Monte Carlo modeling to investigate the suitability of using single-cell DNA sequencing of irradiated cells in the mutation signature analysis of low- and high-LET radiation

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BACKGROUND

- Research work by Behjati et al. (2016) [1] has shown that radiotherapy-associated second cancers exhibit mutation signatures (MS) that are specific to ionizing radiation.
- We predict distinct MS for low- and high-LET radiations.
- But stratifying radiotherapy-associated cancers by LET is an arduous task.
- We hypothesize that cells irradiated in vitro can serve as an alternative to tumor cells to identify radiation-induced MS when performing DNA sequencing at the single-cell level.

OBJECTIVE

To perform Monte Carlo modeling to investigate if low- and high-LET radiation introduce DNA damage patterns in cells' genomes that may be distinguishable at the single-cell level..

METHODS

- Our single-cell geometric nuclear DNA model [2] (**Fig 1**), developed using the TOPAS-nBio toolkit [3], was exposed to low-LET photons and high-LET neutrons of various

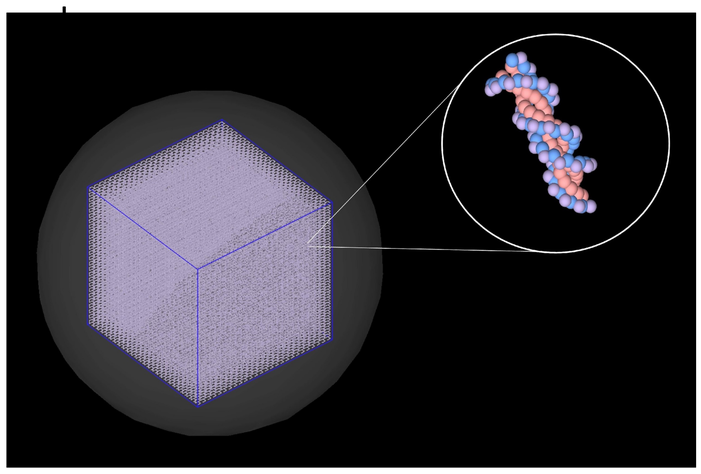


Figure 1: *Geometric nuclear DNA model of a single cell developed in TOPAS-nBio. Previously published by Montgomery et al. (2021) [4]*

- Various types of DNA damage were scored with repeated simulations (**Fig 2**).

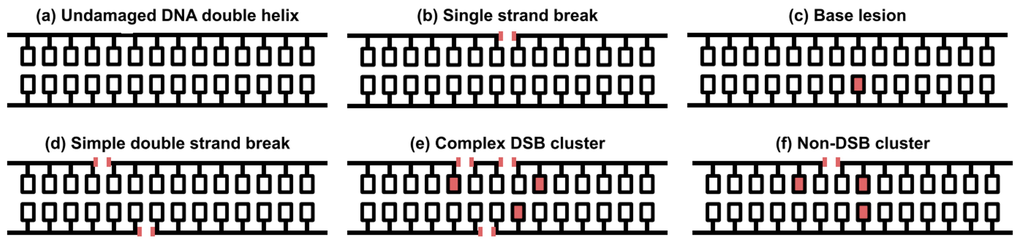
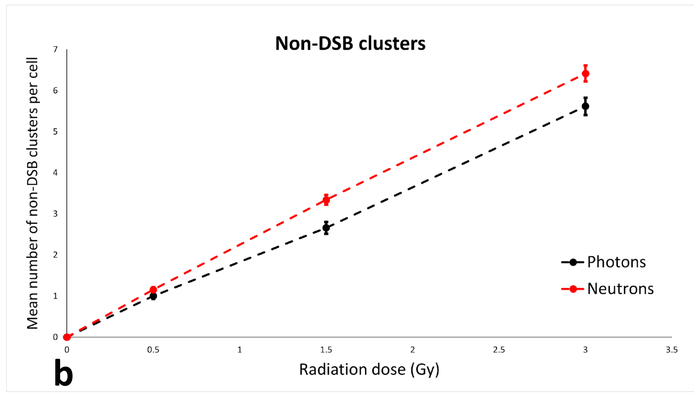
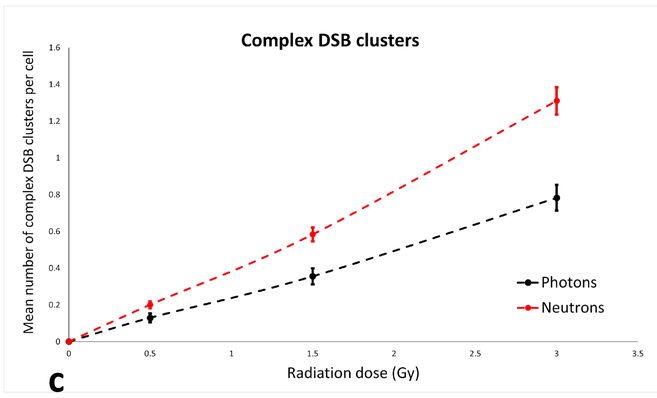


Figure 2: *Schematic examples of the types of DNA damage considered in our simulations. (a) An undamaged DNA double helix wherein each square represents a nitrogenous base attached to the sugar-phosphate backbone. (b) A single strand break (SSB) depicted as a red separation in the backbone. (c) A generic base lesion depicted as a red base. (d) A double strand break (DSB) containing two SSBs on opposing strands within 10 base pairs of each other. (e) A complex DSB cluster containing two or more damage sites, including at least one DSB, each within 40 base pairs of each other. (f) A non-DSB cluster containing two or more SSBs or base lesions, each within 40 base pairs of each [4].*

RESULTS





- Photon and neutron irradiation simulations introduced distinguishable DNA damages in our single-cell model.
- Mean number of base lesions per cell (**a**) was higher for photons while the number of clustered damages (**b**&**c**) were more for neutrons as expected from their LET differences.

CONCLUSION

Our simulations show that the DNA damage induced by low- and high-LET radiations should be distinguishable in a cell population using single-cell sequencing.

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