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# FINAL REPORT ON THE INTEREST PROGRAMME

RADIATION BIOPHYSICS MODELING AT CELLULAR SCALE:
chromatin breaks and chromosome aberrations

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**Abstract**

Ionizing radiation causes both a wide range of molecular damage in the cellular DNA and subcellular damage of chromatin fragmentation and massive chromosomal aberrations. This work focuses on radiation-induced chromatin breaks and chromosomal aberrations in two different mammalian cell types, specifically, Chinese hamster V79 fibroblasts and human lymphocytes. A precalculated database of initial DNA damage and its spatial distribution in the irradiated cells was used in modeling the formation of chromosomal aberrations. A simplified model of non-homologous end joining and microhomology mediated end joining pathways was used to simulate repair kinetics of chromatin breaks. The measure of spatial misrepair was determined using a Gaussian probability function defining the interaction between break ends with respect to the distance between them.

The simulation findings indicate a highly biphasic loss of chromatin breaks in V79 cells and non-linear increases in chromosome aberrations in lymphocytes at higher doses which are congruent with increased DNA damage clustering. These data point to the importance of intrinsic nuclear architecture and pathway-specific repair responses to produce different radiosensitivity patterns. The model is effective in connecting physical patterns of initial DNA damage with biological consequences, which gives the understanding of cell-type-specific radiation responses.

## Introduction

The ionizing radiation leads to a wide spectrum of molecular damage by direct ionizing the DNA and indirectly by radiolysis of water. These mechanisms can quickly generate reactive oxygen species that can damage nucleic acids, lipids, and proteins, but double-strand break (DSBs) stands as the most biologically significant lesion due to its ability to damage both strands of the helix at once thus becoming significantly harder to repair [1] (Reindl et al., 2023 pp.84-90). The fact that DSBs can produce chromatin fragmentation and extensive chromosome aberrations in case of inaccurate repair is also a significant danger. There is also spatial clustering of DNA DSBs which is driven by chromatin compaction and nuclear geometry which again enhances the likelihood of complex DNA damage which supports the importance of chromatin structure in determining radiation sensitivity.

The chromatin structural differences can be seen in the comparison of the human lymphocytes and Chinese hamster V79 fibroblasts [2, 3]. Lymphocytes have tightly packed chromatin domains and tend to generate more densities of ionization tracks per unit volume leading to more clustered DSBs. Therefore, it is common to see lymphocytes with increased initial DNA damage and increased rates of misrepair. In comparison, V79 fibroblasts have a higher number of open chromatin structures that cause a decrease in spatial crowding of breaks and better recruitment of repair complexes. These architectural differences have an effect on both early DSB induction and downstream aberration formation.

DSBs that result due to radiation are repaired mainly through non-homologous end joining (NHEJ) and microhomology-mediated end joining (MMEJ) in the early phases of cell cycle [1]. NHEJ is a high efficiency, fast repair pathway that can repair a large number of simple DSBs within a short period of time following irradiation. MMEJ on the other hand is more error-prone and slower and relies on microhomologous sequences that predispose to loss or misalignment of the sequence. These pathways are characterized by a mechanistic kinetic model where every DSB is allocated pathway-specific repair probabilities and rate constants, and the complexity of damage leads to the prevalence of one or the other pathway.

Additionally, the likelihood of the correct and incorrect end-joining is defined by the spatial distribution of DSB ends. In theoretical studies [4, 5] the Gaussian distance-dependent joining function is widely used, which mathematically bridges nuclear geometry to chromosomal rearrangement probability, enabling the quantification of the effect of DNA-end proximity on misrepair to be realised. This correlation is critical in making forecasts on chromosome aberrations like deletions and dicentrics.

These parameters are combined in radiobiological models, which model the dynamics of break-repair and formation of chromosome-aberrations, using initial DSB induction, simplified repair pathway kinetics, and spatial end-joining probability. In such a context, this work aims to model the formation of chromatin breaks and chromosome aberrations following radiation-induced cellular DNA damage.

## Method

A precalculated database [6] of initial DNA damage and its spatial distribution in irradiated cells was used in this study. The radiobiological damage model is based on fundamental physical interactions of radiation with biological materials, taking into account radiochemical processes and chromatin geometries at the atomic level.

