

# Validation of Monte Carlo Simulations to Assess DNA Damage from $^{225}\text{Ac}$ for Radiopharmaceutical Therapy

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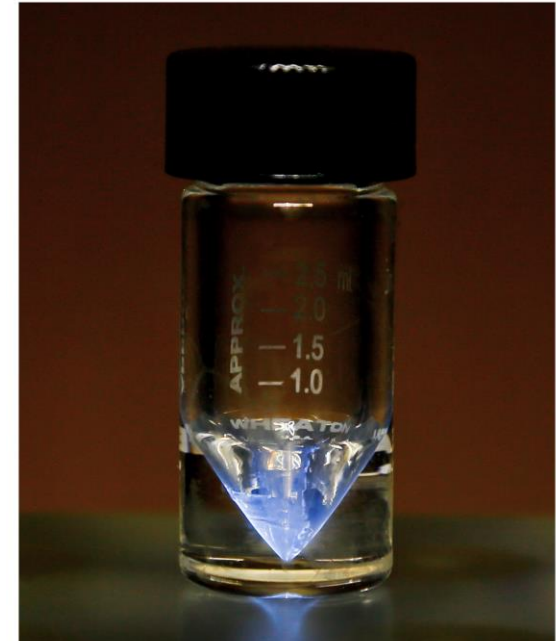
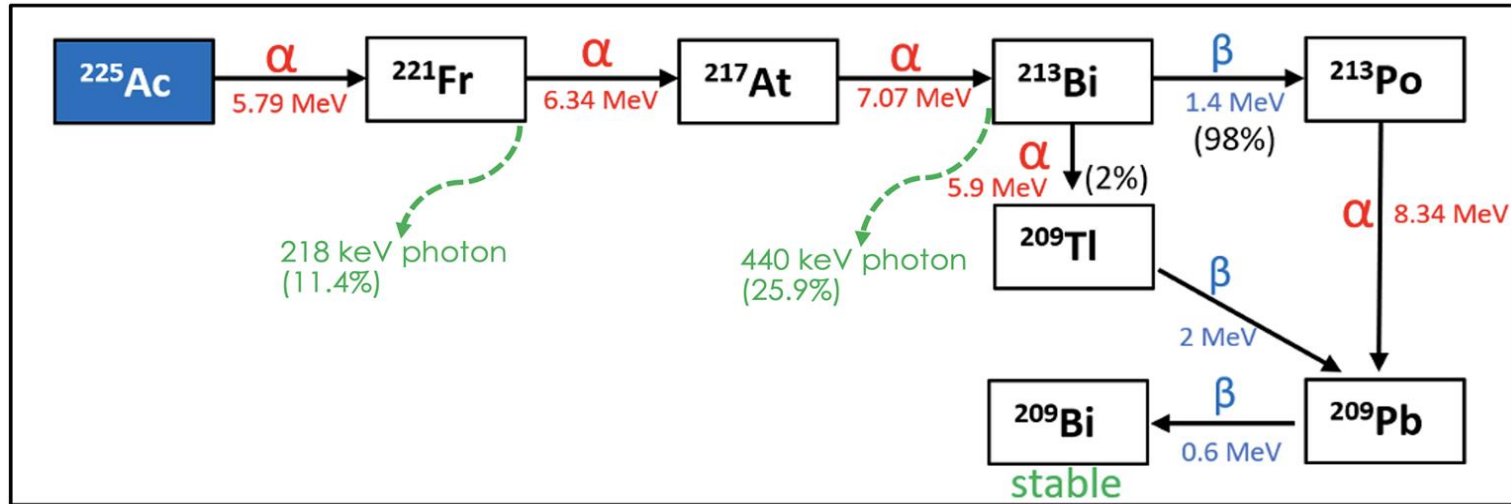
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# Outline

- Background and introduction
  - Decay chain of  $^{225}\text{Ac}$  ( $T_{1/2} = 10$  days)
  - Biological effect, DNA strand breaks
- Methods
  - Cell culture experiment using mouse breast cancer cell line
  - Monte Carlo simulations in Geant4 and TOPAS-nBio
  - Comparison of DNA double strand breaks
- Results
- Conclusion and future work

