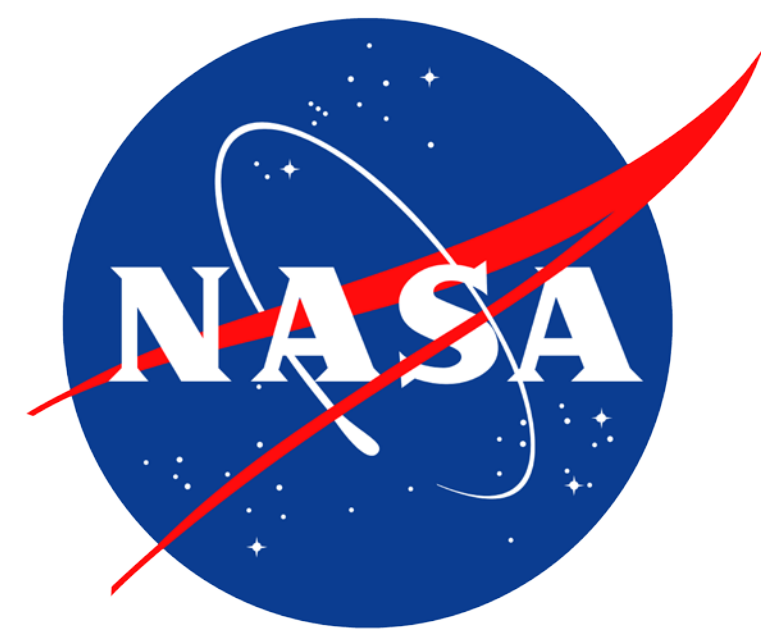


Predicting cell death and mutation frequency for a wide spectrum of LET by assuming DNA break clustering inside repair domains

National Aeronautics and
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Introduction

Cosmic radiation, which is composed of high charged and energy (HZE) particles, is responsible for cell death and mutation, which may be involved in cancer induction. Mutations are consequences of mis-repaired DNA breaks – especially double-strand breaks (DSBs) – that induce inter- and intra-chromosomal rearrangements (translocations, deletions, inversion).

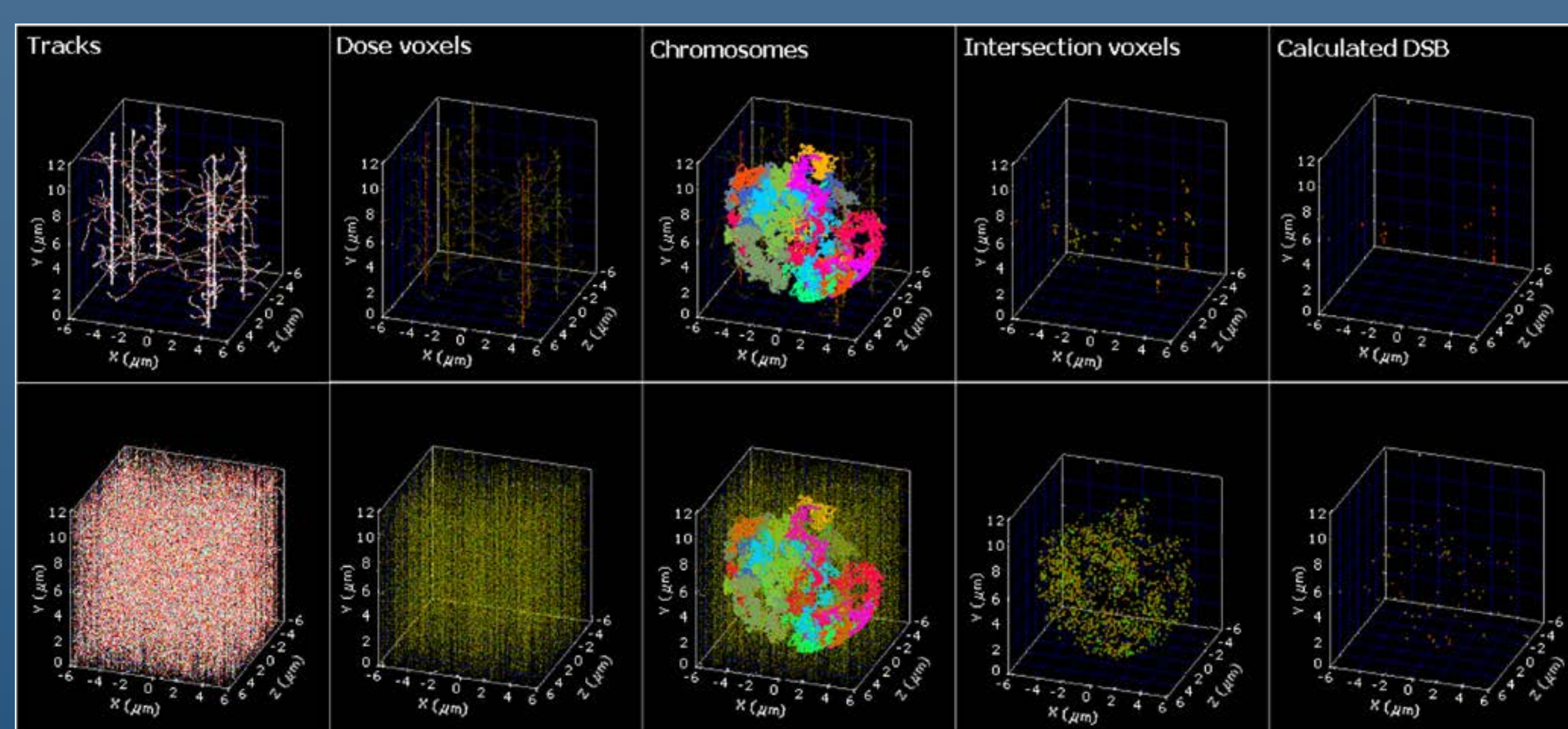
In this study, we investigate the clustering of DNA double-strand breaks (DSBs) in repair domains, previously evidenced by our group in human breast cells [1], and introduce a computer model based on experimental data measuring persistent 53BP1 radiation-induced foci (RIF) to explain the high relative biological effectiveness (RBE) of HZE for both cell death and DNA mutation frequencies.

