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

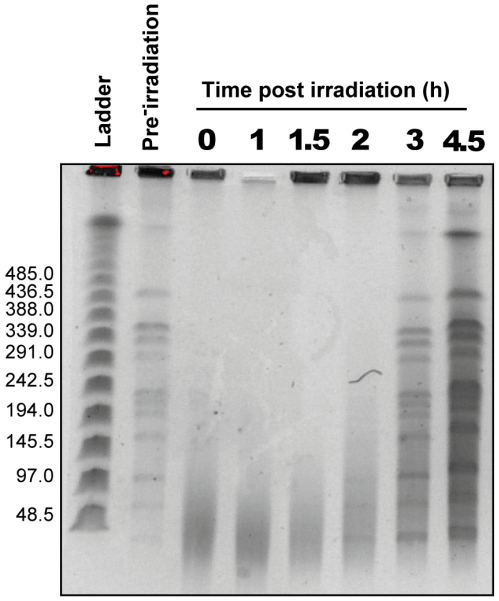
Dousatsu Sakata for the Geant4-DNA Collaboration

National Institutes for Quantum and Radiological Science and Technology

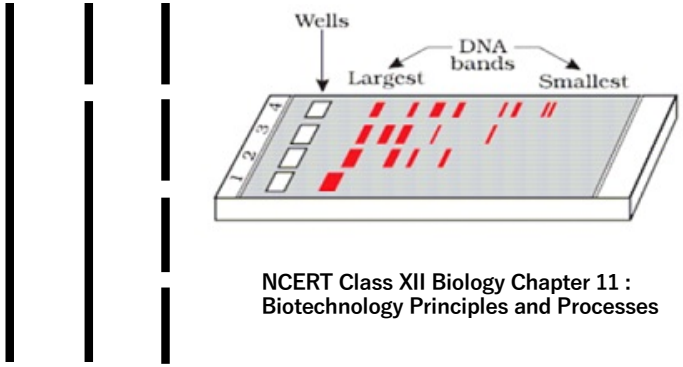
National Institute of Radiological Science

Radiobiological Experiments

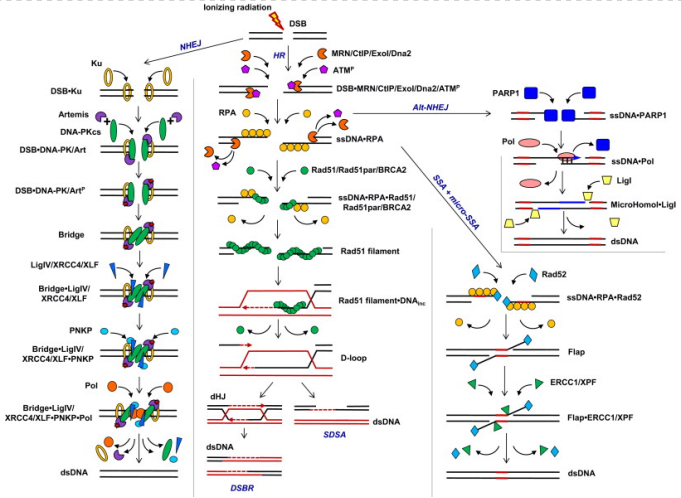
Electrophoresis



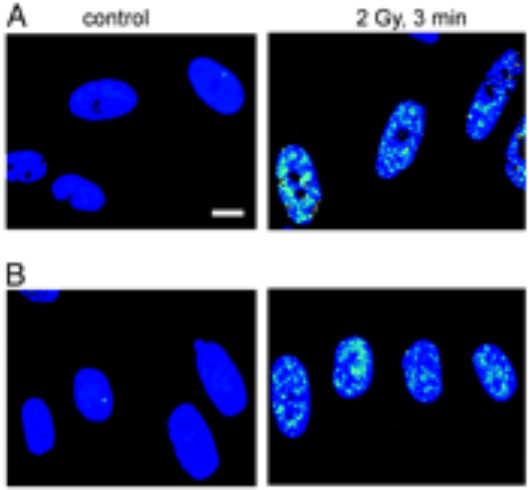
PLoS Genet 6(1): e1000799.



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.

Issues should be addressed

- More realistic biological geometry
  - $\rho_{bp} \sim 0.008$ bp/nm^3 (typical $\rho_{bp} \sim 0.015$ bp/nm^3)
  - ➢ Developed new Geom. $\rho_{bp} \sim 0.012$ bp/nm^3
- Improve computing performance
  - $T_{sim} \sim$ 3 weeks
  - ➢ Implement IRT chemistry (Mathieu's ver), $T_{sim} \sim$ 10h
- Introduce biological repair process
  - ➢ Introduce biological repair model