One of the most severe types of damage in cellular DNA is the double-strand break (DSB), which can lead to chromatin breaks and chromosome aberrations. For an absorbed dose of 1 Gy

of X-rays, the average number of initial DSBs ($N_0$) is 36 in a single V79 cell and 62 in a human lymphocyte cell during the G1 phase of the cell cycle. The kinetics of isolated and complex DSB repair ($N_t$) is simulated via the cellular pathways of NHEJ and MMEJ in the G1 phase of both cell types:

$$N_t = N_0\, exp(-k\_NHEJ \cdot t) + N_0\, exp(-k\_MMEJ \cdot t). \quad (1)$$

Two chromatin fragments can undergo end-joining according to a Gaussian probability function of the form

$$\lambda = exp(-d^2 / 2\sigma^2), \quad (2)$$

which depends on the initial distance, d, between the two fragment ends [4, 5]. For NHEJ and MMEJ, the total probability of each break being correctly repaired is given by

$$P_{corr} = [1 - exp(-2\sum\lambda)] / (2\sum\lambda). \quad (3)$$

The total number of incorrectly repaired DSBs at a given time can be calculated as

$$N_{mis} = (N_0 - N_t)(1 - P_{corr}). \quad (4)$$

In the G1 phase of the cell cycle, the total number of chromosome aberrations can be calculated as the total number of deletion $N_{del}$ (asymmetric intra-chromosomal) and dicentric $N_{dic}$ (asymmetric inter-chromosomal) events:

$$N_{del} = 0.5 \cdot N_{mis} \cdot P_{intra}, \quad (5)$$

and

$$N_{dic} = 0.5 \cdot N_{mis} \cdot (1 - P_{intra}), \quad (6)$$

where P_intra is the probability of the interaction being intra-chromosomal events (λ).

**Results**

To reproduce experimentally observed chromatin breaks [3], the simulated chromatin-break kinetics of V79 cells (Fig 1) that were exposed to 3 Gy and 8 Gy X-rays provide a distinct dose-dependent yet similarly biphasic pattern of repair. At early times (t = 0-1 h) the two curves show a sharp fall since the fast NHEJ component overtakes the repair process. At 3 Gy, the breaks reduce by 27 to 22 and 8 Gy condition by 32 to 18 and 13 respectively 2 hours later. This fast step is an expression of the prompt elimination of the isolated DSBs expressed by the exponential term (1).

After 2 hours, the repairing rate becomes significantly lower, and it suggests the growing role of the slower MMEJ-mediated component. Between 2-14 hours, the two doses meet in a gradual manner, in which 3 Gy and 8 Gy decrease respectively between 5 to 3.2 and 3.5 to 1.5 breaks. This convergence with time is due to the fact that only complex spatially separated DSBs are left, and their repair kinetics do not depend much on dose. The general trend is quite consistent with the generally anticipated biexponential trends as suggested by the model.

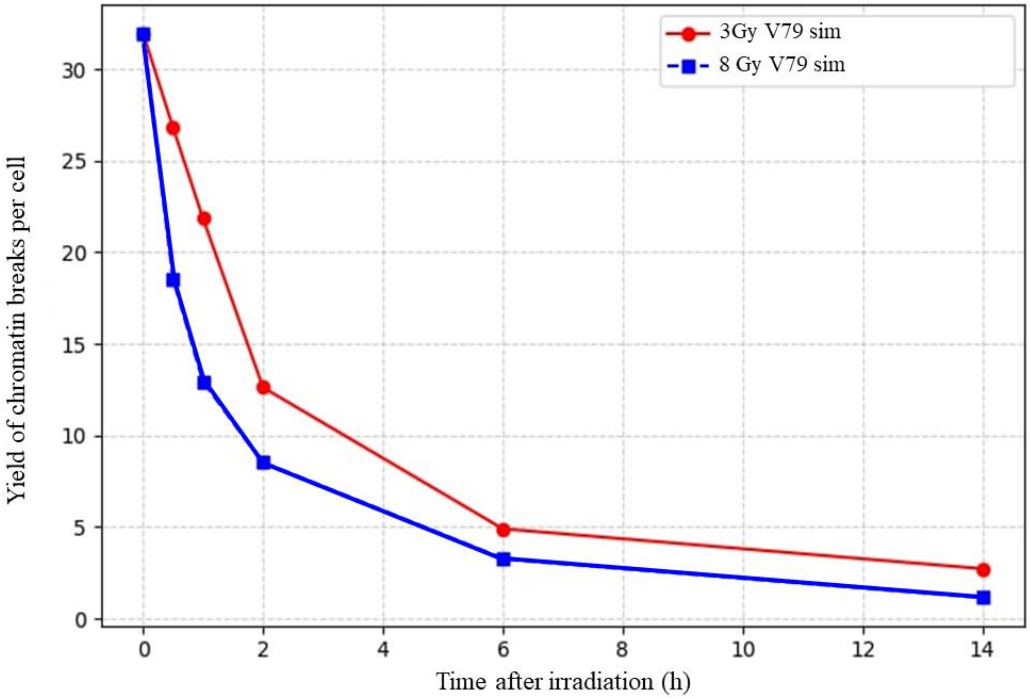


Fig 1. Repair kinetics of chromatin breaks in V79 after exposure to X-rays at the dose of 3 Gy and 8 Gy.