We first validate our DSB cluster model using a new track model deployed on a simple geometrical configuration for repair domains in the nucleus [2]; then we extend the DSB cluster model's scope from cell death to mutation induction. This work introduces a new and unique mechanism based on DSB repair process to explain several biological effects induced by HZE particles on different type of living cells.

Generation of DSB distribution

The DSB distribution in cells is obtained using the code RITCARD (Radiation-Induced Tracks, Chromosome Aberrations, Repair, and Damage). This code is composed by three parts: a chromosome break model, a repair kinetics algorithm and an algorithm to classify aberrations. For this work, only the chromosome break part is used.

- Chromosome structure model [3]
 - The chromatin has physical and scaling properties analogous to those of long polymer chains.
 - A chromosome is approximated by a random walk model, with each monomer contains 1,000 base pairs.
 - Each chromosome is predominantly located in a part of the cell (domain) that restricts the random walk.
 - Many large and intermediate size DNA loops are present.
 - The shape of the nucleus (spherical, ellipsoid) can be changed by using scaling factors.
- Stochastic radiation track structure and voxel dose
 - A volume encompassing the nucleus is defined.
 - The number of tracks in a simulation for a given dose is obtained from sampling of a Poisson distribution
 - The tracks in the volume are simulated by the code RITRACKS [4]
- Simulation of DSBs in chromosomes
 - The probability to have at least one DSB within a monomer is given by:
$$\psi = 1 - \exp(-QD)$$
 - where D is the voxel dose, and Q is a sensitivity parameter related to the DSB yield (35 DSBs/Gy).



