First Semester Report

Doctoral School of Physics

Statistical Physics, Biological Physics and Physics of Quantum Systems Program

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Thesis title: Examining the biological effect of low dose ionizing radiation.

Introduction

Research related to radiation protection plays a crucial role in establishing safety regulations for both professionals and the public. According to the Linear Non-Threshold (LNT) model, which defines globally accepted radiation protection principles, there is a linear relationship between health risk and absorbed dose (International Commission on Radiological Protection, 2023). However, biological processes observed at low doses of ionizing radiation, such as genomic instability, adaptive response, or hypersensitivity, suggest a different relationship in many types.

The proportion of surviving cells in the 0–1 Gy dose range in many tissues and cell lines differs from the prediction of the linear-quadratic (LQ) model, even though it remains accurate at higher doses. During hyper-radiosensitivity (HRS), the proportion of surviving cells is lower than the LQ prediction. This region of increased cell mortality is then sometimes, but not always, followed by a region of increased cell survival, a phenomenon called Increased Radioresistance (IRR). There is no widely accepted biological explanation for these phenomena (Marples and Collis, 2008).

A proposed explanation for the HRS/IRR phenomena is the Minimum Mutation Load (MML) model (Polgár and Madas, 2025). This model suggests that the variations in cell survival are the result of a tissue-level optimization process that, through cell-cell communication, aims to minimize the total mutagenic damage within the tissue. This is achieved by cells comparing their own mutagenic damage to the average mutagenic damage in their neighborhood, and choosing apoptosis should theirs exceed the average.

Description of research carried out in current semester

During the semester, I continued investigating the effect of cell density on the cell survival curves predicted by the Minimum Mutation Load (MML) model, work that I started during my MSc thesis. As shown in Figure 1, varying cell densities result in distinct cell survival curves.

My goal was to determine whether introducing cell density (δ) as an additional fitting parameter, alongside the mutation induction rate (μ) and spontaneous mutation rate (m_s), would enable more accurate fitting of experimental data. I focused specifically on datasets exhibiting a significant initial drop in cell survival, which were previously difficult to model accurately (Polgár and Madas, 2025).

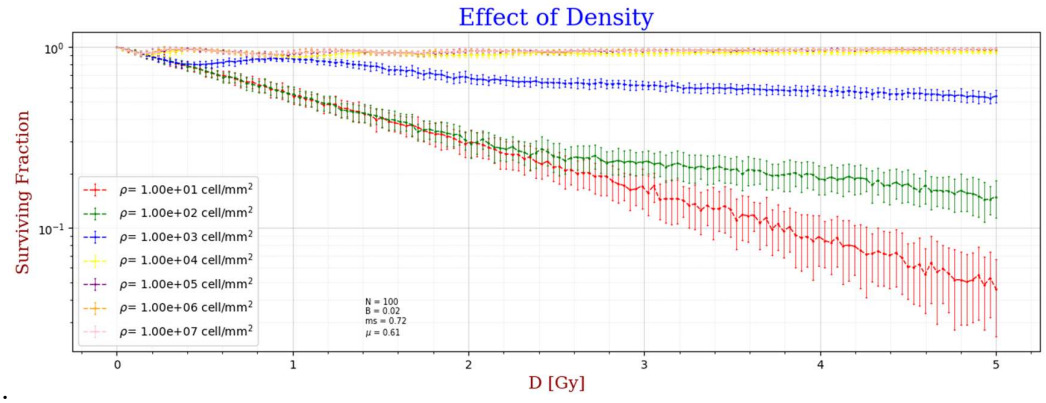

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Figure 1: MML model survival curves at different cell densities

To estimate the three simulation parameters, I generated a library of MML simulations covering a range of values for each parameter. The experimental data were then compared to the library entries by calculating the Sum of Squared Differences (SSD), and I selected the parameter set from the entry yielding the lowest SSD. For the LQ extension of the MML model, which allows for accurate fitting at higher doses, the α and β parameters were derived by fitting the experimental data to the Induced Repair (IR) model. Subsequently, to further refine the fit, the Nelder-Mead method was employed for a maximum of 50 iterations on each experimental survival curve. Two examples of the fittings can be seen below.

