DNA breaks clustering into radiation-induced foci predicts cell death for a broad range of radiation quality

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Context

- Space radiation environment and particle therapy exposes healthy tissues to high charge and energy **(HZE) ions** that have a broad range of linear energy transfer (LET)
- High LET ions induce complex **clusters of DNA double-strand breaks** (DSB)
- Repair proteins form **Radiation-Induced Foci** (RIF) at site of breaks
- Clustered DNA DSB promote **cell death**

Objectives

- A **mathematical formalism** predicting **cell death** based on the **clustering of DSB at sub-micrometer** scale due to chromatin movement is **validated for five normal human cell lines** [1].
- The model is used to predict the **effect of change in nuclear and beam geometry** on cell death

Methods

DSB simulation

- Track structure simulation with Monte Carlo tool RITRACKS [2]
- DSB calculation with RITCARD [3,4]

DSB clustering into RIF

- The cell nucleus is divided in cubical repair domains of side length d_{dom} (parameter)
- DSB within a cubical domain cluster together inside a RIF

Simulation set-up

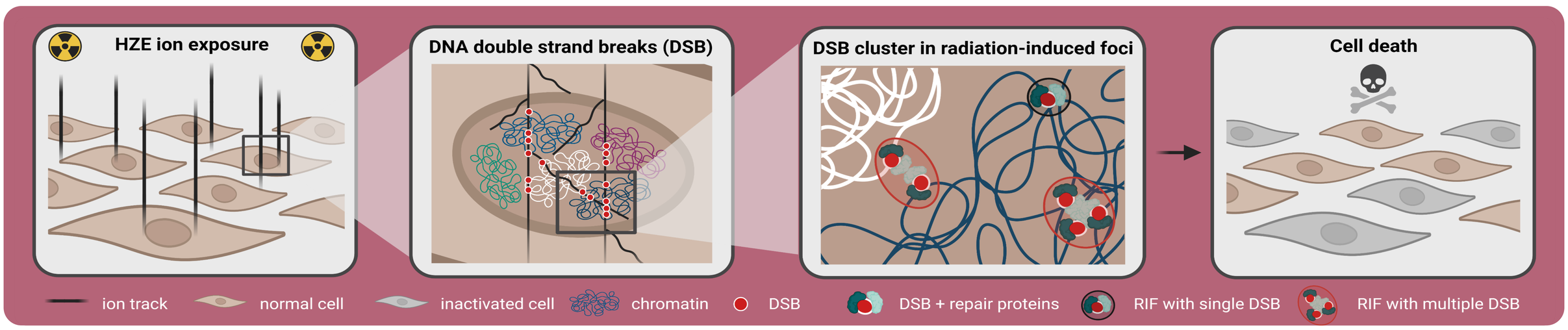
- 1000 simulated cell nuclei for each condition below
- $D \in$ [0.25-2] Gy for ions and [0.25-6] Gy for photons
- $\mathrm{Z} = 1, 2, 6, 8, 10, 14, 18, 22, 26,$ and Cs-137
- $\mathrm{E} = 5, 10, 50, 100, 200, 400, 800, 1000, 1600$ MeV/n
- Example: a cell i contains 7 RIF: 4 RIF with 1 DSB, 2 RIF with 2 DSB, 1 RIF with 5 DSB.
  $n_{comb} = 2 \times C_2^2 + 1 \times C_2^5$
  $n_{comb} = 2 \times 1 + 1 \times 10 = 12$

Cell survival

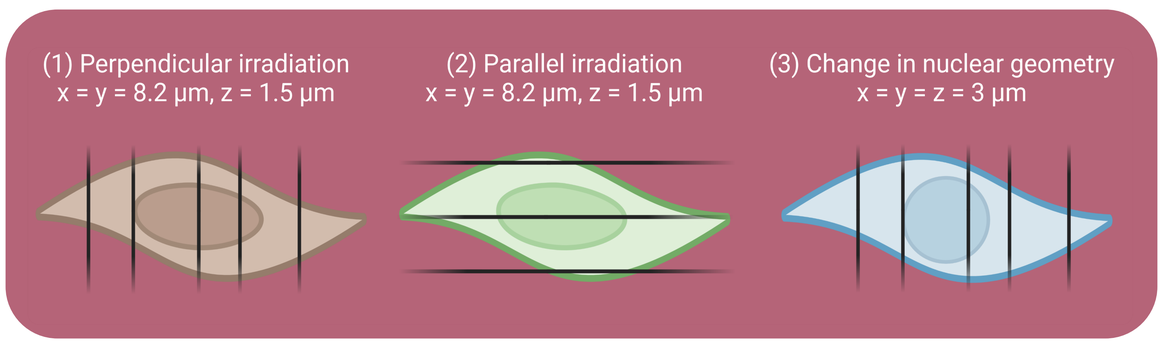
$$P_{\mathrm{surv}}(D) = \frac{1}{N_{cell}} \sum_{i=1}^{N_{cell}} \exp -\left(\gamma n_{comb,i}(D)\right)$$

$$n_{comb,i} = \sum_{j=2}^{Cl_{max,i}} n_{i,j} C_2^j \quad \text{with } C_2^j = \frac{j(j-1)}{2}$$