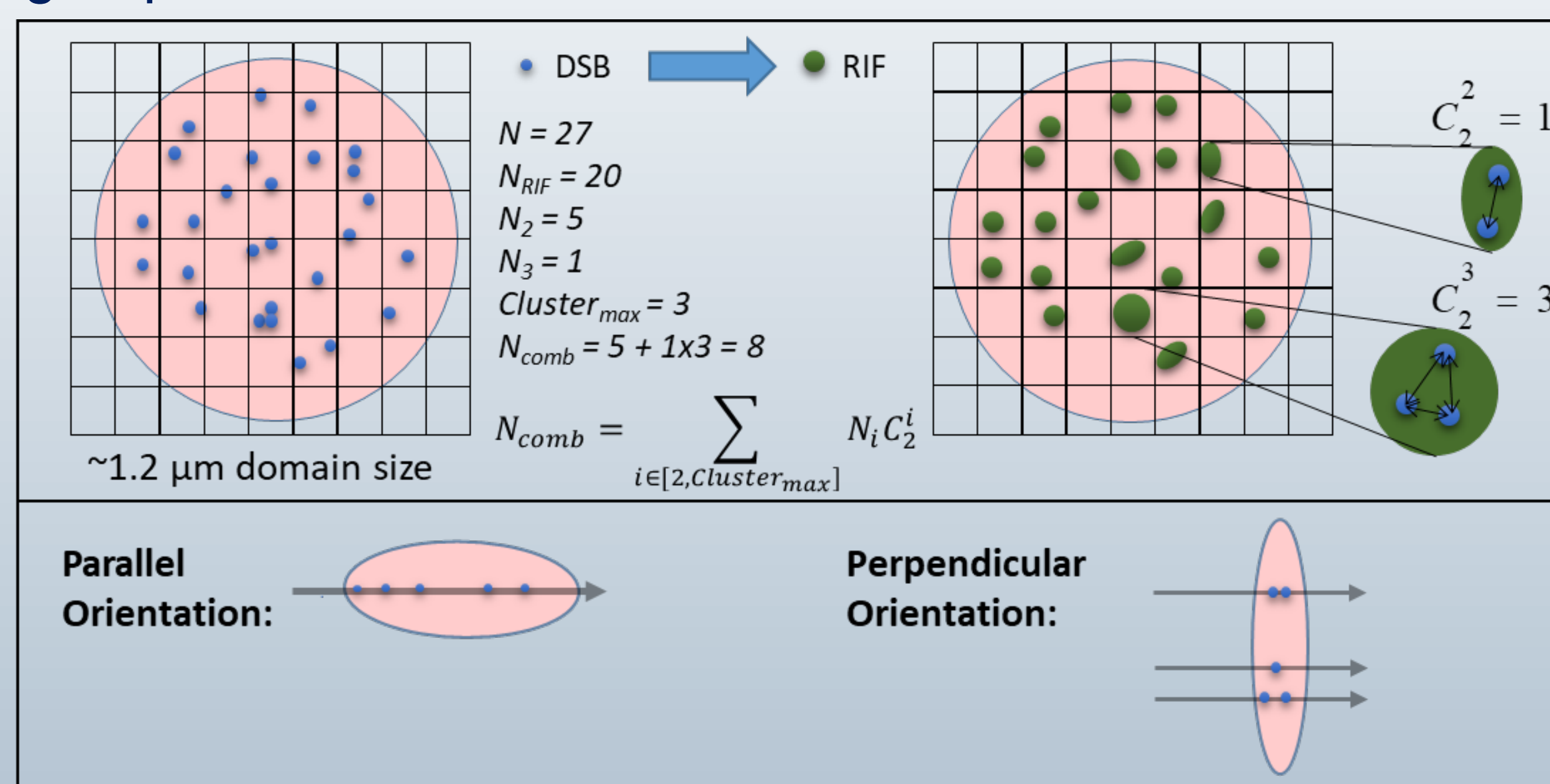
Irradiation of a cubic volume of $12 \mu\text{m} \times 12 \mu\text{m} \times 12 \mu\text{m}$ by 6 iron particles, 1 GeV/amu (top) and by 2700 protons, 300 MeV (bottom). In both cases, the dose deposited is ~ 1 Gy. From left to right: tracks, dose in 20 nm voxels, human chromosomes (only 1 through 10 are shown to enhance visualization, but the calculations were performed on the 46), intersection voxels with equation (1) applied. Figure from Ref [5].

Modeling of DSB clustering

- The nucleus is divided into cubical repair domains (approximation)
- DSBs within the same domain lead to one single radiation-induced foci (RIF)
- The number of pairwise DSB interactions is given by:

$$N_{comb} = \sum_{i \in [2, cluster_{max}]} N_i C_2^i$$

Where N_i is the number of clusters with i DSBs, and C_2^i is the number of potential DSB pairs that can be formed in a group of i DSBs.