# Decay chain of $^{225}\text{Ac}$



Actinium-225 in a vial

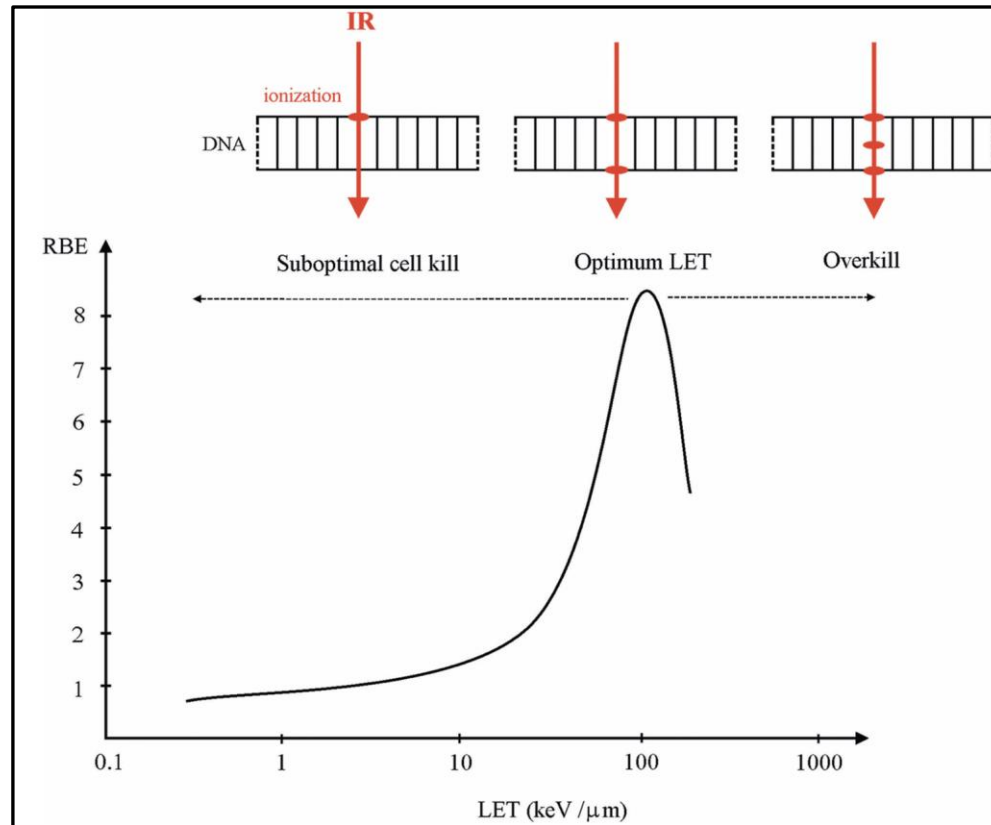
- Max range of 2 MeV  $\beta^-$  = 10 mm
- Max range of 1.4 MeV  $\beta^-$  = 6.3 mm
- Max range of  $\alpha$ -particles from decay chain =  $\sim 95 \mu\text{m}$

# Radiobiology: Biological effect

- Energy deposition in volumes corresponding to single cells or cell organelles
- Particles release energy differently along their tracks (LET): sparse ionizations ( $\beta^-$ ), dense ionizations ( $\alpha$ )
- Biological effect of radiation depends upon the LET
- DNA is the critical target for radiation-induced cell death

Particle types	Energy (MeV)	LET (keV/ $\mu\text{m}$ )
electron	0.1	0.42
	1.0	0.25
250 kV x-rays	0.25	2.0
proton	10	4.7
	250	6.5-14
alpha	5	50-200

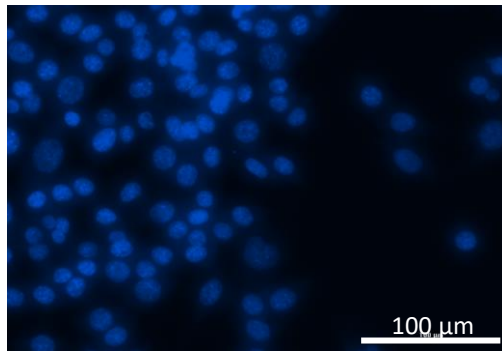
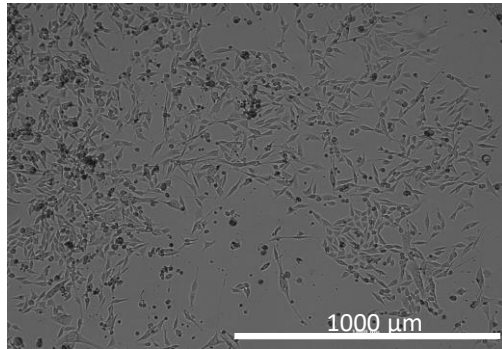
# RBE as a function of LET



- Ratio between the dose from a standard radiation and the test radiation to produce the same biological effect
- One track of x-rays (100 kV) is unlikely to cause a DSB
- Efficient radiation is the one with LET approximately 100 keV/μm, as the distance between two consecutive ionization events is equal to the diameter of the DNA
- Further increases in LET beyond 100 keV/μm results in a decrease in RBE

# Cell culture experiment with $^{225}\text{Ac}$

Cell line before irradiation



Nucleus staining shows  $\sim$ rounded nucleus with an average diameter of 10  $\mu\text{m}$