DNA Geometry

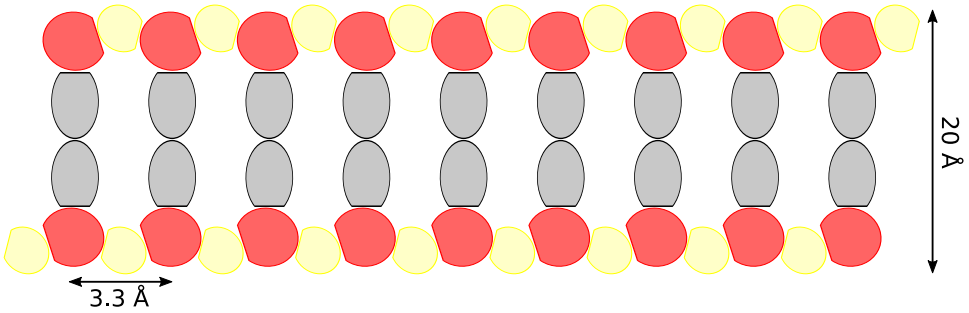
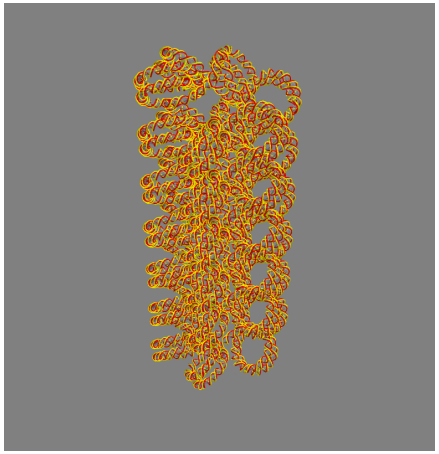
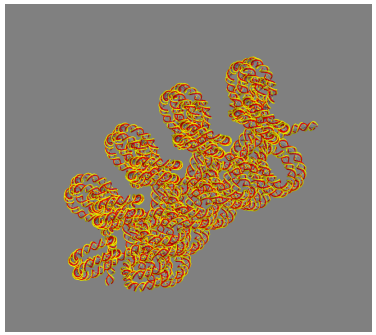
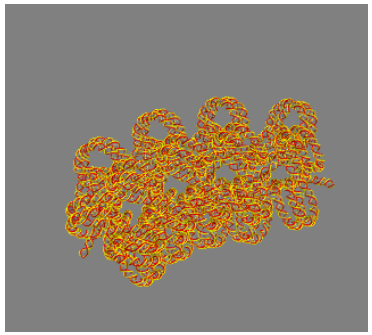
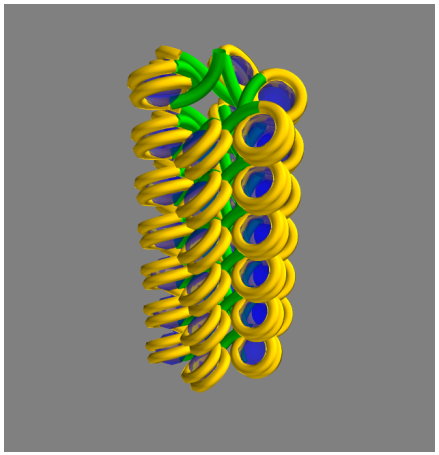
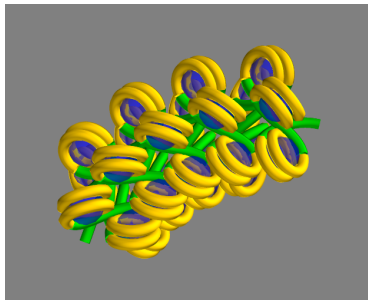
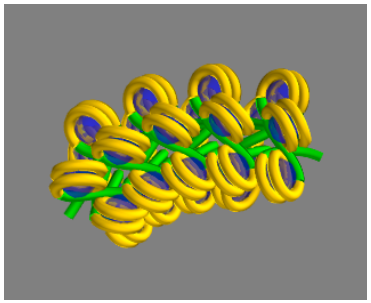


TABLE I. The minimum allocation molecule geometries

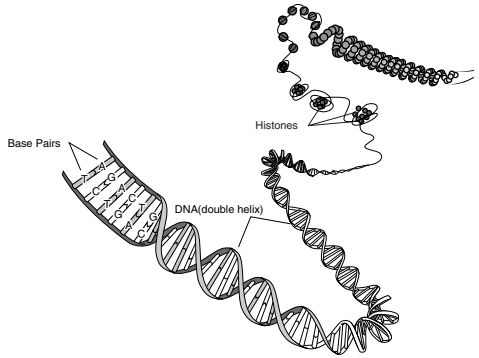
Name	Chemical formula	Volume shape	Radius (X) [Å]	Radius (Y) [Å]	Radius (Z) [Å]
Phosphate	H_3PO_4	Sphere	2.28	2.28	2.28
Deoxyribose	$C_5H_{10}O_4$	Sphere	2.63	2.63	2.63
Guanine	$C_5H_5N_5O$	Ellipsoid	3.63	3.80	1.89
Adenine	$C_5H_5N_5$	Ellipsoid	3.43	3.74	1.93
Cytosine	$C_4H_5N_3O$	Ellipsoid	3.60	3.07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

