Quantitative estimation of biological effects after irradiation by MPEXS-DNA

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Background

- Geant4 Japan has been involved in Geant4 since even before the Geant4 collaboration established
    - KEK leads university groups in Japan
- MPEXS is developed in collaboration with Stanford University and SLAC to solve calculation time for some of Geant4 applications using GPU
- MPEXS-DNA is corresponding to Geant4-DNA to speed up simulation as an extension to MPEXS

Goals

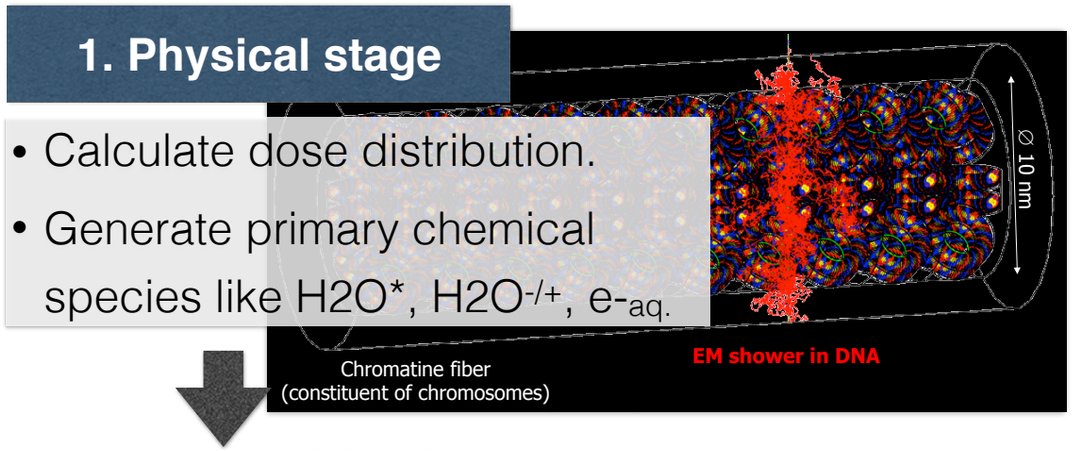
- Geant4-DNA simulation needs a long computation time
  - Tracks a large number of particles and molecular species with the Monte Carlo method
  - **Days-weeks** simulation on CPU typically

- MPEXS-DNA: A nanodosimetry simulator running on GPU
  - Boosts up computing performance for physics and chemistry simulation drastically
    - **2,900 times speedup** against Geant4-DNA
  - Boosts simulation studies in nanodosimetry

- Next step:
  - Implementing an alternative model for chemistry simulation
  - Quantitative DNA damage estimation

MPEXS-DNA: A Nanodosimetry simulator on GPU

- Rewrite Geant4-DNA (10.2.p3) in CUDA
  - EM Physics with lower energy range (down to meV)
    - Calculate local energy loss and generate primary molecules like H_2O^* and $H_2O^{+/-}$
  - Radiolysis of water
    - Diffusion and reactions for molecular species
    - Adopting the *step-by-step* method
  - The biological stage not yet implemented
- Collaboration between  and 
- Published a paper on MPEXS-DNA from Medical Physics



Estimate SSBs and DSBs using distributions of energy loss and molecular species inside the cell nucleus.

MEDICAL PHYSICS
The International Journal of Medical Physics Research and Practice

doi:10.1002/mp.13370

Research Article

MPEXS-DNA, a new GPU-based Monte Carlo simulator for track structures and radiation chemistry at subcellular scale

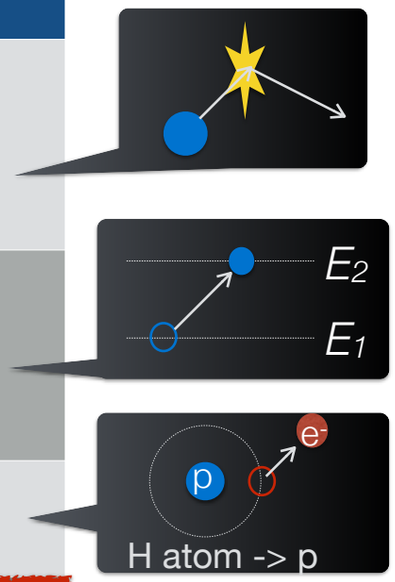
Shogo Okada, Koichi Murakami, Sebastien Incerti, Katsuya Amako, Takashi Sasaki

First published: 28 December 2018 | https://doi.org/10.1002/mp.13370

Physical Stage (1)

Electromagnetic interactions for Geant4-DNA are available

Particles		Electrons	Protons	Hydrogen atoms	Helium atoms (He^{++}, He^{+}, He^{0})	Li, Be, B, C, N, O, Si, and Fe
Physics Processes	Elastic scattering	9 eV - 10 keV Uehara 10 keV - 1 MeV Champion	100 eV - 1 MeV Hoang		100 eV - 10 MeV Hoang	–
	Excitation	10 eV - 10 keV Emfietzoglou 10 keV - 1 MeV Born	10 eV - 500 keV Miller Green 500 keV - 100 MeV Born	10 eV - 500 keV Miller Green	1 keV - 400 MeV Miller Green	–
	Electron-exchange	–	100 eV - 10 MeV Dingfelder	100 eV - 10 MeV Dingfelder	1 keV - 400 MeV Dingfelder	–
	Ionization	10 eV - 10 keV Emfietzoglou 10 keV - 1 MeV Born	100 eV - 500 keV Rudd 500 keV - 100 MeV Born	100 eV - 100 MeV Rudd	1 keV - 400 MeV Rudd	0.5 MeV/u - 1.0×10^{6} MeV/u Rudd
	Vibrational excitation	2 - 100 eV Michaud et al.				
	Disociative attachment	4 - 13 eV Melton				



- **Atomic deexcitation**
  - **Emits auger electrons and fluorescent X-rays**

$AB + e^{-} \rightarrow AB^{-} \rightarrow A + B^{-}$

- **Yields excited/ionized water molecules**
  - **Then, decays into molecular species at the physico-chemical stage**

The Livermore model for fluorescent X-rays	
Compton scattering	100 eV - 1 GeV
Photoelectric effect	100 eV - 1 GeV
Gamma conversion	100 eV - 1 GeV
Rayleigh scattering	100 eV - 1 GeV

Physical Stage (2)

- All physics lists for Geant4-DNA are covered
- Some physics models released after 10.2 are not implemented
  - Physics interactions for materials other than water:
    - DNA components
    - Gold for nano particle simulation
    - …