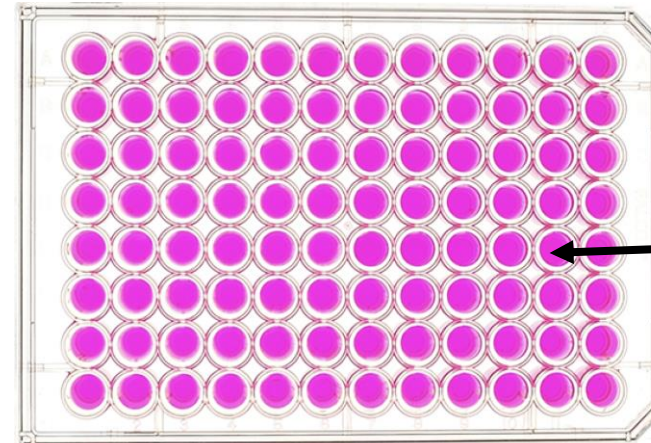
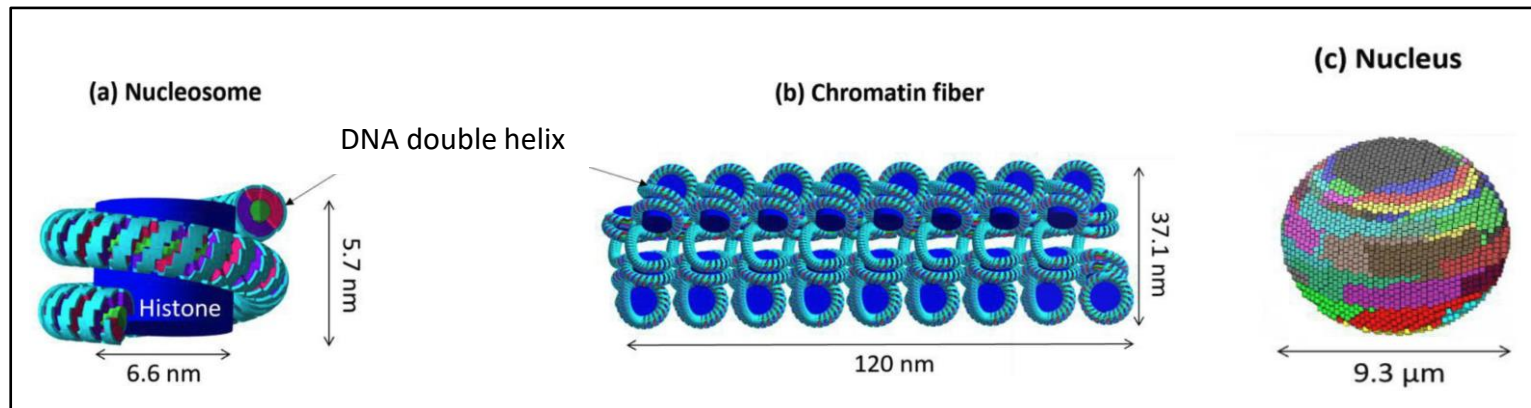


Fig: Cell well plate with 96 wells

- Mouse breast cancer cell line (E-0771)
- Cells seeding density:  $(1.5-3) \times 10^3$  cells/well
- Cells were irradiated with varying levels of  $^{225}\text{Ac}$  for 24 h: **2.4, 5.3, 11.8, 18.9, 41.5, 83.0, 175.1, and 345.2 nCi/well**
- Excess activities were removed after 24 h using the phosphate-buffered saline (PBS)
- Stage of cells in a cell cycle were not controlled
- DNA DSBs estimated using  $\gamma$ -H2AX immunofluorescent staining

# TOPAS-nBio Monte Carlo Simulation

- TOPAS-nBio is an extension of TOPAS Monte Carlo toolkit, supports radiobiology simulation
- Direct, indirect and complex DNA damage can be scored
- Full nucleus DNA model is available in TOPAS-nBio (Zhu et al, 2020)

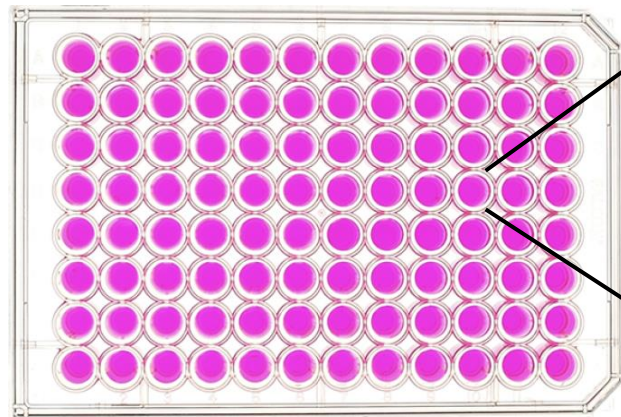


- (a) Nucleosome with 200 base pairs (bp)
- (b) Chromatin fiber with 15.15 kbp
- (c) Nucleus with 6.08 Gbp and 46 chromosomes  
Voxels of same color represent chromosome  
Total voxels in nucleus = 14,328 filled with chromatin fibers