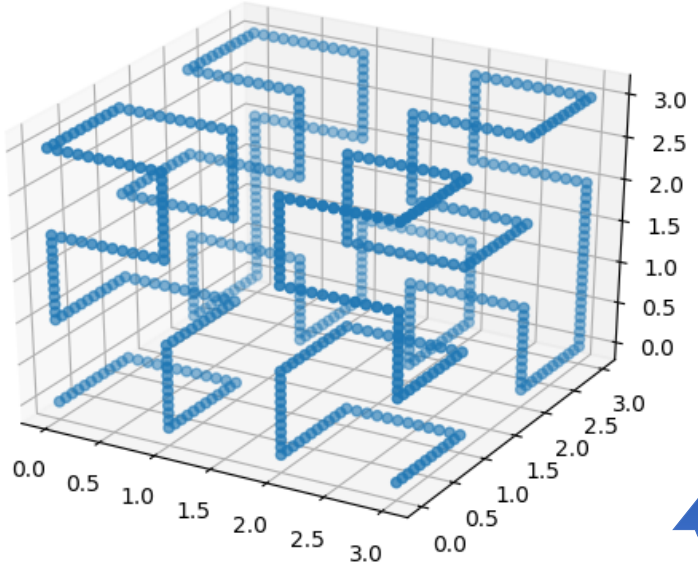







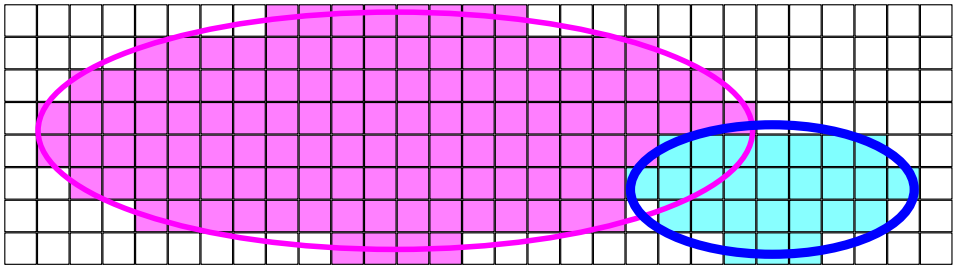
Newly developed in this work

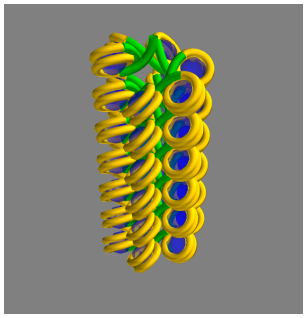


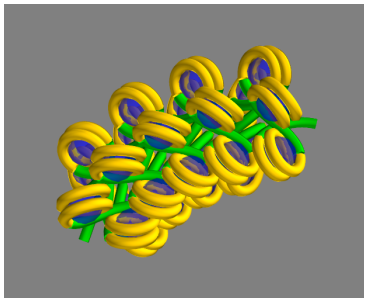
Type of Unit Geometry
- Straight
- Turn
- Turn-Twisted