→ will be implemented soon…

✔: Available, ✘: Later

Physics lists / models for G4-DNA (10.5.1)	MPEXS-DNA
G4EmDNAPhysics	✔
G4EmDNAPhysics_option1	✔
G4EmDNAPhysics_option2	✔
G4EmDNAPhysics_option3	✔
G4EmDNAPhysics_option4	✔
G4EmDNAPhysics_option5	✔
G4EmDNAPhysics_option6	✔
G4EmDNAPhysics_option7	✔
G4EmDNAPhysics_option8	✔
Others (ex. DNA components)	✘

Physico-Chemical Stage

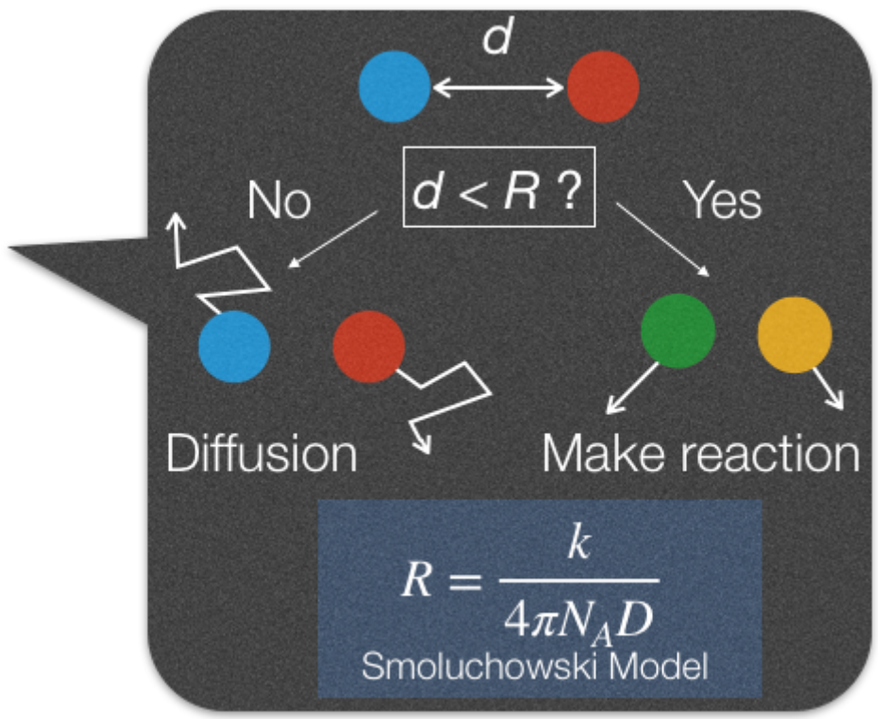
(a.k.a. Pre-chemical Stage)

- All processes in Geant4-DNA are implemented in MPEXS-DNA:
  - Dissociation, relaxation, and electron-hole recombination for H_2O^+/H_2O^-, H_2O^* molecules
  - Thermalization for electrons
    - Transform into solvated electrons (e^-_{aq})

Electronic state	Process	Dissociation channel	Fraction (%)
Ionization state	Dissociative decay	$H_3O^+ + \bullet OH$	100
Excitation state: A1B1	Dissociative decay	$\bullet OH + H\bullet$	65
	Relaxation	$H_2O + \Delta E$	35
Excitation state: B1A1	Auto-ionization	$H_3O^+ + \bullet OH + e^-_{aq}$	55
	Dissociative decay	$\bullet OH + \bullet OH + H_2$	15
	Relaxation	$H_2O + \Delta E$	30
Excitation state: Rydberg, diffusion bands	Auto-ionization	$H_3O^+ + \bullet OH + e^-_{aq}$	50
	Relaxation	$H_2O + \Delta E$	50
Dissociative attachment	Dissociative decay	$\bullet OH + OH^- + H_2$	100
Electron Hole Recombination	Dissociative decay	$\bullet OH + \bullet OH + H_2$	15
	Dissociative decay	$\bullet OH + H\bullet$	55
	Relaxation	$H_2O + \Delta E$	30

Chemical Stage

- Simulate diffusion and chemical reactions for molecular species from 1 ps to 1 us after irradiation
  - Reactions based on the Smoluchowski theory
  - Molecular diffusion with a ***step-by-step*** method
    - Dynamical time-stepping
    - Calculate encounter probability using the Brownian-bridge method



- Two sets of parameters:
  - G4EmDNAChemistry and G4EmDNAChemistry_option1

Diffusion Coefficients [x10^{-9} m^2/s]

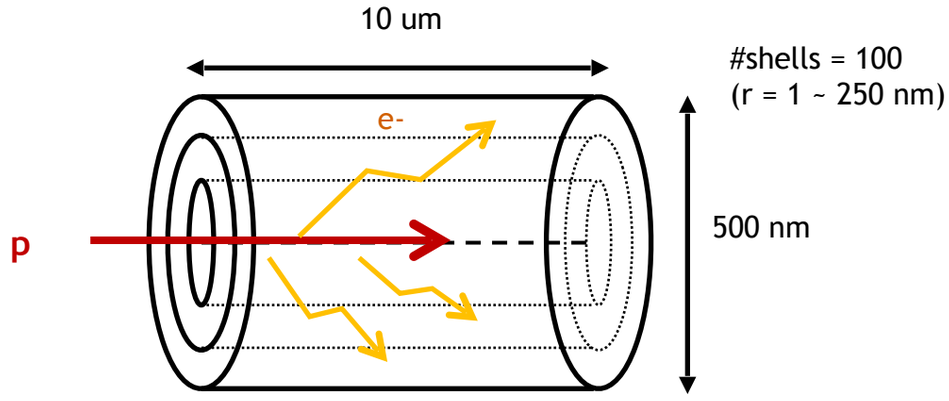
	G4EmDNAChemistry	G4EmDNAChemistry_opt1
H_3O^+	9.0	9.46
H•	7.0	4.8
OH^-	5.0	5.3
e^-_{aq}	4.9	4.9
H_2	4.8	4.8
•OH	2.8	2.2
H_2O_2	2.3	2.3

Reaction Rate Constants [x10^{10}/(M•sec)]