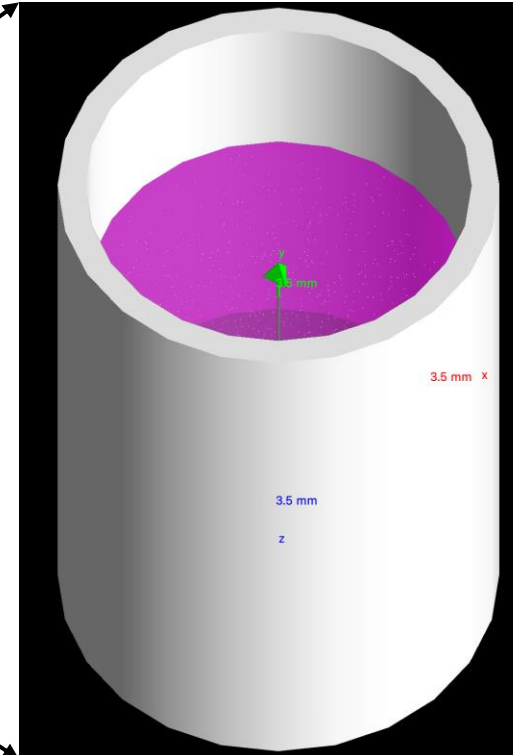
## Scoring of DNA strand breaks

- Strand break was scored when accumulated energy deposition exceeded 17.5 eV
- If at least 2 strand breaks occurred within 10 base pair distance, then it was recorded as DSB, otherwise recorded as SSB

# Monte Carlo Simulation of Cell Culture



Cell well plate with 96 wells



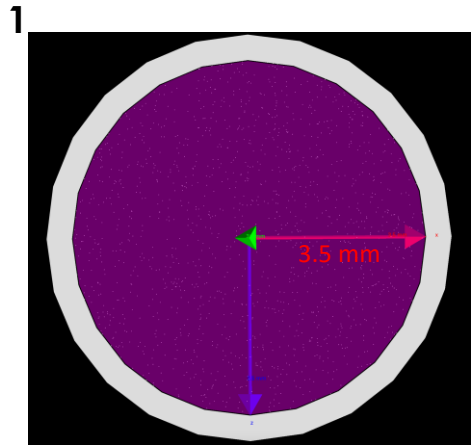
Monte Carlo setup in Geant4 using a single well

Cell well dimension:

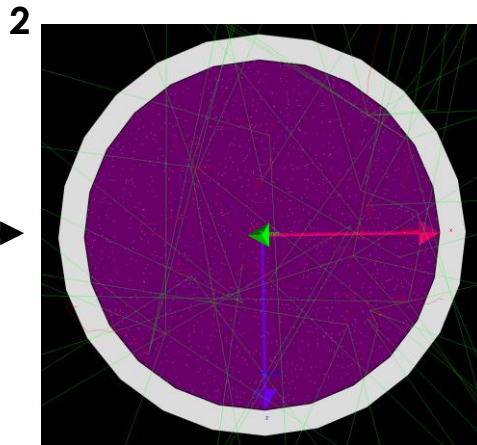
- Height 10.8 mm
- Well diameter 7.15 mm
- Solution height 5 mm
- Wall thickness 0.5 mm



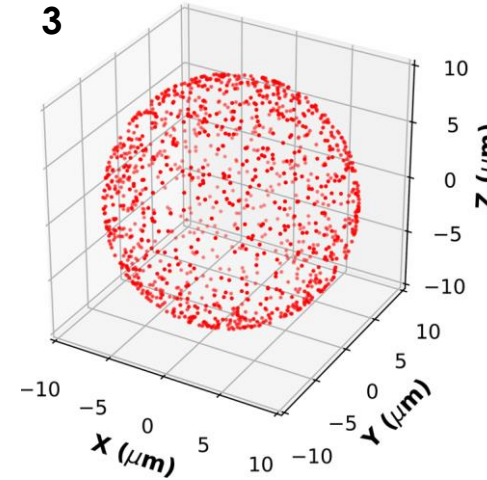
# Simulation workflow for DNA damage estimation



1 Cell well in Geant4, small dots are spherical cells (1500 cells)

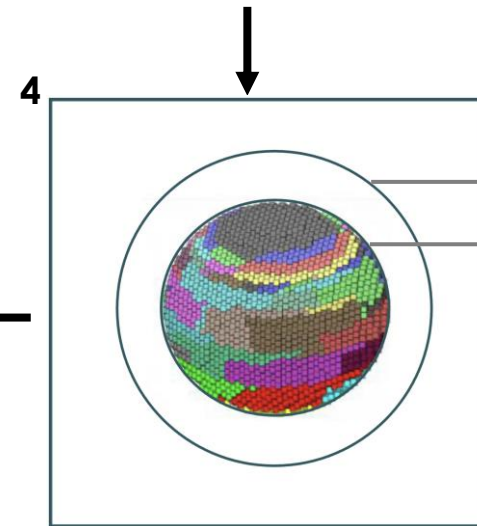


2 <sup>225</sup>Ac decays in well, green lines photons, red electrons, and blue alpha particles