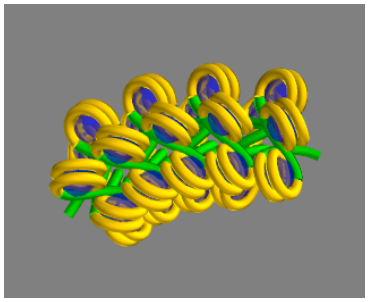
DNA Fractal Geometry





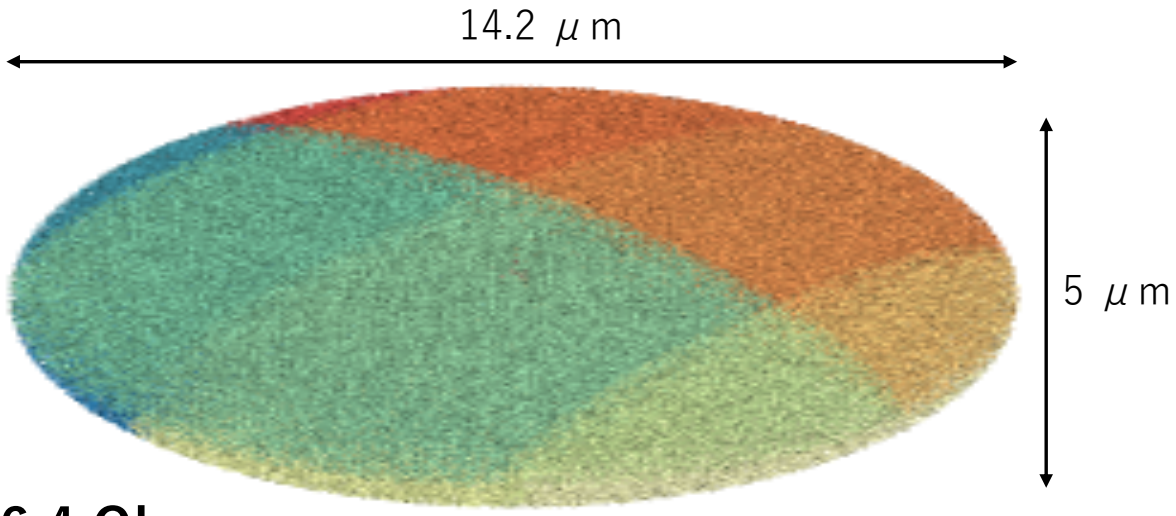




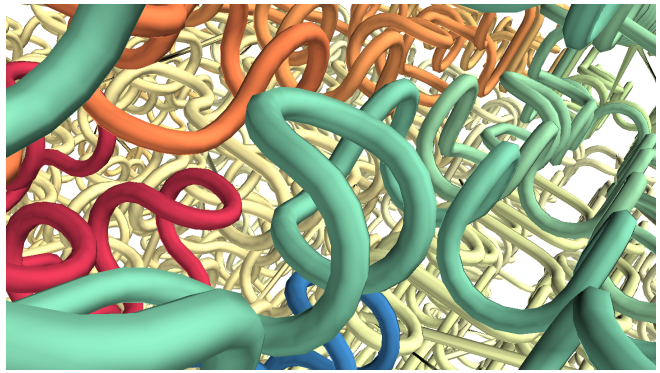


N. Lampe et al, Phys. Med. 2018; 48:146-155

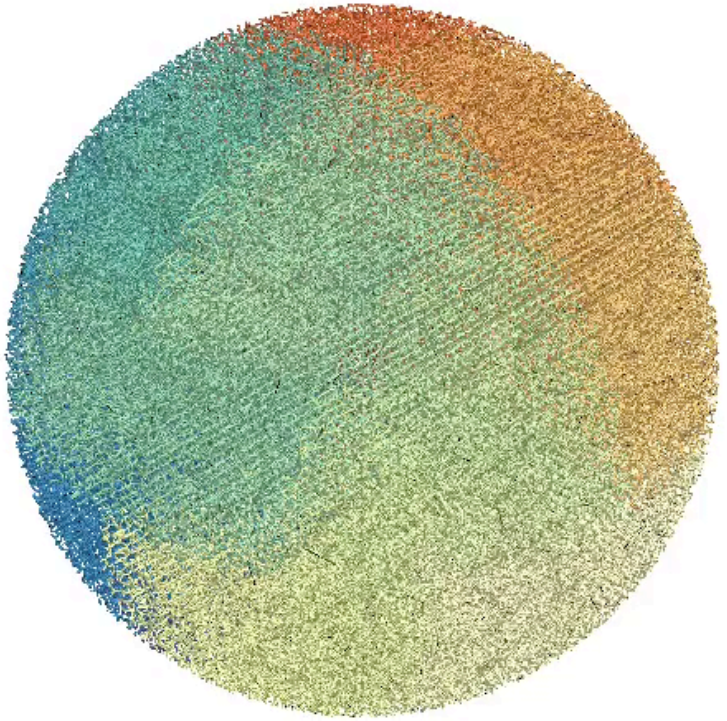
A Whole Cell Nucleus



6.4 Gbp



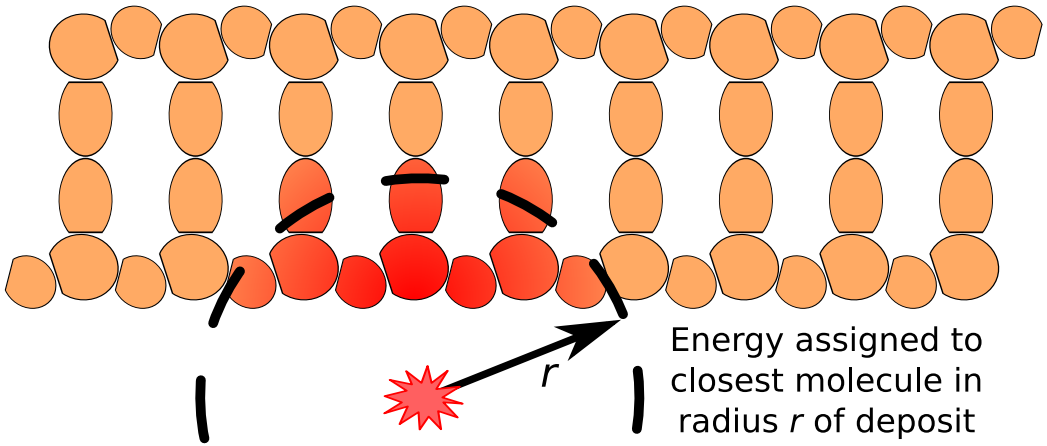
0.17 Gbp