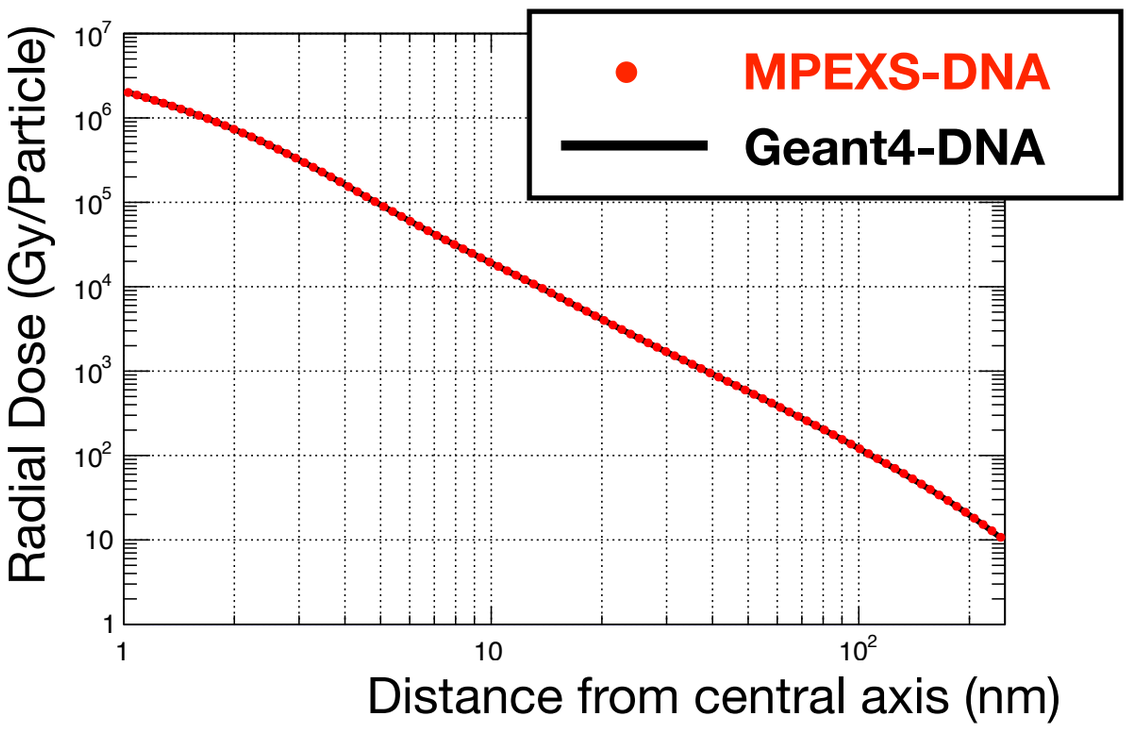
	G4EmDNAChemistry	G4EmDNAChemistry_opt1
$2e^-_{aq} + 2H_2O \rightarrow H_2 + 2OH^-$	0.50	0.636
$e^-_{aq} + •OH \rightarrow OH^-$	2.95	2.95
$e^-_{aq} + H• + H_2O \rightarrow OH^- + H_2$	2.65	2.50
$e^-_{aq} + H_3O^+ \rightarrow H• + H_2O$	2.11	2.11
$e^-_{aq} + H_2O_2 \rightarrow OH- + •OH$	1.44	1.10
$•OH + •OH \rightarrow H_2O$	0.44	0.55
$•OH + H• \rightarrow H_2O$	1.44	1.55
$H• + H• \rightarrow H_2$	1.20	0.503
$H_3O^+ + OH^- \rightarrow 2H_2O$	1.43	11.3

Physics Verification/Validation

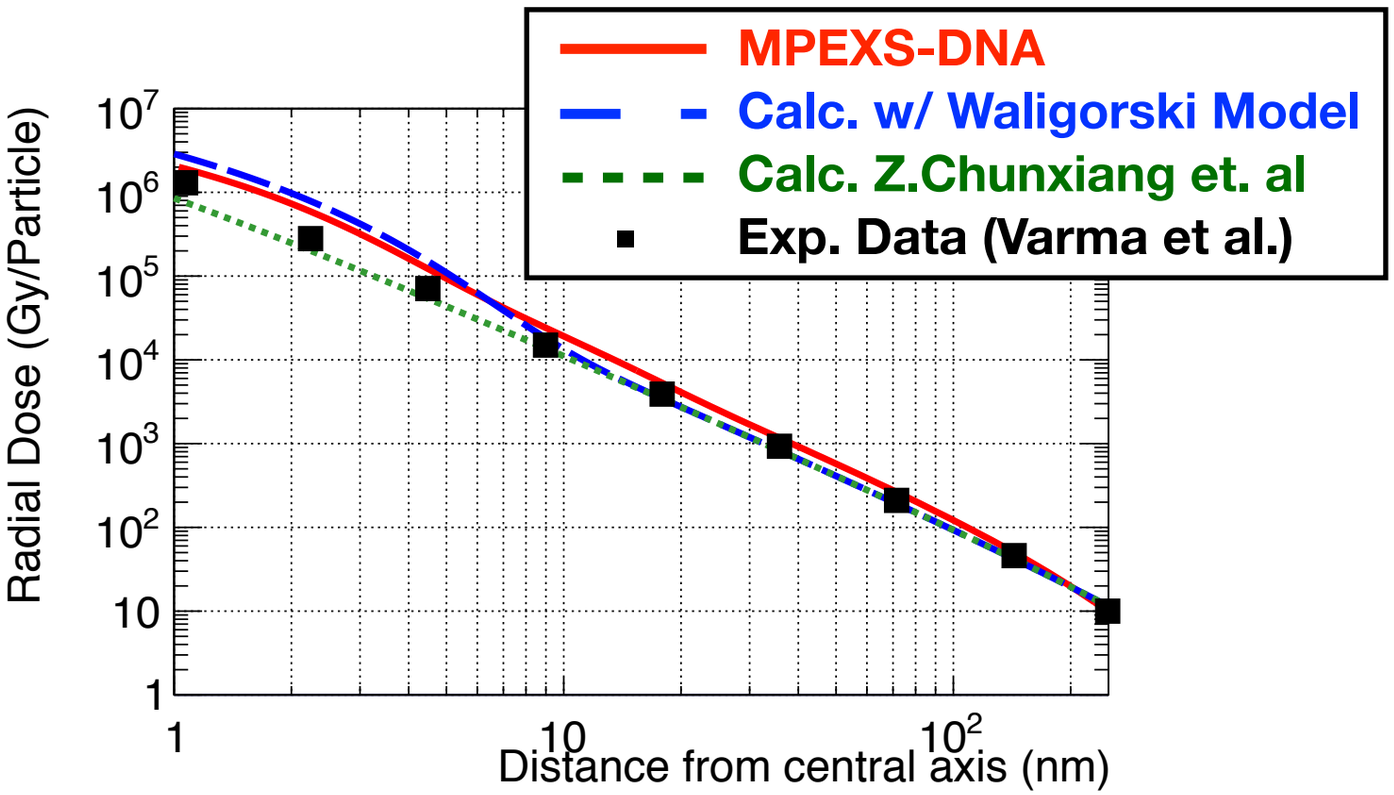
- Compared radial dose distribution of MPEXS-DNA to Geant4-DNA and experimental data
  - Physics List: G4EmDNAPhysics_option4