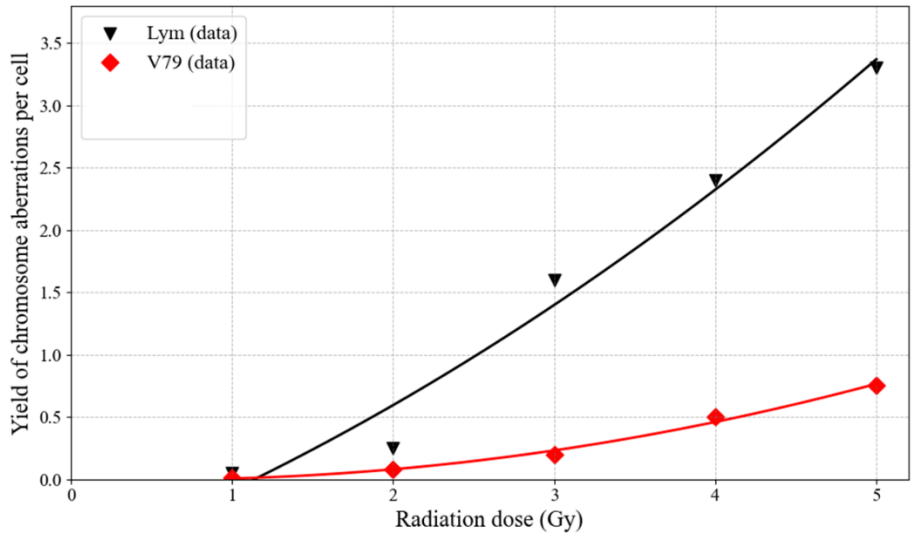


Fig 2. Radiation dose–effect curves plotted for chromosome aberrations in human lymphocytes and V79 fibroblasts produced by X-rays. Experimental data taken from [2].

The different dose-response curves to the formation of chromosome aberrations in human lymphocytes and V79 fibroblasts are obtained using the semi-emperical model (Fig 2). Since lymphocytes produce a greater number of initial DSBs for 1 Gy of dose, the cumulative population of free DNA ends increases at a higher rate with dose, which enhances the cumulative probability of interaction in the Gaussian rejoining model. This decreases the true repair and enhances misrepair with a high upward curvature generated with regard to aberration yield. As depicted in

the figures, the lymphocytes increase virtually to close to zero at 1 Gy to more than 3 aberrations per cell at 5 Gy.

As the results, the dose dependence is much lower in V79 cells. This reduction in their rate of DSB induction leads to reduced spatial crowding of DSB ends and results in reduced misrejoining opportunities. As a result, the yield of aberration is less than 1 up to 5 Gy. The misrepair term of the model is the case in both situations. Through confinement of dose-effect amplification of erroneous end-joining, providing the account of the separation between the two cell types.

## Conclusion

The results of the chromatin-break kinetics and the dose-dependent analysis of the chromosome aberration of the cell are considered together to give us a consistent image of the difference between V79 fibroblast and human lymphocytes to the radiobiological responses, and how the differences naturally arise under the action of the mechanisms outlined in the model. The simulations of time-dependent chromatin-breaks in V79 cells indicate a highly biphasic repair pattern with majority of the simple DSBs being removed in the first 1-2 hours via NHEJ and thereafter slowly by MMEJ as only the complex or spatially distant breaks persist. Whereas early break values increase with dose, late-time residual values become zero, which shows that final lesions are more strongly related with intrinsic chromatin structure as opposed to the dose absorbed.

When these kinetic insights are considered together with the dose-response relations of chromosome aberrations, mechanistic relations are clear. Lymphocytes, which are initially more represented by DSBs/Gy, and have more compact chromatin, have much more events of misrepair with dose increase. This is enhanced by a distance-dependent rejoining probability, whereby the greater the pool size of DSB ends in a dense nuclear environment, the greater the number of mismatched interactions, and hence the more deletion and dicentric formation. This causes the nonlinear and steep rise in aberrations observed in 1 to 5 Gy lymphocytes.

Conversely, there is a moderate and non-linear dose dependence of aberration yield in V79 cells. Their reduced initial DSB density and more open chromatin cause the spatial clustering of breaks to be reduced and thus enhances the chance of successful end-joining. Consequently, at increased doses of 5 Gy, V79 cells have less than one aberration per cell.

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