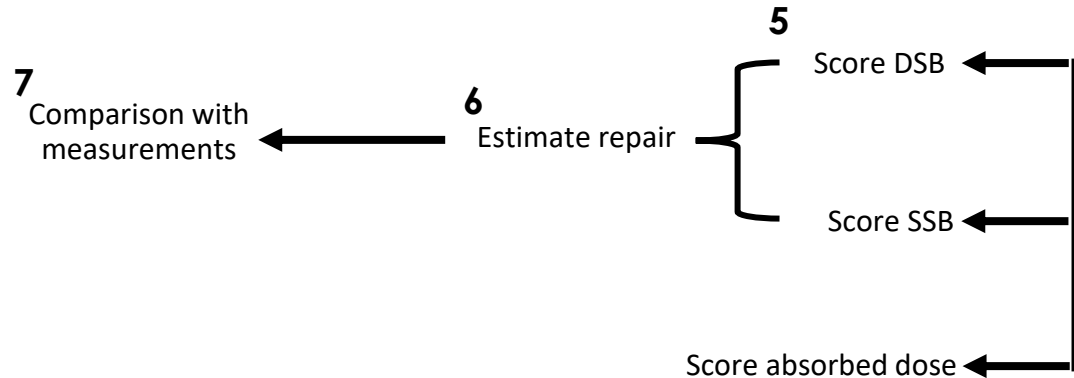
3 Red dots are location of particles entering a single cellular volume

Phase space file records information about particles ( $\alpha$ ,  $\beta$ ,  $\gamma$ 's) entering the cellular volume. This file stores K.E. of particles, their positions, direction cosines, weight, PDG code, etc.