A: Radial dose distribution:
MPEXS-DNA vs Geant4-DNA
(2.57 MeV/u Oxygen atoms)



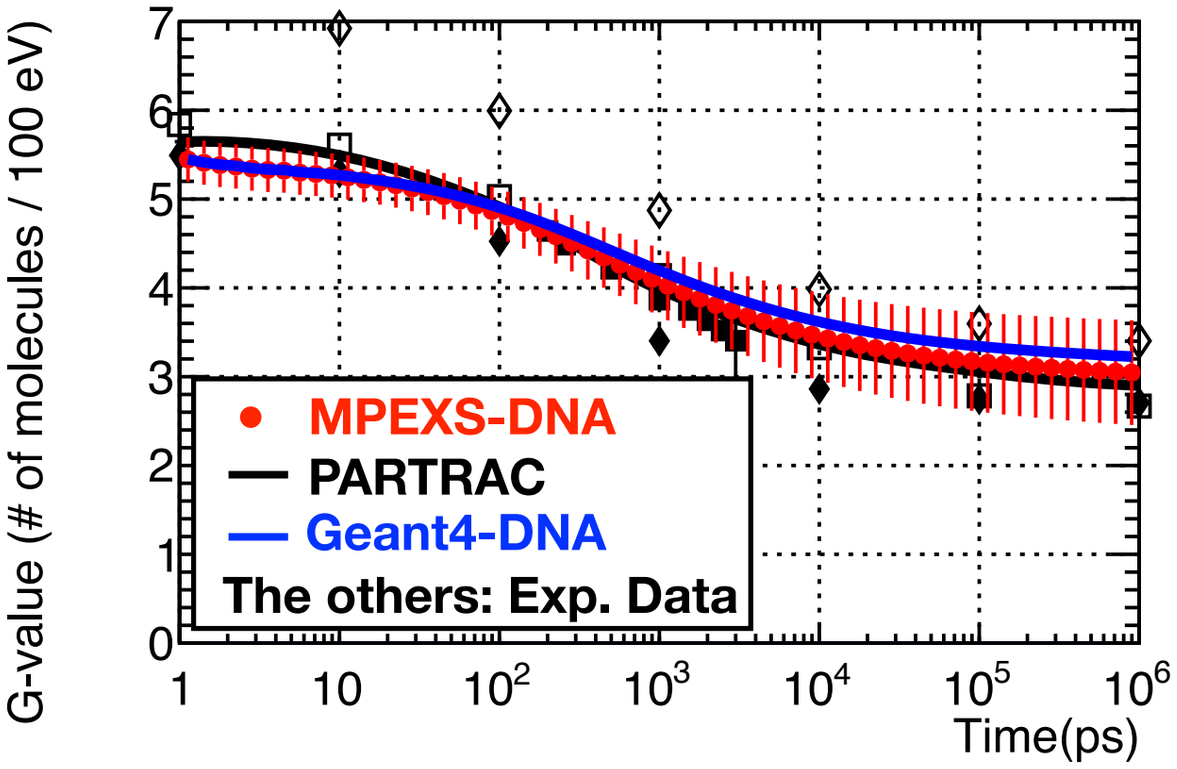
B: Radial dose distribution:
MPEXS-DNA vs measurement data
(2.57 MeV/u Oxygen atoms)



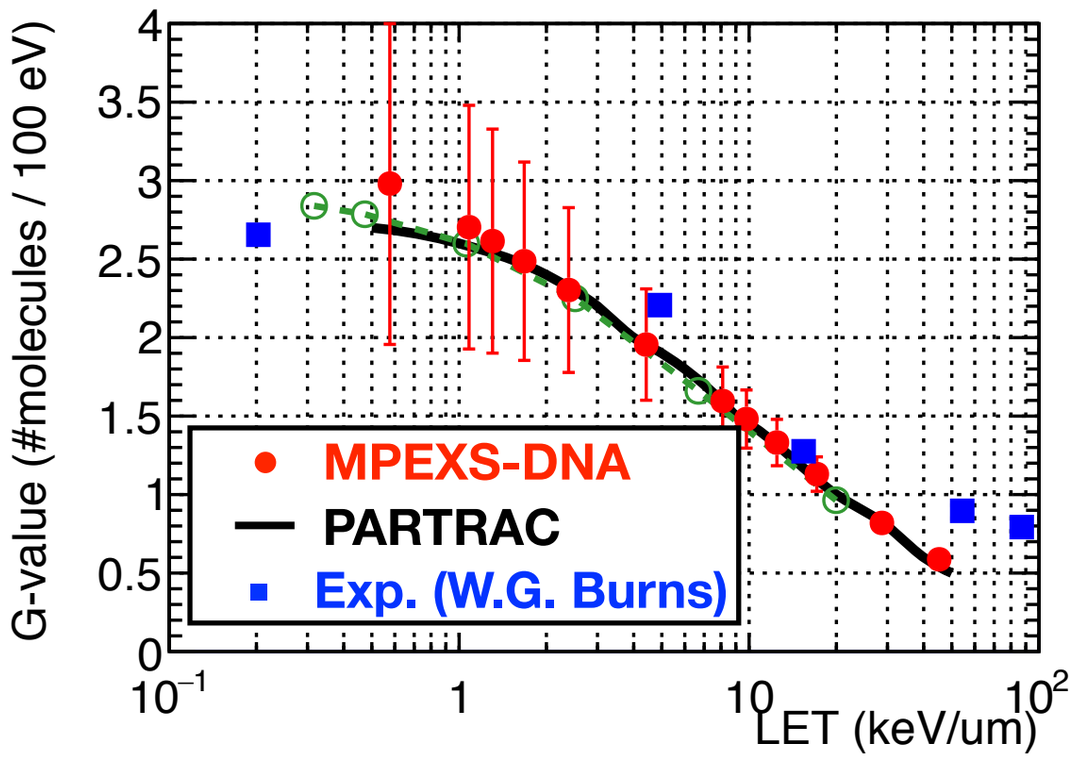
Chemistry Verification/Validation

- Compared G-value plots of MPEXS-DNA to the other MC simulations and measurement data
  - Physics List: G4EmDNAPhysics_option4 and G4EmDNAChemistry

A: G-value time profile for ·OH radicals from 1 ps to 1 μs after irradiation of 750 keV electrons