Prediction of cell survival

In our model, the cell survival probability is given by

$$P_{survival} = \frac{\sum_{i=[1, N_{cell}]} e^{-\gamma(N_i + aN_{comb,i})}}{N_{cell}}$$

where N_{cell} is the total number of modeled cells (1000), N is the number of DSBs generated by the exposure, N_{comb} is the number of pairwise DSB interactions and γ and a are parameters to be determined.

Using the calculated survival curves, the classical survival equation will be fitted to determine α and β .

$$P_{survival} = e^{-\alpha D - \beta D^2}$$

Prediction of cell mutation

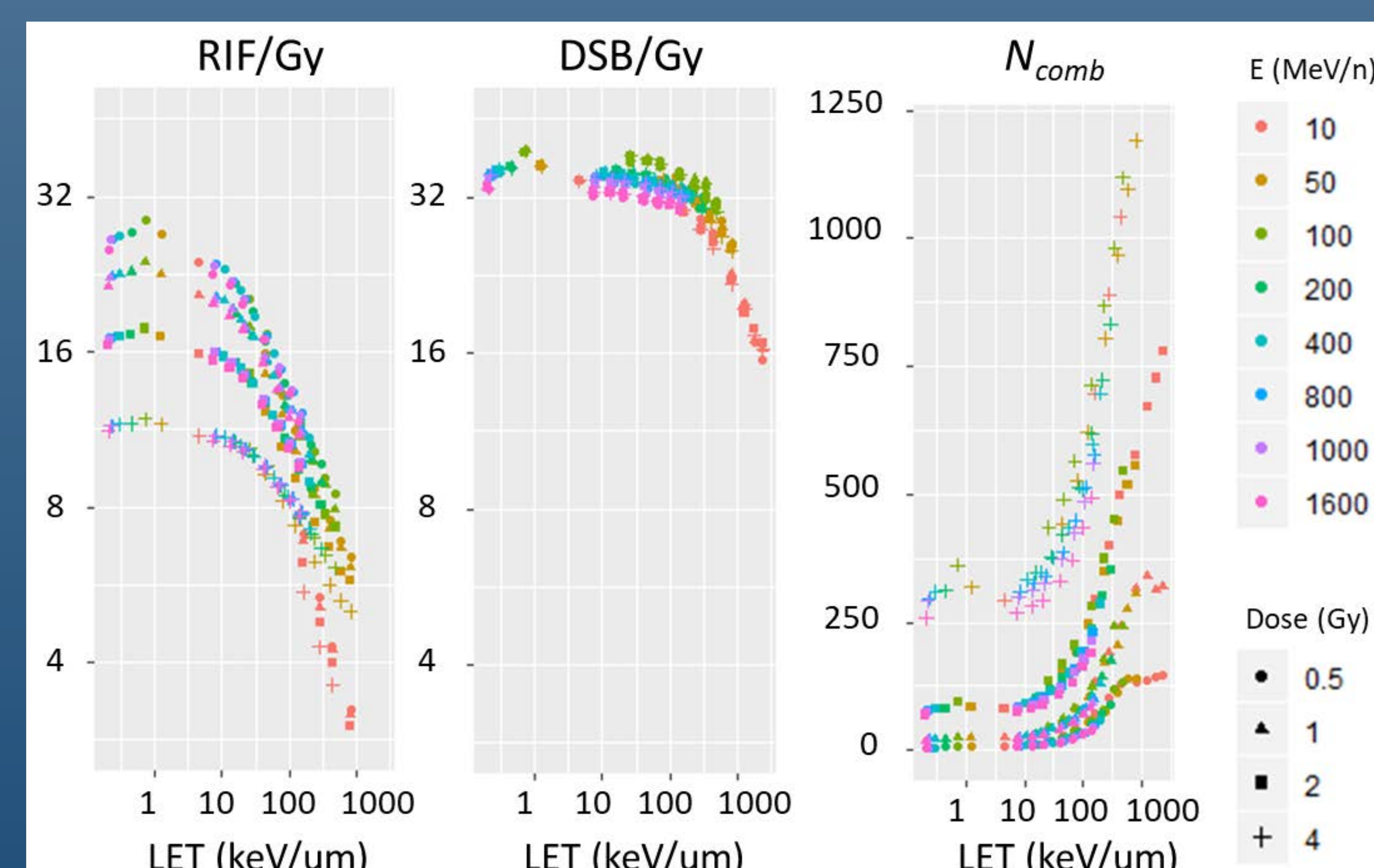
Similarly, the probability of mutation in a cell is given by

$$P_{mutation} = \frac{\sum_{i=[1, N_{cell}]} (\delta(N_i + bN_{comb,i}) * P_{survival,i})}{P_{survival}}$$

where δ and b are parameters to be determined.