4 Single cell with a nuclear DNA geometry, nucleus shows different color voxels representing chromosomes

TOPAS-nBio Simulation



7 Comparison with measurements

6 Estimate repair

5

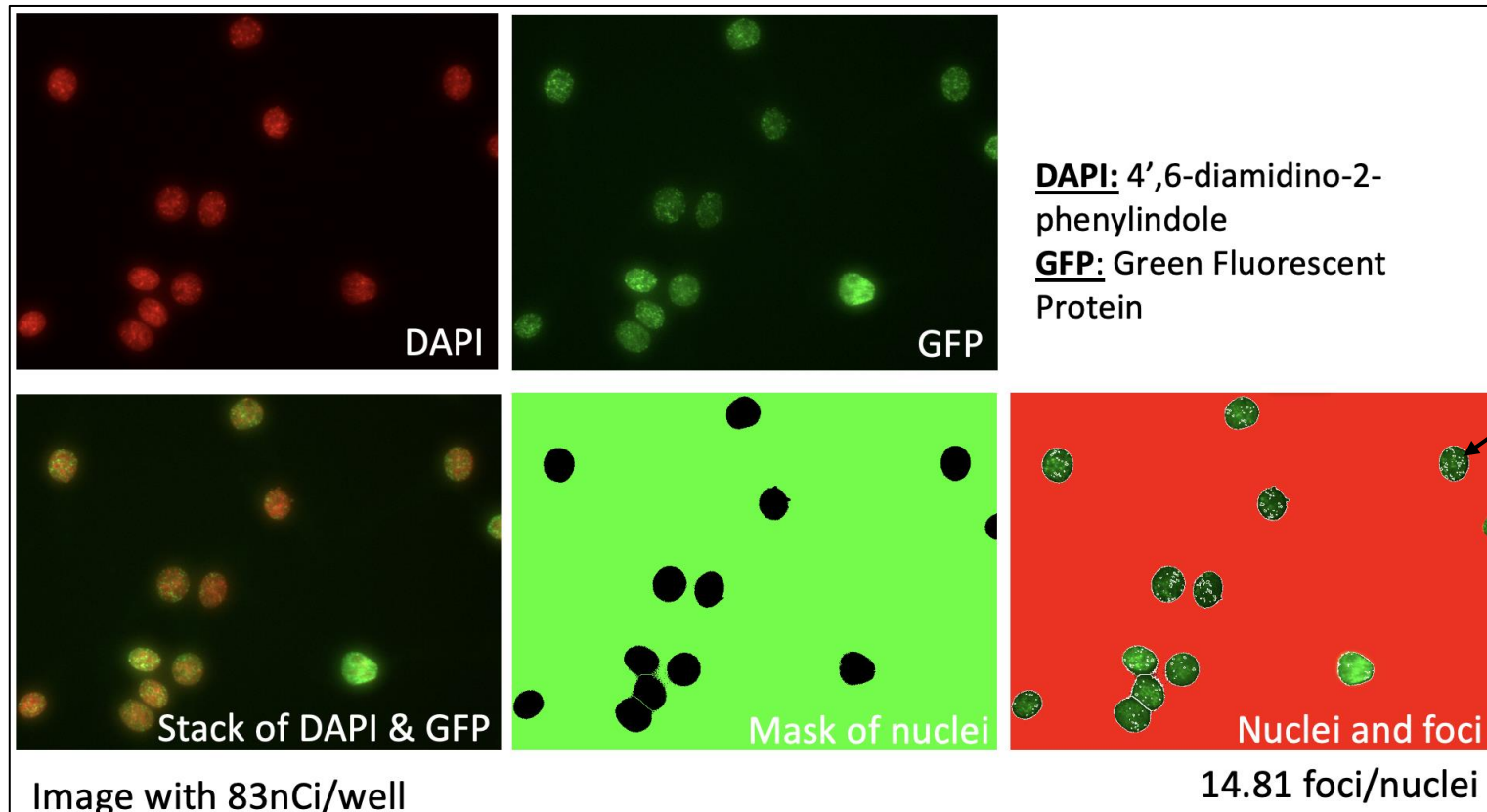
Score DSB

Score SSB

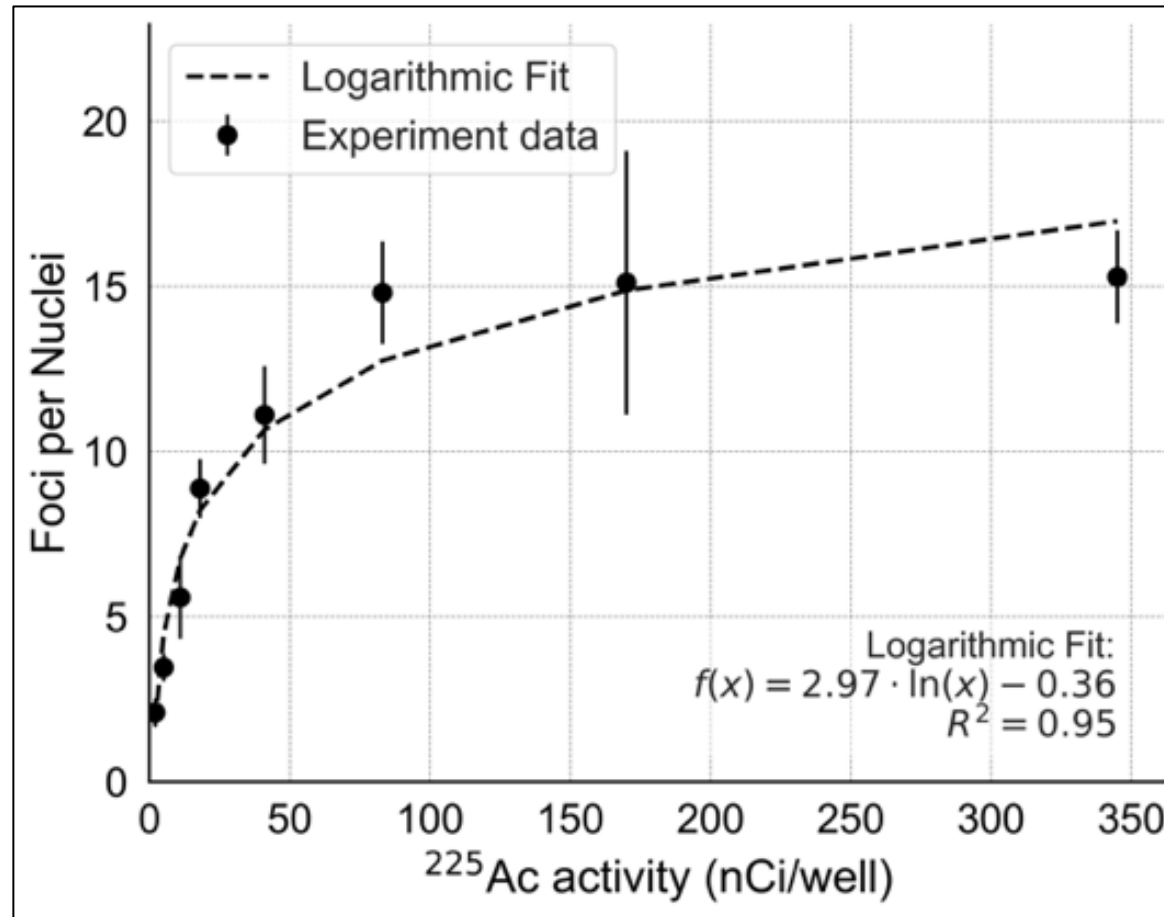
Score absorbed dose

# Results: Experimental measurement

- Measurement results are in #foci/nuclei
- We averaged out the hot or bright spots from the images to get DSBs
- Image analysis were performed in ImageJ software