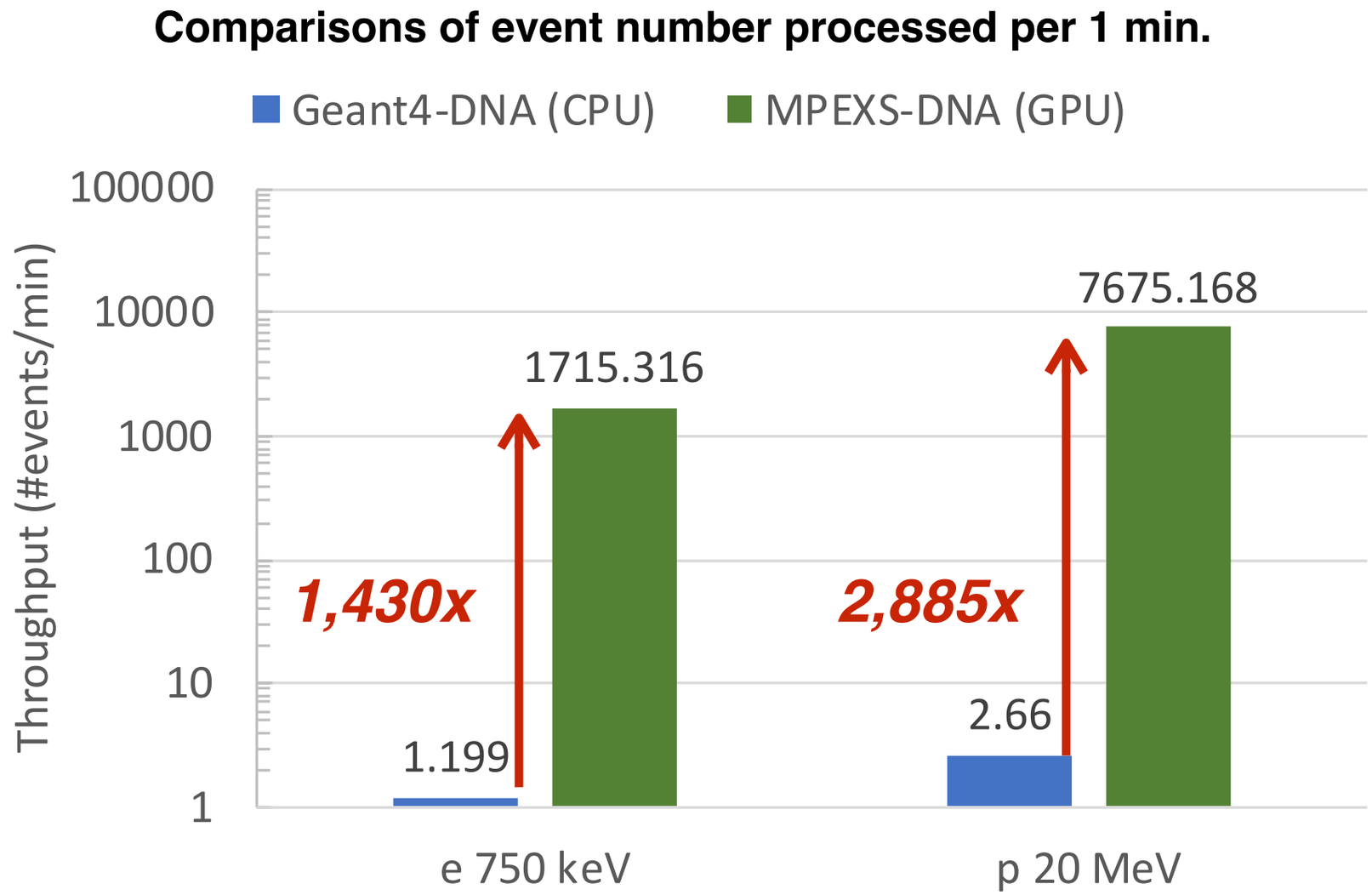


B: LET dependency of G-value for ·OH radicals at 1 μs after proton irradiation



MPEXS-DNA Performance

- MPEXS-DNA is much faster than Geant4-DNA
  - ~ 4 days (CPU) -> **~ 2 min. (GPU)**
  - **1 GPU unit has the equivalent computing power as 2,900 CPU cores**



- GPU: NVIDIA, TITAN V
- CPU: Intel, Xeon E5-2643 v2, 3.5 GHz

MPEXS-DNA Functionalities

	Status
Physics Stage	• Most of physics models in G4DNA can be run • Physics models for materials other water will be implemented

Physico-chemical Stage	• Implemented all processes in G4DNA:
	  • Dissociation, Relaxation, and Electron hole recombination for H_2O^*, H_2O^+/H_2O^-
	  • Thermalization for electrons

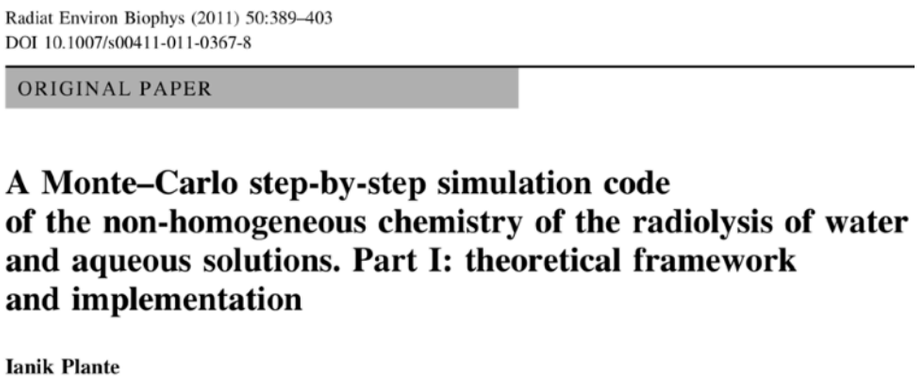
Chemical Stage	• Simulate diffusion and reactions with the same manner as G4DNA • Two-parameter sets: G4EmChemistry and G4EmChemistry_option1

Recent activities on MPEXS-DNA

—Quantitative estimation of early DNA damages induced by radiation—

Implementation of An Alternative Model for Chemistry Stage

- **Plante's approach**
  - Ref.) I. Plante, DOI: 10.1007/s00411-011-0367-8
  - Based on the Smoluchowski theory for reactions
    - Handling electrostatic interactions and spin effects
    - Computing encounter probability by solving the diffusion equation with Green's function
  - "Background reaction"
    - Simulating reactions with homogeneously high-concentrated species in the medium
      - ex. radical scavengers