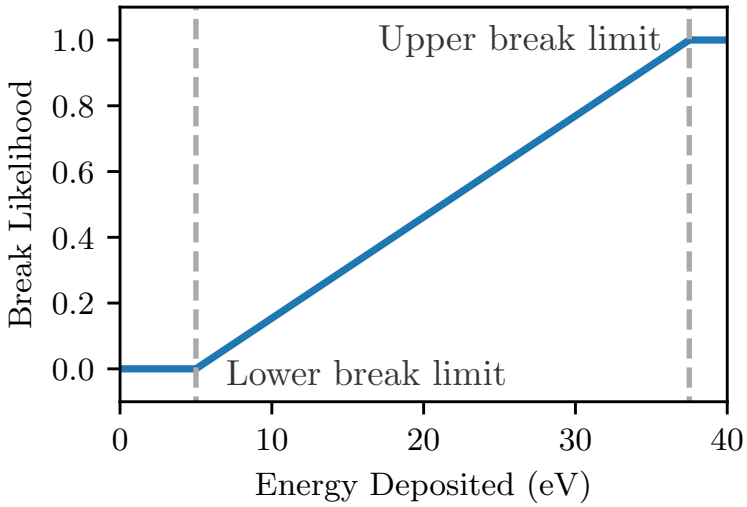
2 μm sphere
as an example

Direct 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

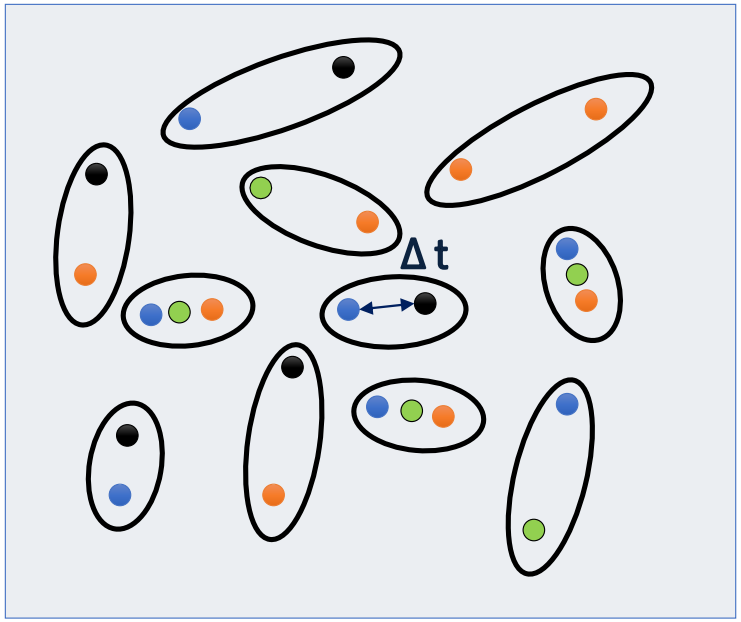
R_{Sugar} ~ 2.63 angstrom

$R_{HydShell}$ < 2 angstrom

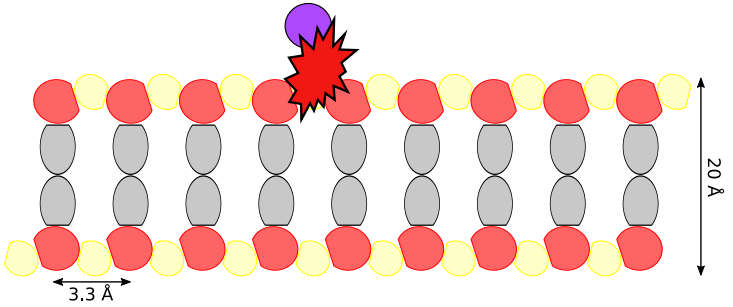
PARTRAC : 5 – 37.5 eV

KURBUC : 17.5 – 17.5 eV

Indirect Damage and Histone Scavenging