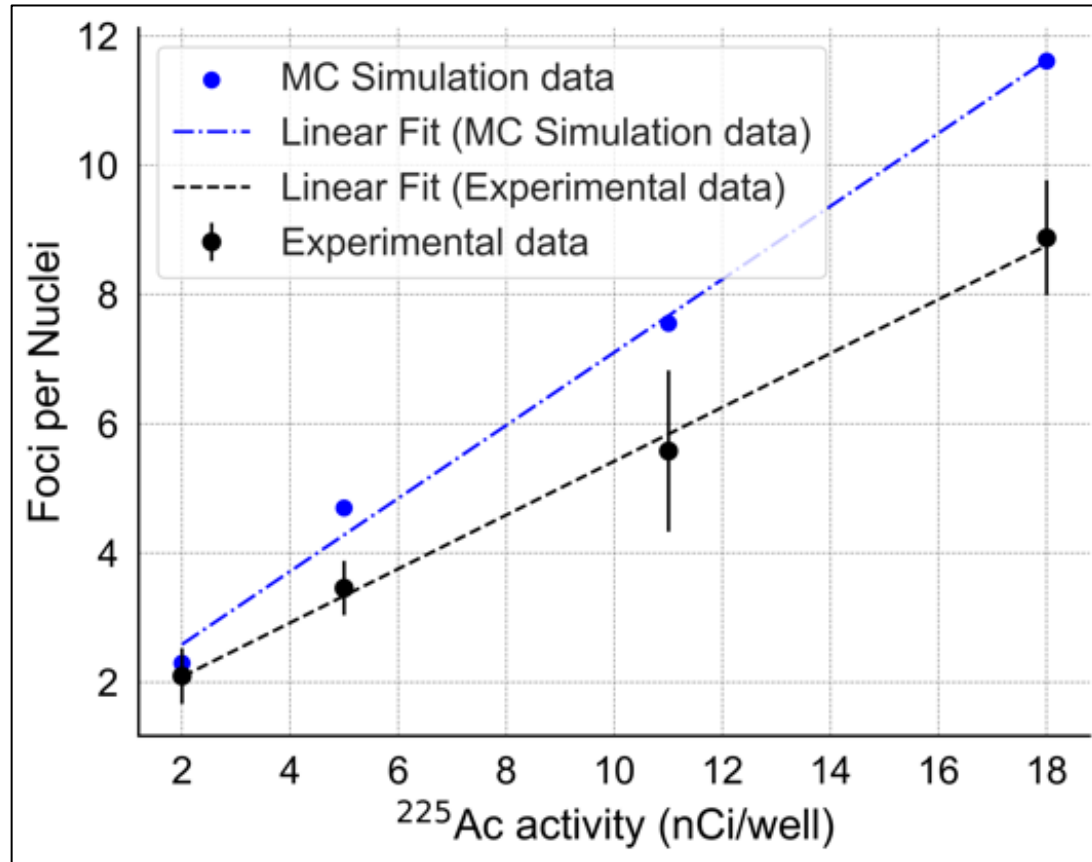


# Results: Experimental measurement – preliminary



- We observed a linear dose-response curve at low activity of <sup>225</sup>Ac
- Saturation/plateau occurred at higher doses
- This indicates that effects of indirect damage at higher doses (activity) become less significant compared to the direct damage

# Results: Experimental vs Simulation



## Limitations of this work:

- Small sample size
- Cells were randomly defined, does this truly reflect the experimental situation?
- Generic nuclear model was used
- Effects of cross talk of radiation between different wells is not included
- DNA repair simulations

# Conclusion and future works

- Experimental measurement of DSB agrees with Monte Carlo simulation
- This work did not incorporate the cross-talk between the particles in cell well, future work should include this information
- DNA repair simulations should be the next step, because repair can happen immediately after irradiation
- Monte Carlo simulation with TOPAS-nBio platform seems a great tool for radiation biology simulations