Radiat Environ Biophys (2011) 50:389–403
DOI 10.1007/s00411-011-0367-8

ORIGINAL PAPER

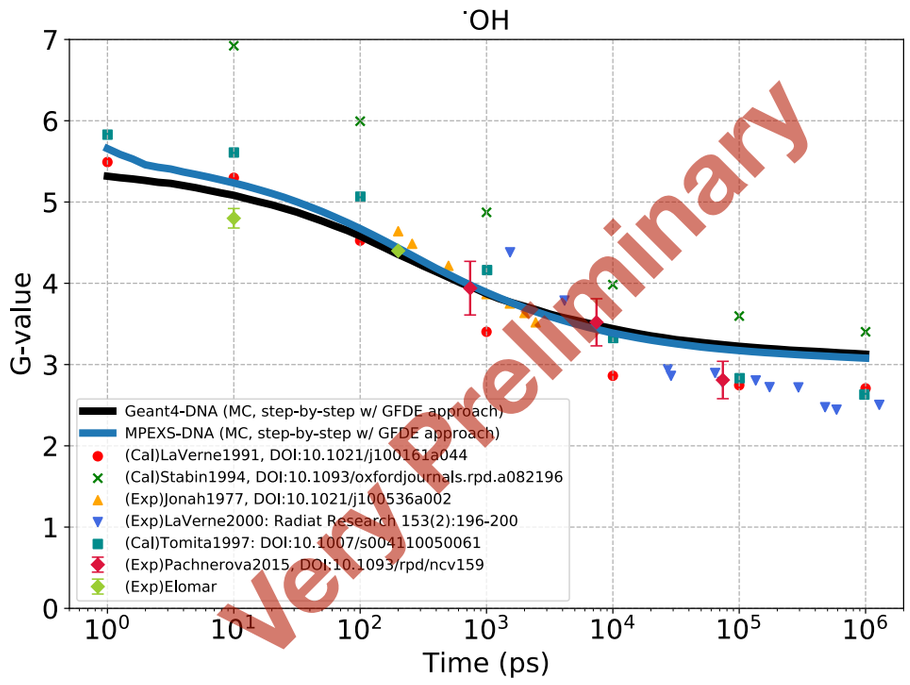
A Monte–Carlo step-by-step simulation code of the non-homogeneous chemistry of the radiolysis of water and aqueous solutions. Part I: theoretical framework and implementation

Ianik Plante

- **Implementation of Plants's approach in MPEXS-DNA**
  - Diffuse molecules ***step-by-step*** by Brownian motion
    - Adopting static time-stepping
  - Implemented using G4DNA (10.5 and 10.6 beta) tentatively

- **Plante's approach with *IRT* for Geant4-DNA**
  - Developing by Wook (CENBG) and Hoang (IRNS) with the support from Jose (UCSF)

G-value time profile for •OH radicals from 1 ps to 1 *μ*s after irradiation of 750 keV electrons



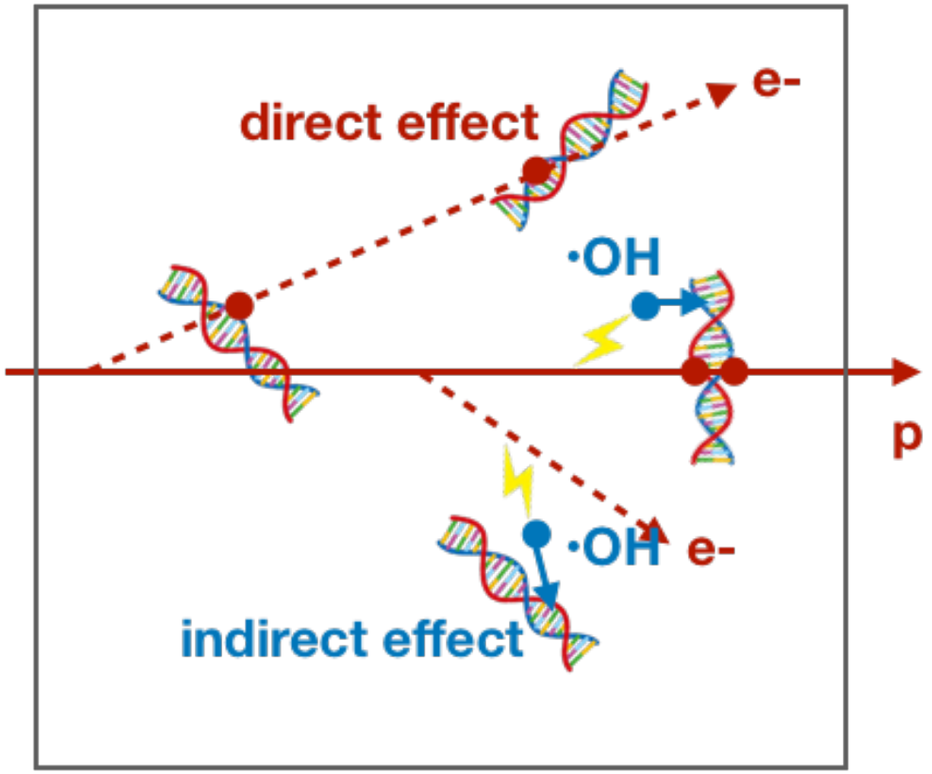
Estimation of DNA Damages

- Geant4-DNA calculates early radiation damages using a complex geometry of the cell nucleus
  - Process flow:
    1. Calculate distributions of energy loss and molecular species
    2. Score the positions at which physical and chemical interactions occurred with DNA molecules in a cellular geometry
    3. Evaluate DNA damages with higher geometrical accuracy
  - Reproduce experimental data and the other simulation results well

- We are trying to estimate DNA damages with an alternative approach
  - Simple cell model for geometry
  - Clustering model for DNA damages

Quantitative Estimation of DNA Damage Using Clustering Model

- *"clustering"*: An extended example for Geant4-DNA
  - Evaluates DNA damage induced by direct effects
  - Ref.) DOI:10.1016/j.cmpb.2010.12.012



- We extend the *"clustering"* application
  - Estimate DNA damages by ***indirect effects*** as well as direct effects