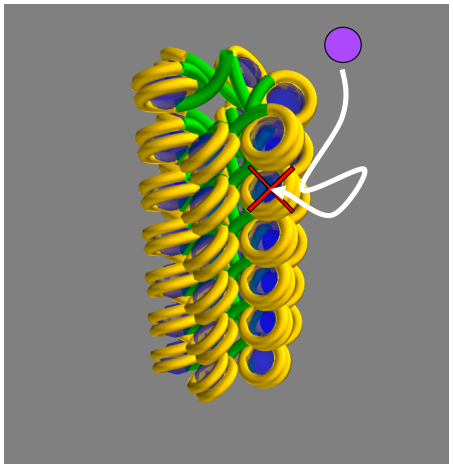
● •OH ● e^-_{aq}
● H• ● OH^-



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

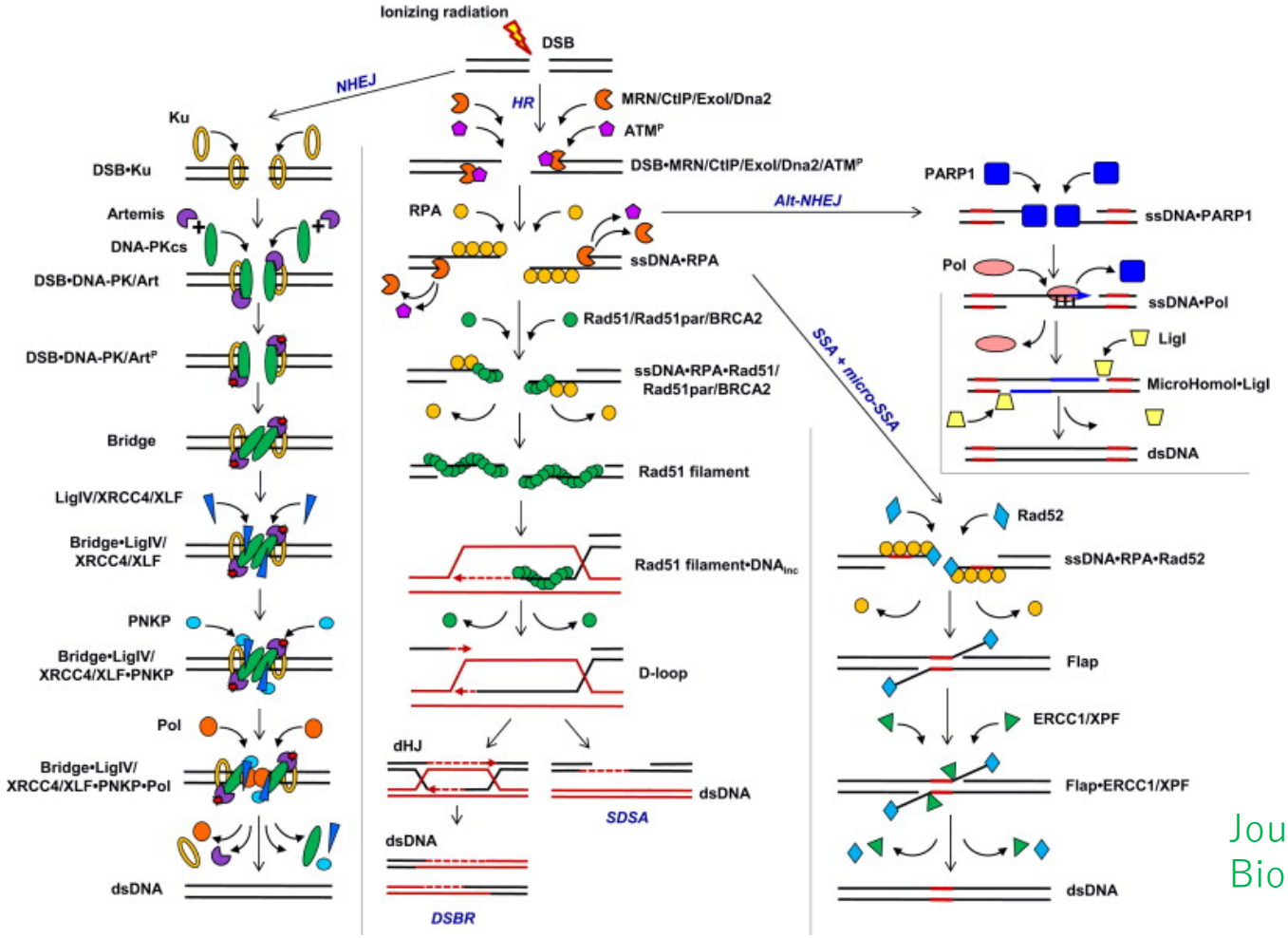
$P_{OH} = 0.13$	: KURBUC (1997)
$P_{OH} = 0.13$	: PARTRAC (2003)
$P_{OH} = 0.4$	: Lampe (2018)
$P_{OH} = 0.405$	**: This work**
$P_{OH} = 0.42$	: Meylan (2016)
$P_{OH} = 0.7$	: Kreipl (2009)