Similarly, the mutation probability is modeled by a linear-quadratic equation:

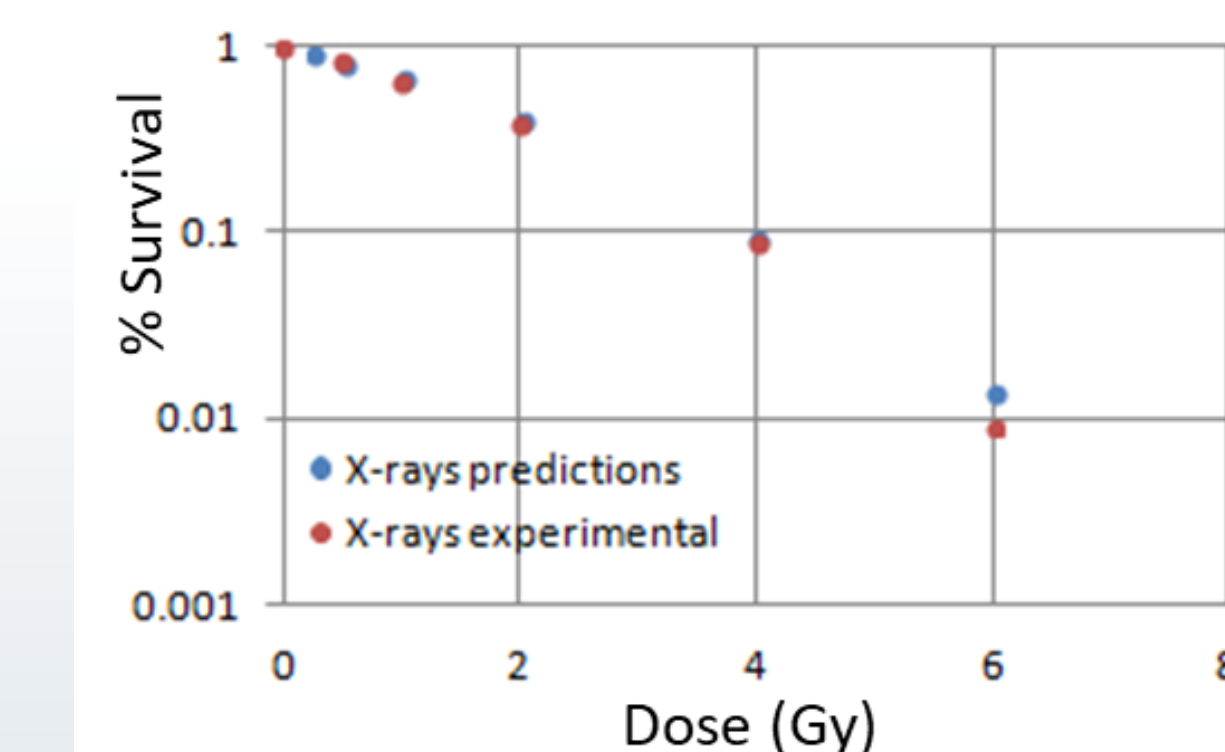
$$P_{mutation} = \alpha D + \beta D^2$$