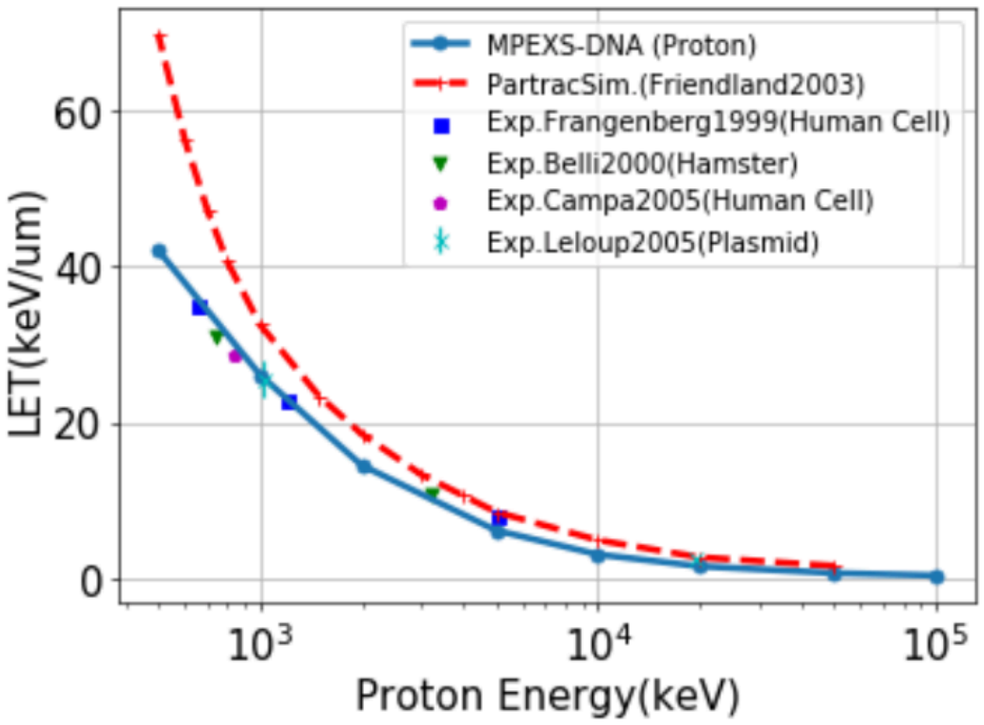
- Assume that DNA molecules are homogeneously diluted in a box geometry (Simple cell model)

  - Simulate track structure of charged particles and molecular species
    - Using the Plante's approach for chemistry simulation

  - Sample the positions at which reactions with DNA components occurred, then evaluate DNA damages

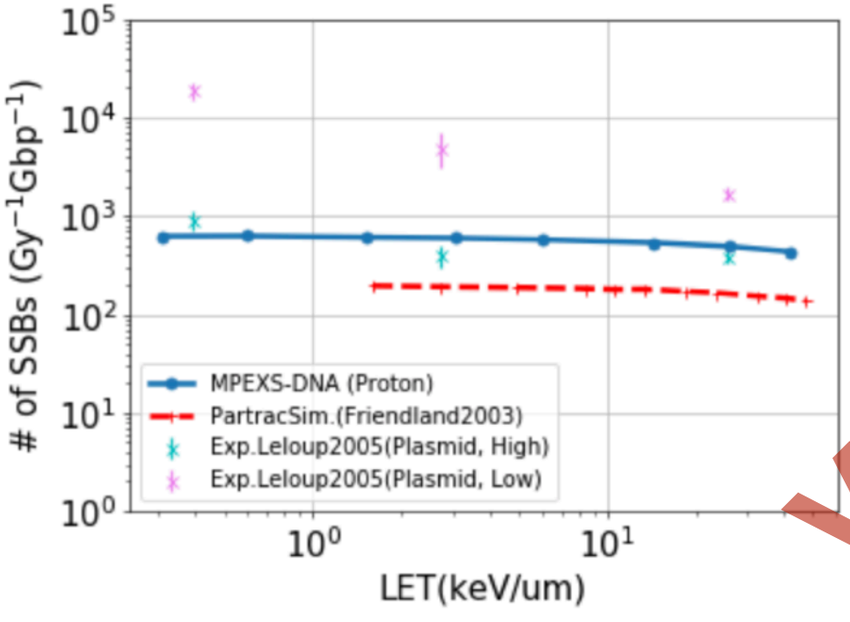
Damage Estimation for Proton Irradiation

A: LET (keV/um) vs Proton Energy (keV)

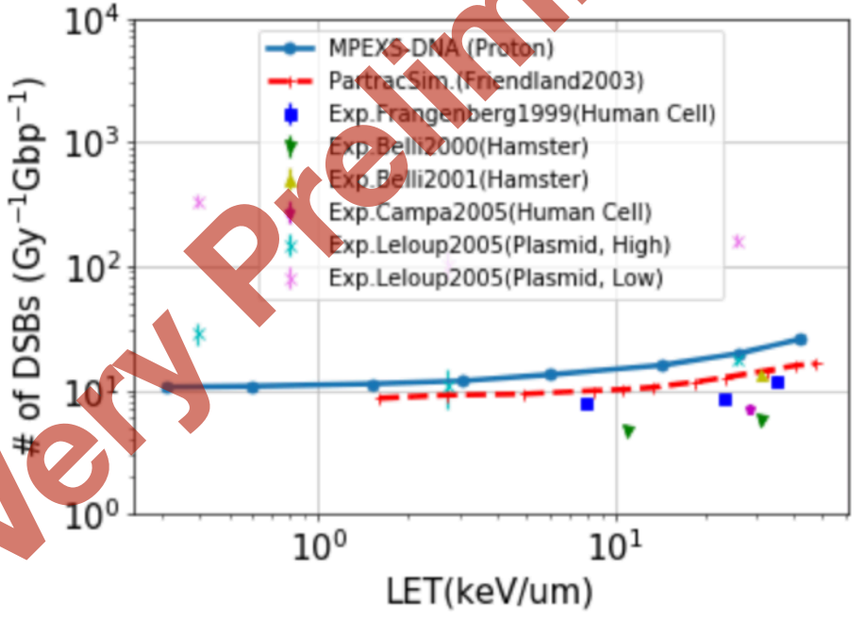


- Primary particles:
  - Protons with E_{kin} = 500 keV - 100 MeV
- LET:
  - Consistent with measurements
- DNA damages:
  - Reasonable agreement with the experimental data and the PARTRAC simulation result

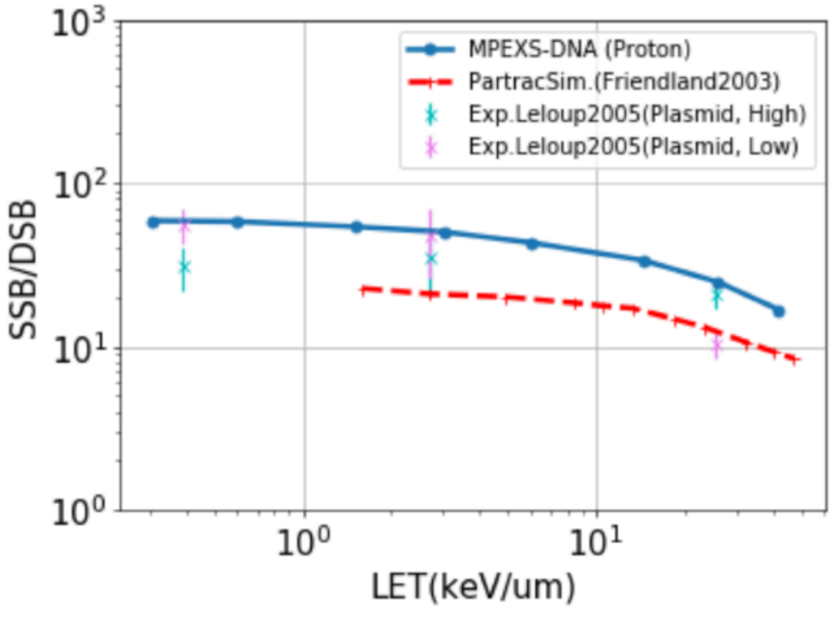
B: Single Strand Break(SSB)