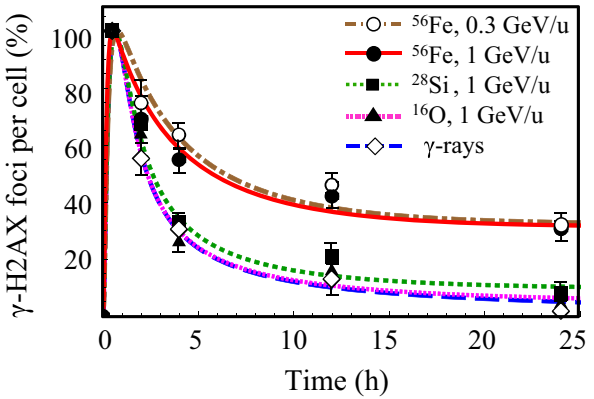
Chemistry Limits
Time duration : 5ns
Correspond Diff. Dist. : 9nm

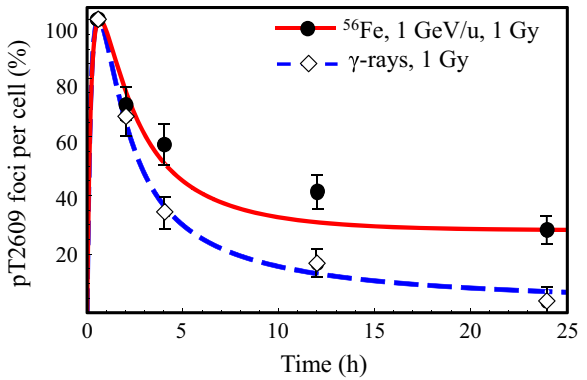


Histone Size
PARTRAC : 45 nm
This work : 25 nm

Biological Repair Prediction



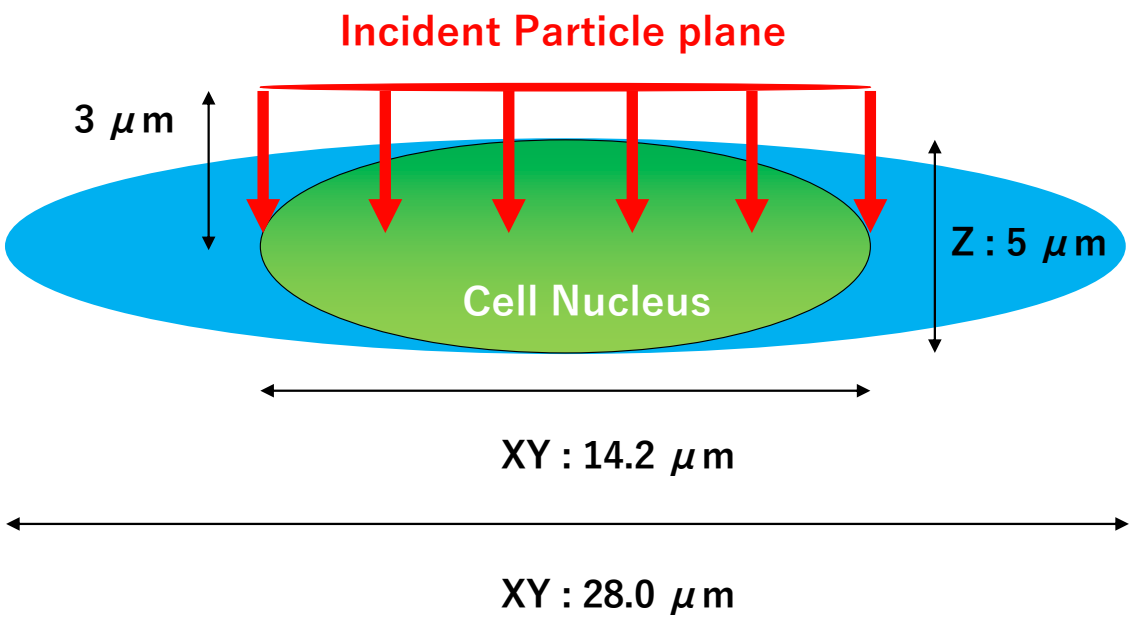




Journal of Theoretical Biology 366 (2015) 115–130

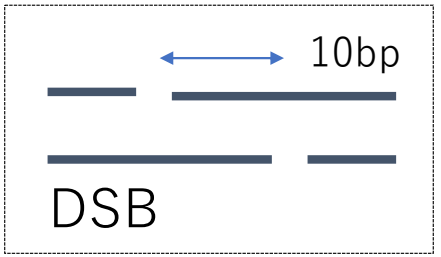
Simulation Configuration

6.4 Gbp : 0.012 bp/nm^3

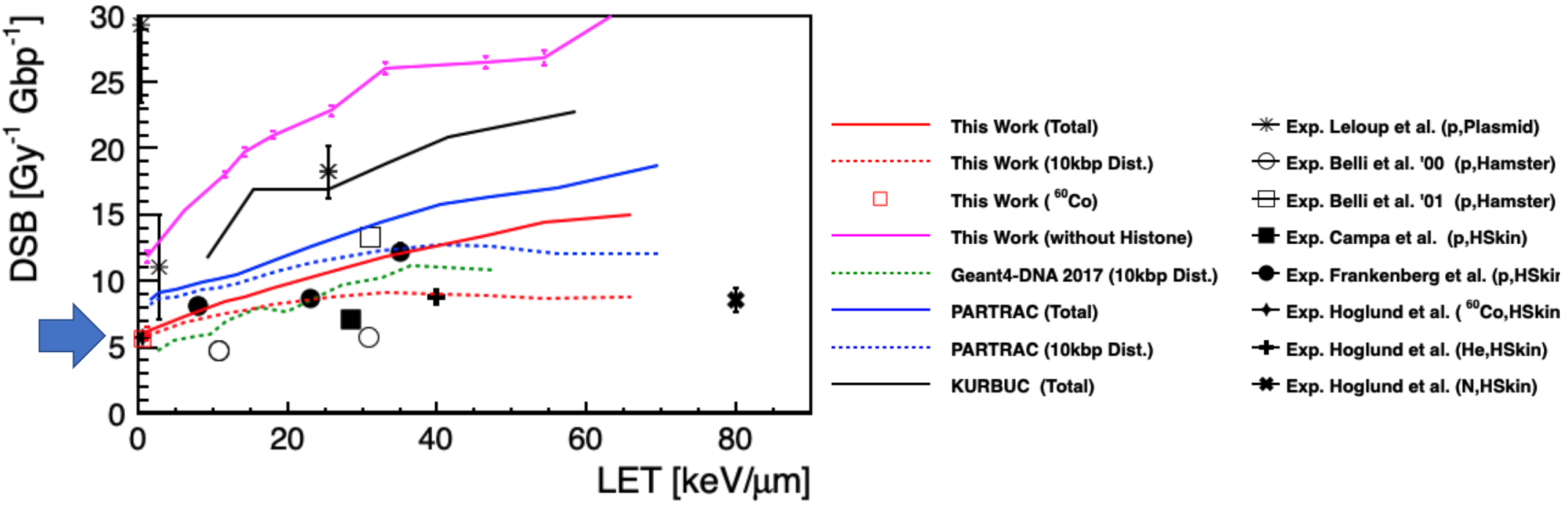


Simulation parameters

R_{direct}	: 3.5 ang
Eth_{direct}	: 5-37.5eV
P_{OH}	: 0.4
T_{chen}	: 5.0ns
R_{kill}	: 9.0 nm

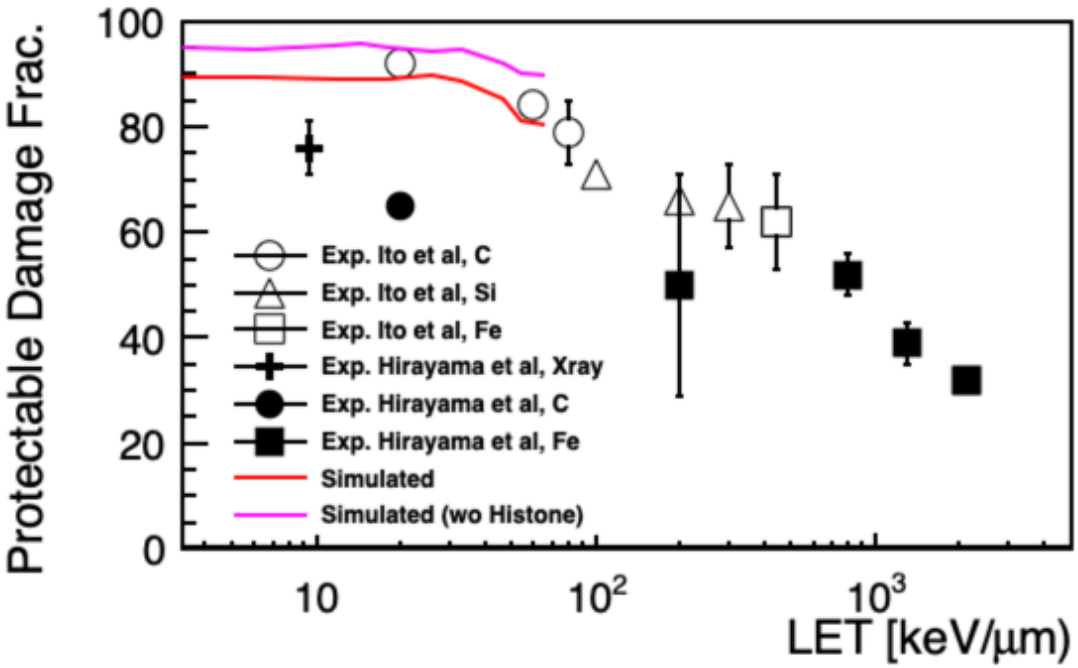


DSB Yields



Simulated SSB/DSB yields are good agreement with Exp. data for both of proton and gamma.