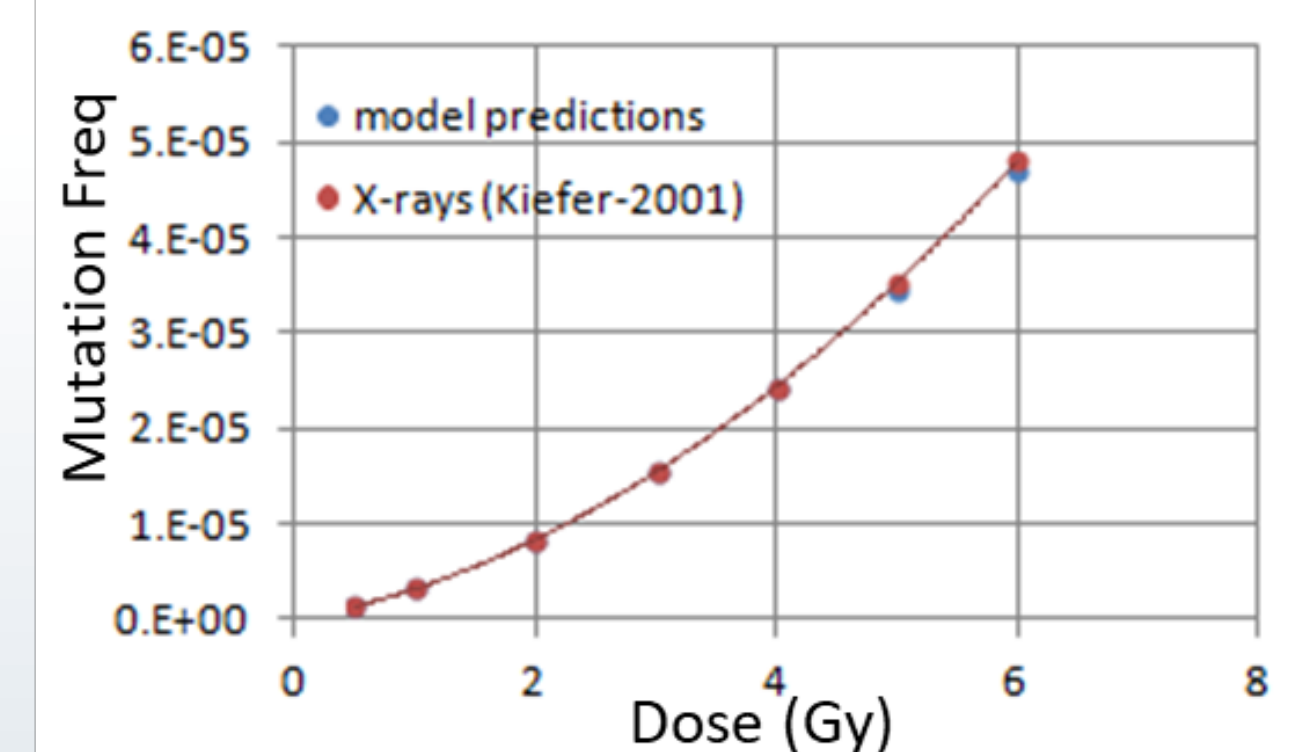
Determination of parameters for human breast cell line

The parameters of our model are determined from experimental data for MCF10A cell line [6].