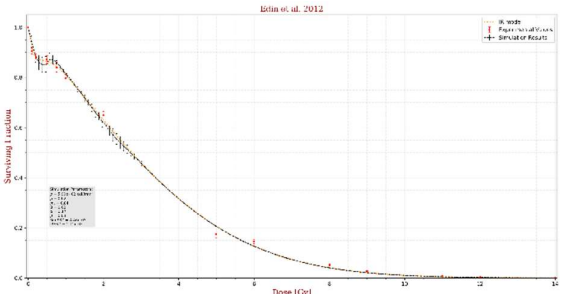

Figure 2: Fitting of experimental results from (Edin *et al.*, 2012)

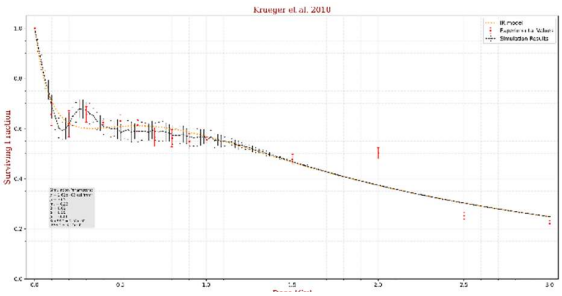

Figure 3: Fitting of experimental data from (Krueger *et al.*, 2010)

Upon examining the survival curves at various densities, the curve corresponding to a density of 100 $cell/mm^2$ proved particularly notable. On a logarithmic scale, this curve displays two distinct linear segments within the simulated dose range, suggesting that the system is characterized by two separate exponential decay phases demarcated by a transition point.

I propose that this behavior stems from heterogeneity in local cell densities, which results in two distinct populations: clustered cells and isolated cells. Cells located within clusters benefit from enhanced protective signaling from neighboring cells, leading to a higher likelihood of survival. In contrast, isolated cells exhibit a higher probability of cell death. The change in slope observed at the transition point marks the threshold where the dominance shifts between these two sub-populations.

To test this hypothesis, I analyzed the spatial distribution of cells using several methods, including the radial distribution function (RDF) of dead cells, the average distance between dead cells, and the nearest neighbor distances of both dead and surviving cells. Based on the results of these analyses, the spatial distribution of dead cells appears to be independent of dose. Consequently, the proposed two-population hypothesis appears to be incorrect.

A recurring question concerning the MML model is the nature of the signal responsible for communicating mutagenic damage levels between cells. During the semester, I conducted an extensive literature review on intercellular signaling mechanisms. Based on this review, I found exosomes, a type of extracellular vesicle, as the most probable candidates for mediating the MML signal, as they can influence recipient cells via their bioactive cargo

The biological effect of exosomes depends primarily on the donor cell type and the environmental stress to which it is exposed (Jelonek, Widlak and Pietrowska, 2016). Research has demonstrated that exosomes play a role in cancer development (Zhang *et al.*, 2015) and the tissue response to ionizing radiation (Al-Mayah *et al.*, 2015). Furthermore, radiation has been shown to increase both the secretion and uptake of exosomes (Jelonek, Widlak and Pietrowska, 2016; Mutschelknaus *et al.*, 2016). Experimental data suggest that exosomes enhance the survival of irradiated cells (Mutschelknaus *et al.*, 2016), making them a promising candidate for the signaling mediator in the MML model. In the future, I hope to participate in experiments aimed at validating this hypothesis.

Since November, I have also been engaged in a collaborative project titled "AI-Assisted Dosimetry" with the Radiation Protection Department of the HUN-REN Centre for Energy Research. My role in this project is to contribute to the development of a comprehensive interface that serves as a unified framework for integrating various internal dosimetry calculation methods. Additionally, I will be responsible for incorporating AI-driven features designed to identify and estimate missing parameters required for these calculations. The project is currently in its initial phase, with efforts primarily dedicated to developing the interface.

Studies in current semester

During the semester, I completed the following classes:

- Ionizing radiation in the human environment, their biological and potential health effects (KÖR-2/82)
- Advanced machine learning lab (FIZ/3/093)

References

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