- D: irradiation dose
- N_{cell}: total number of cells
- γ parameter
- $n_{comb,i}(D)$: number of combinations for cell i
- $n_{i,j}$: number of RIF containing j DSB for cell i
- $Cl_{max,i}$: maximum DSB within a RIF for cell i



Results

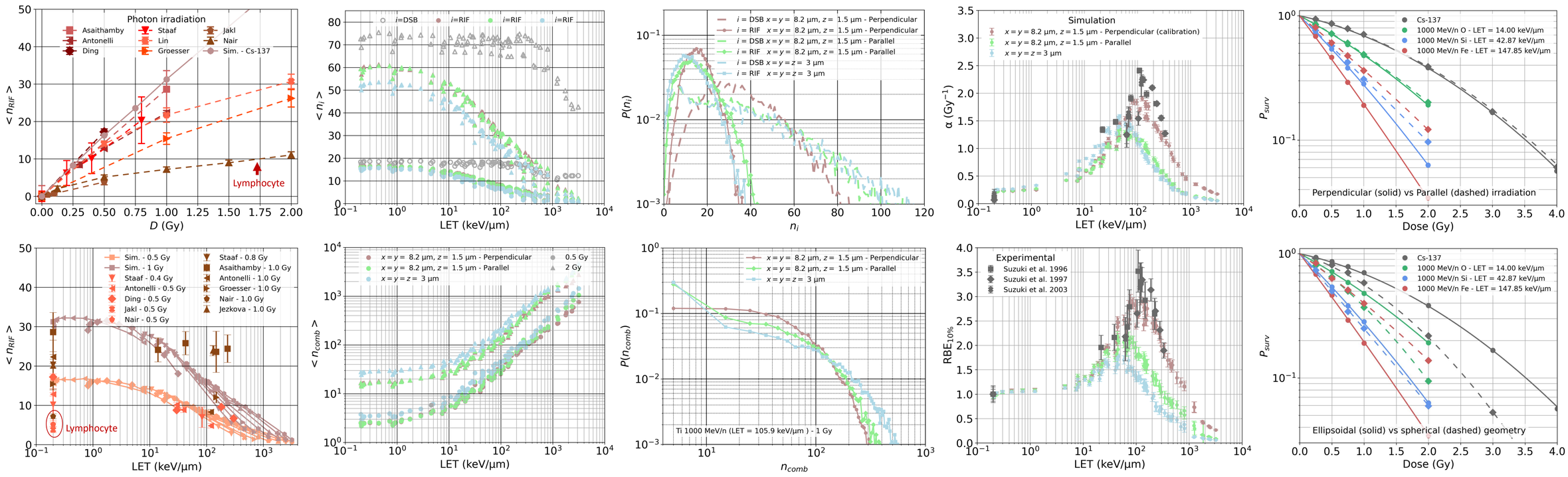


Definitions

- $< n_{DSB} >, < n_{RIF} >, < n_{comb} >$: average number of DSB, RIF or comb. per cell
- $P(n_{DSB}), P(n_{RIF}), P(n_{comb})$: cellular distribution of DSB, RIF or comb.
- $P_{surv}(D) = \exp(-\alpha D - \beta D^2)$ and $RBE_{10\%} = D_\gamma(P_{surv} = 10\%)/D_{ion}(P_{surv} = 10\%)$

Experimental data

- RIF per cell: 30 min to 1h post irradiation; cell lines: HSF42 [5], AG01522 [6], MRC5 [7], Lymphocyte [8,9], MCF10A [10-12], VH10 [13], NHDF-Neo [14]
- Survival: cell line: HE, calibration: $d_{dom} = 0.9$ µm and $\gamma = 0.063$ [15-17]



$< n_{RIF} >$ reproduces experimental data **[5-14]** (LET and dose saturation)

$< n_{DSB} >, < n_{RIF} >, < n_{comb} >$ depend on nuclear geometry but not on beam geometry

$P(n_{DSB}), P(n_{RIF}), P(n_{comb})$ depend on nuclear and beam geometry for high LET

P_{surv} predicted by number of pairwise comb. of DNA DSB in RIF for 5 cell lines HE **[15-17]** and AG1522, HF19, HSF, NB1RGB **[18]** (not shown)

P_{surv} depends **nuclear and beam geometry**

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Acknowledgement. This work was supported by the Lawrence Berkeley National Laboratory Innovation grant #DE-AC02-05CH11231, NASA grant NNL15AA08I and NASA Human Research Project grant NNJ16HP24I (PI. Costes); the NASA Langley Research Center Cooperative Agreement 80LARC17C0004 (F.P.); the Translational Research Institute for Space Health through NASA Cooperative Agreement NNX16AO69A (E.P.); the Human Research Program under the Space Operations Mission Directorate at NASA (S.B., T.S.); the NASA Human Health and Performance contract NNJ15HK11B (I.P. and A.P). Image created with Biorender.com.