C: Double Strand Break(DSB)

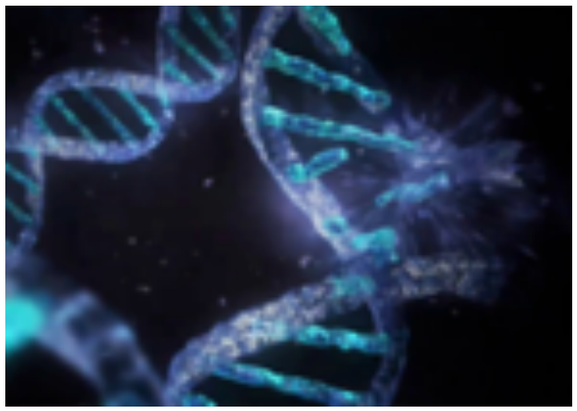


D: SSB/DSB



Future Plans

- **Extending functionalities in MPEXS-DNA for nanodosimetry simulations**
  - More complex geometry exported from CAD
    - ex. DNA double helix structure



  - Various materials other than water (ex. DNA components)
  - Multi-GPU simulations on Cloud services / Supercomputer
    - **“Almost infinite”** scalability
      - ex. 27,648 GPUs (TESLA V100) @ Summit
    - MPEXS-DNA will pioneer a scientific frontier in raidobiology
      - Better understanding mechanism of DNA damages
      - More precise estimation of effects on chronic radiation exposure
        - ex. Astronauts, Airline crew, medical diagnostic, …
      - Quicker development of next-generation radiotherapy technique
        - ex. Flash radiotherapy
      - …

→ **Further developments are continuing**

MPEXS License Model

Two models:

- Collaboration license
    - Only for groups who expect to submit a paper jointly within 1 year
    - Free of charge
    - The newly earned intellectual properties in the collaboration are requested to be donated to KEK or to be put in the public domain
        - Also shall not exercise the moral rights of the author or any other similar rights

- General license
    - Contracts with KEK are required
    - A license fee will be requested

Summary

- MPEXS-DNA is a nanodosimetry simulator based on Geant4-DNA running on GPU
    - Most of functionalities in Geant4-DNA are available
    - A paper on MPEXS-DNA was published from Medical Physics
        - DOI: 10.1002/mp.13370

- Recent activities:
    - Implemented Plante's approach with a step-by-step method as an option of chemistry simulation
    - Quantitative estimation of radiation damages of DNA molecules with a simpler approach
        - Simple cell model / clustering model
        - Reasonable agreement with the measurement data
    - These developments will be delivered soon in both MPEXS-DNA and Geant4-DNA
    - MPEXS-DNA also boosts the development of Geant4-DNA

- MPEXS-DNA is NOT open source
    - Collaboration based on license contract is available
    - Contact: Prof. Takashi SASAKI (KEK, takashi.sasaki@kek.jp)

- MPEXS-DNA is promising to pioneers a new promising frontier in radiobiology!

Backup

How To Estimate Early DNA Damages

- Water target: 1 x 1 x 1 um^3

- Volume fraction of DNA region against the target: 2%
  - Base pair density: ~0.018 bp/nm^3
  - ~0.015 bp/nm^3 for human cell

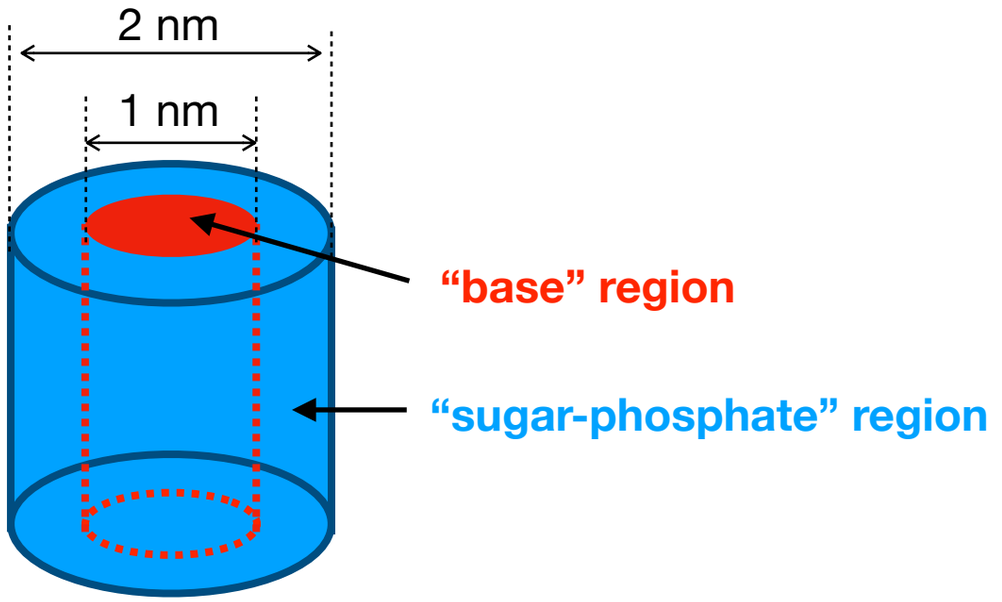
- Energy deposition above 10.79 eV into DNA segment yields a single strand break (SSB)

- Reactions with a DNA molecule by •OH radical is handled as “background reaction” of the Plante’s approach
  - $P(\Delta t) = 1 - \exp(-ck\Delta t)$

- Prob.(a sugar radical -> SSB) = 0.4
  - Ref.) Nathanael’s work
    - DOI: 10.1016/j.ejmp.2017.12.008

- Scavenging capacity: 4.0 x 10^8 /s
  - Life time for •OH radicals: 2.5 ns

Simple DNA geometry of double helix structure
Ref.) Phys. Med. Biol 63 (2018) 175018 (19pp)



Ref.) DOI:10.1038/s41598-017-11851-4

Reaction	Reaction rate ($10^9 M^{-1} \cdot s^{-1}$)
2-deoxyribose + $OH^•$	2.5
Adenine + $OH^•$	6.10
Guanine + $OH^•$	9.20
Thymine + $OH^•$	6.40
Cytosine + $OH^•$	6.10