For survival



For mutations



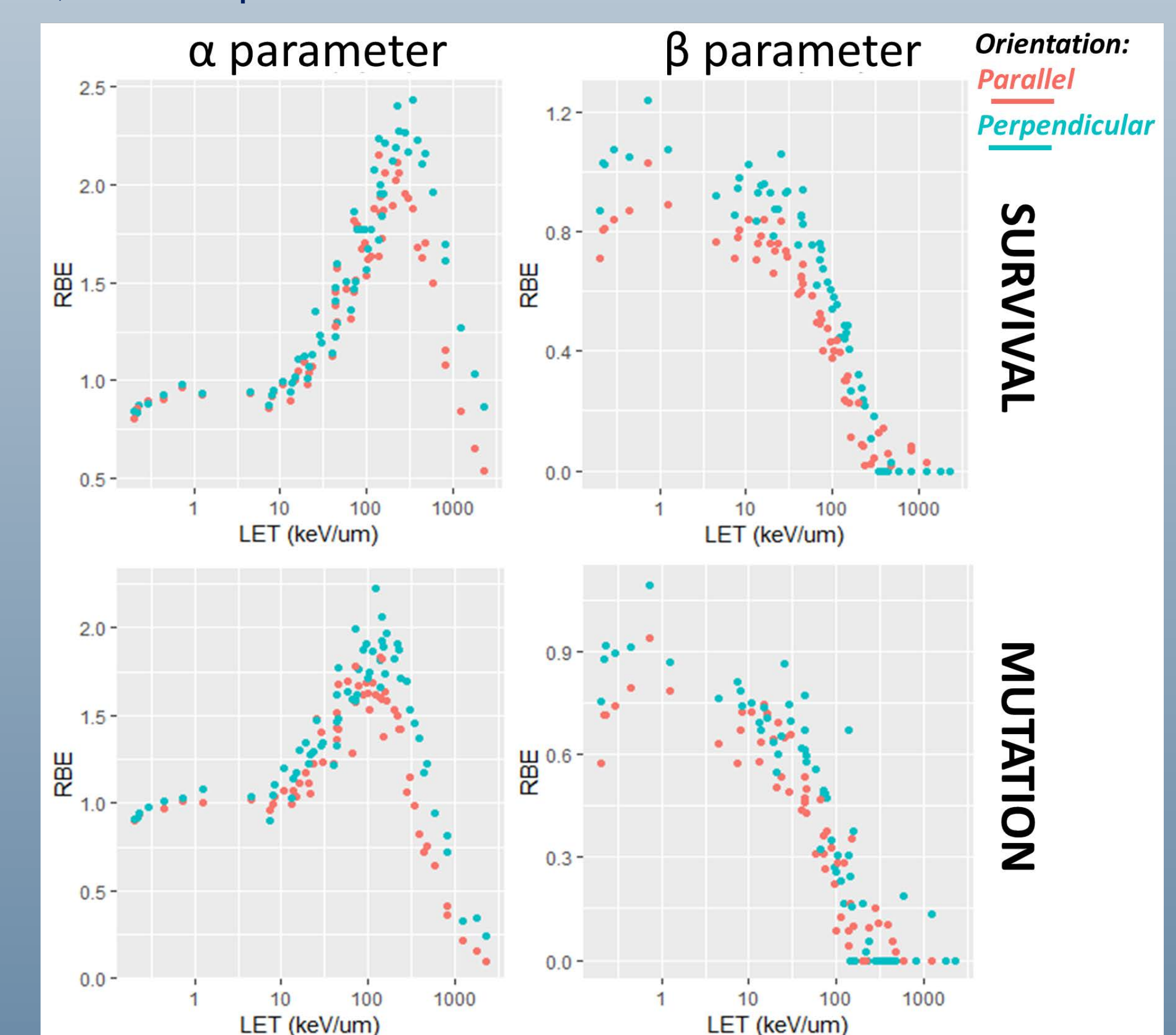
The optimal parameters are determined as domain size = $2.5 \mu\text{m}$, $\gamma=0.0097$, $\alpha=0.03$, $\delta=8e-8$, $\beta b=3.5e-7$.

RBE for survival probability and mutations in human breast cell line

We did simulations consisting of all combinations of

- Particles types: H, He, C, O, Ne, Si, Ar, Ti, and Fe (corresponding $Z = 1, 2, 6, 8, 10, 14, 18, 22, 26$)
- Energies: $E = 10, 50, 100, 200, 400, 800, 1,000, \text{ and } 1,600 \text{ MeV/n}$.
- Dose points: $D = 0.5, 1, 2, \text{ and } 4 \text{ Gy}$.

This led to 288 different simulations, covering a LET range extending from $\sim 0.2 \text{ keV}/\mu\text{m}$ to $\sim 2,300 \text{ keV}/\mu\text{m}$.



Discussion

In this work, we propose a formalism to predict cell death and mutation across a large range of LET with the same parameters, which were primarily derived from low-LET data. However, to fully validate the model, one needs to obtain from the same cell line three different experimental data types: i.e. Radiation Induced Foci, Clonogenic Survival and Mutation frequency. This has turned out to be quite challenging as data across various laboratories using the same cell line suffer from batch effects, which may prevent the model from being able to predict all data across all LET and doses using a single set of parameters. Preliminary data using another cell line where both mutation frequency and clonogenic survival was obtained from the same research laboratory could be predicted across four different LET, but required a much smaller repair domain than seen for human breast cell lines. More work is needed to confirm the robustness of this model across various cell lines. When using parameters derived from the breast cell line MCF10A, we predicted an orientation effect suggesting charged particles traversing a cell perpendicularly to its two longest axes, had a higher RBE. Such findings remain to be verified experimentally. Overall, this new approach offers exciting applications for optimizing treatment planning for hadron therapy and developing risk models from galactic cosmic rays.

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