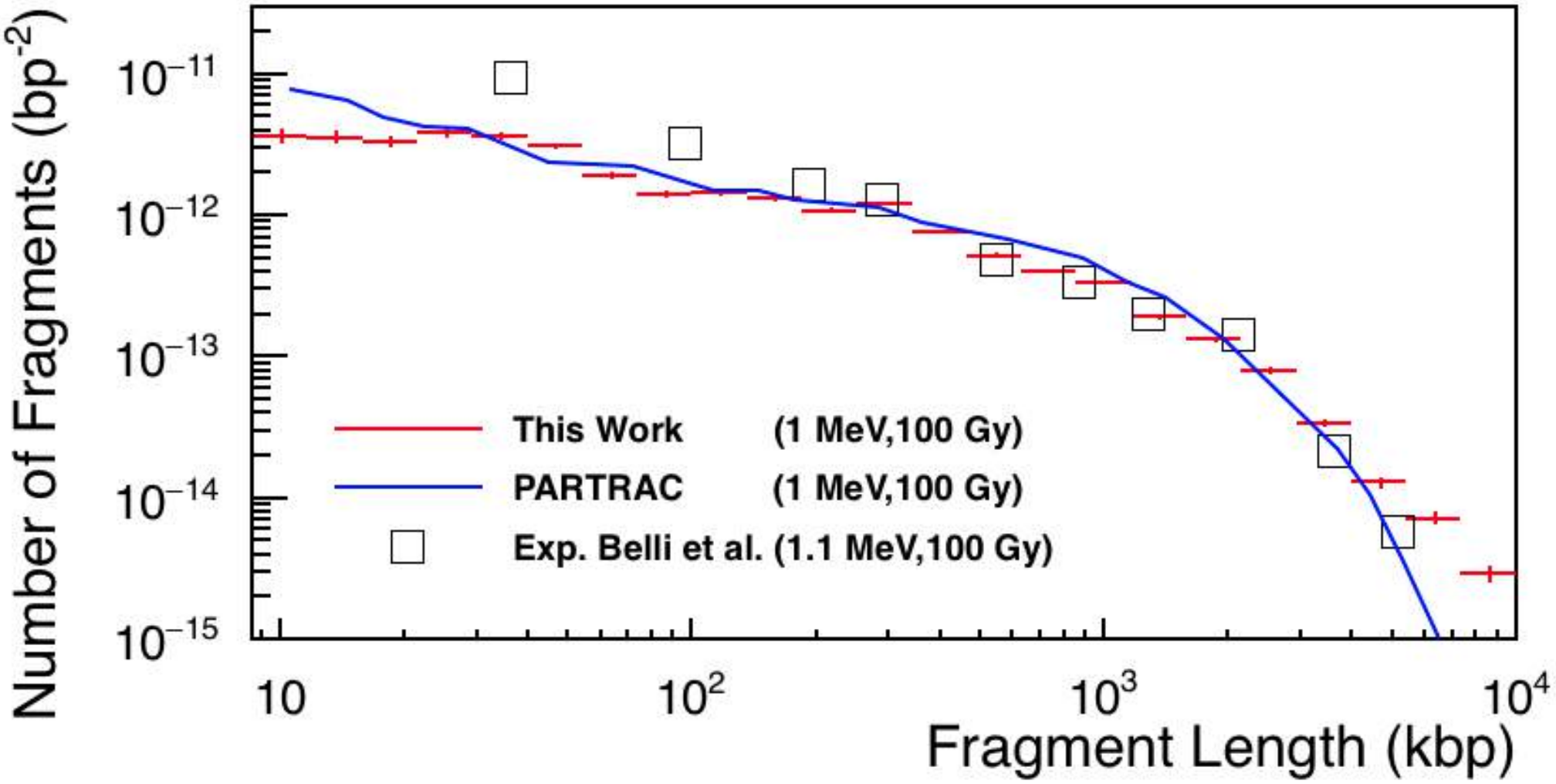




Results

Fragment Distribution

Using different damage parameters



Conclusion

- After 10 years from Geant4-DNAlaunched, we have achieved to develop applications for evaluating ionising radiation induced DNA damage, as a milestone of the Geant4-DNA studies.

- We are now ready to explore the mechanisms of ionising radiation induced DNA damage.

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Original paper

Evaluation of early radiation DNA damage in a fractal cell nucleus model using Geant4-DNA

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