# Thank you



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# Cross-talk: Ongoing work

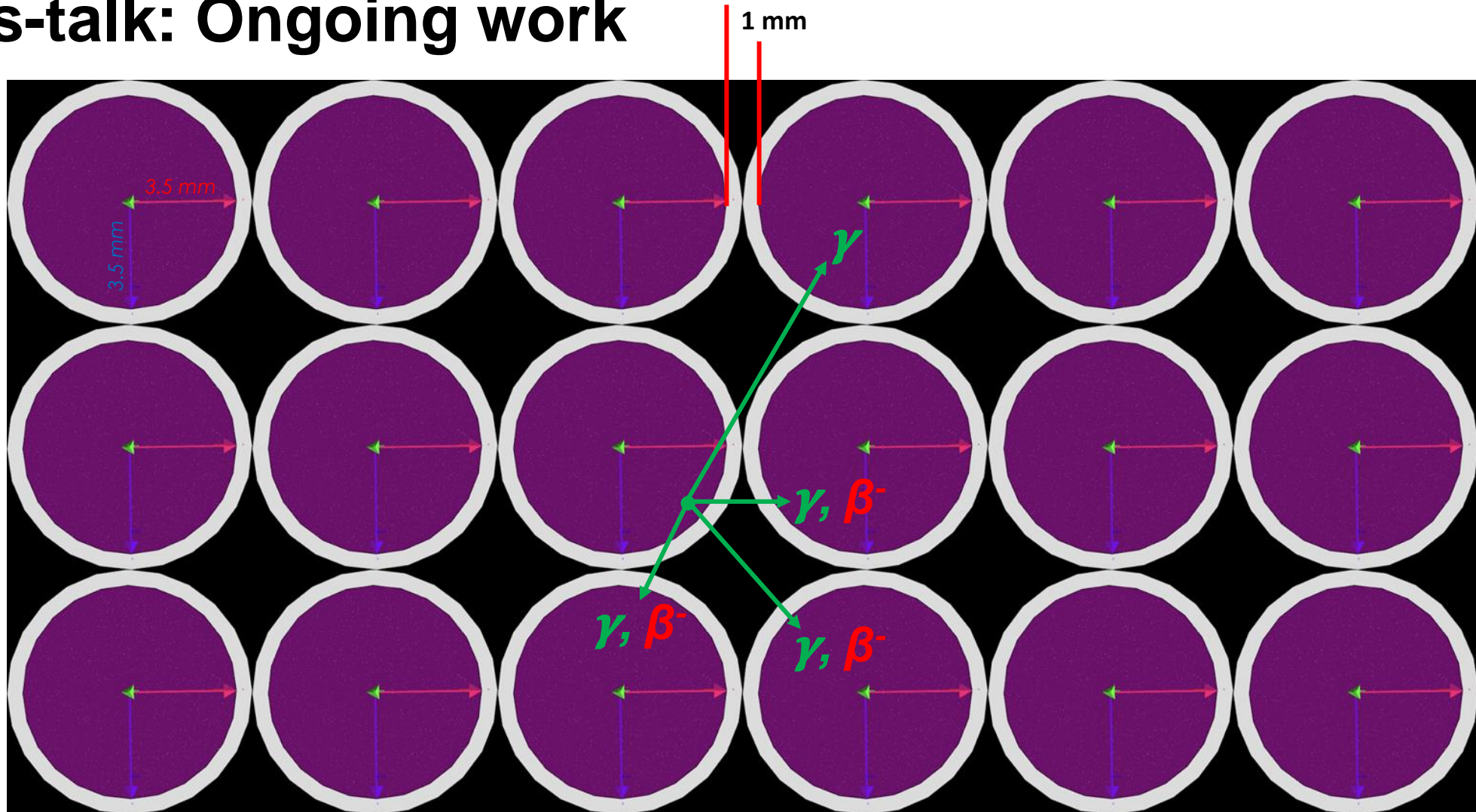
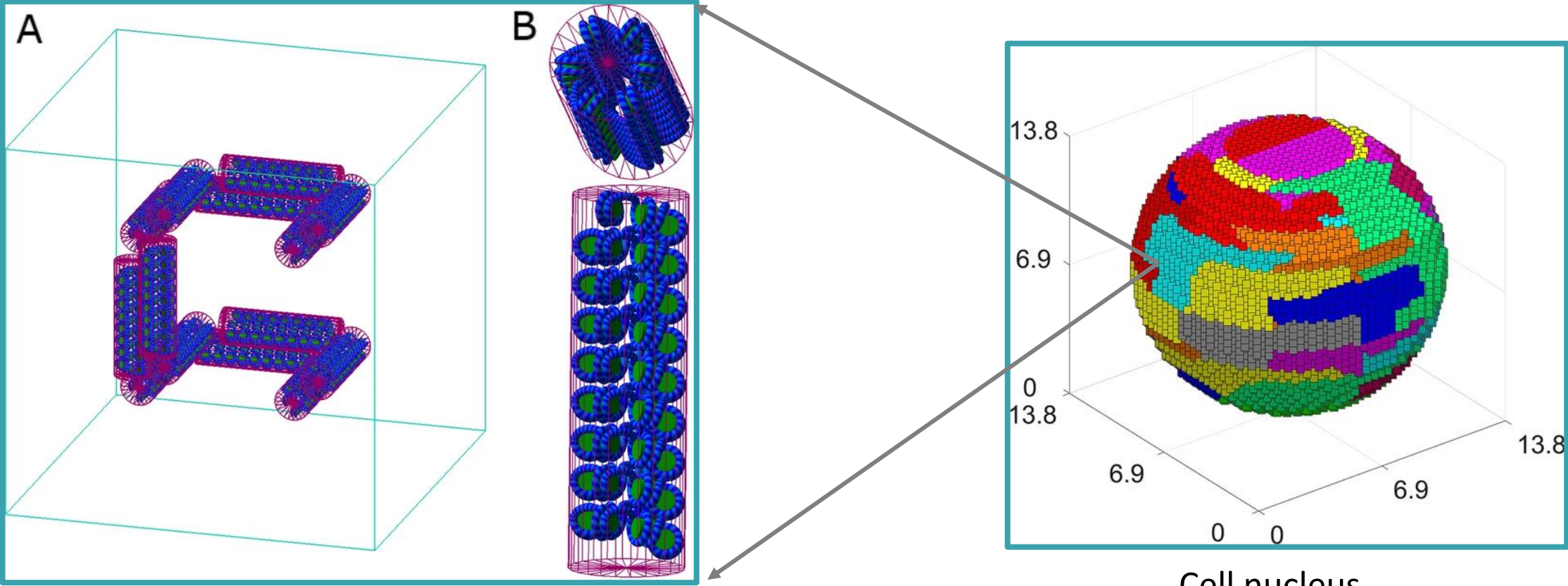


Figure: Illustration of cross-talk

- Cross talk from  $\alpha$  is ZERO
- Cross talk from  $\beta$  is non-zero, as the wall thickness of cell well is  $\ll$  than the max. range of  $\beta$  particles
- $\gamma$  can easily escape from the wells



# Nucleus voxel filling mechanism



Voxel is filling using a fractal pattern based on a 3D Hilbert space-filling.