Protectable Damage Fraction

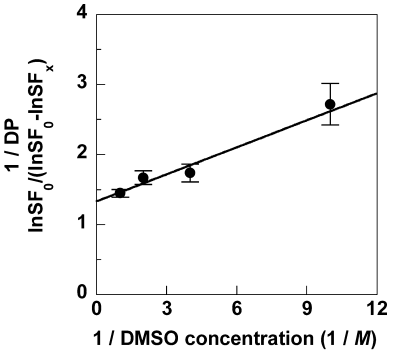


RADIATION RESEARCH 171, 212–218 (2009)

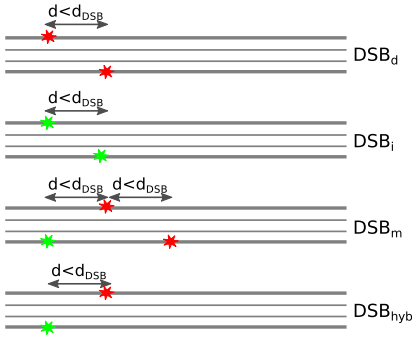
Experiment :
Estimate degree of protection (DP) at infinite dimethylsulfoxide (DMSO) concentration.

$$DP = \frac{\ln SF_0 - \ln SF_x}{\ln SF_0}$$

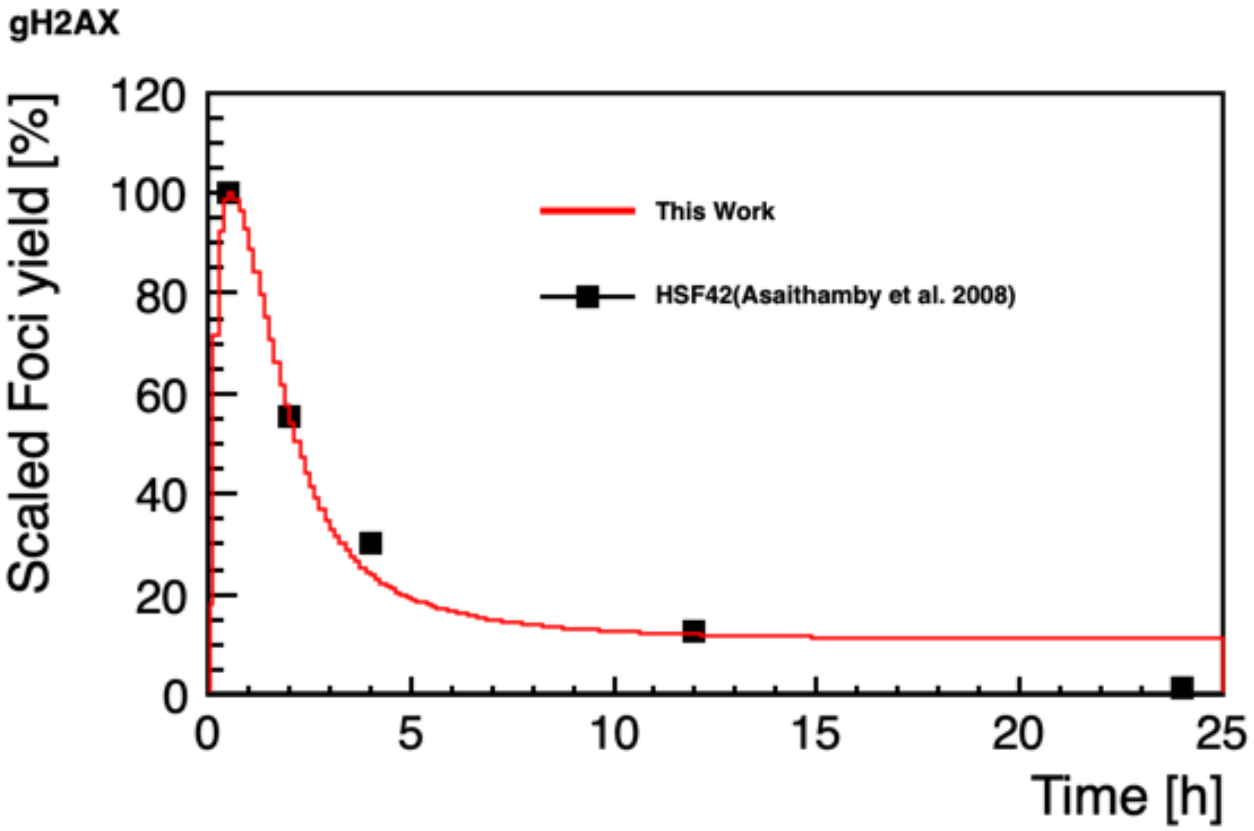
$$\frac{1}{DP} = k \cdot \frac{1}{x} + y_\infty$$



Simulation : Fraction of DSBi+DSBhyb



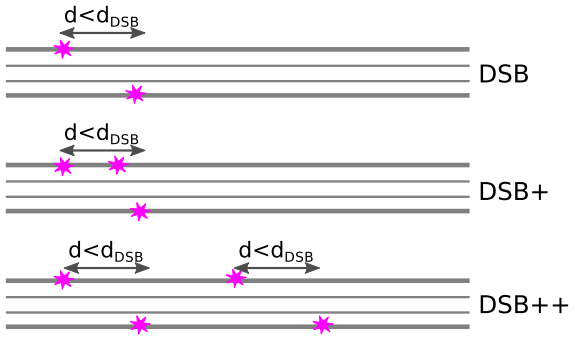
Biological Repair Curve



DSB : 5.66±0.27 /Gy/Gbp

Irreparable Frac. : 0.89 %

$$= \frac{(DSBp+2DSBpp)}{(DSB+DSBp+2DSBpp)}$$



γ ray from ^{60}Co

Conclusion

- After 10 years from Geant4-DNA launched, we have achieved to develop applications for evaluating ionising radiation induced DNA damage, as a milestone of the Geant4-DNA studies.
- The simulated results describe good agreements with the radiobiological experiments for gamma and proton.
- We are now ready to explore the mechanisms of ionising radiation induced DNA damage.