Second Semester Report

Doctoral School of Physics

Statistical Physics, Biological Physics and Physics of Quantum Systems Program

Student: Márton Juhász (juhaszmarton2000@gmail.com)
Supervisor: Gergely Balázs Madas
Thesis title: Examining the biological effect of low dose ionizing radiation.

Introduction

Hyper-radiosensitivity (HRS) and Increased Radioresistance (IRR) are phenomena occurring in the 0–1 Gy absorbed dose range that presents a deviation from the cell survival prediction of the linear-quadratic (LQ) model. During 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 an IR region of increased cell survival.

A proposed explanation for the HRS/IRR phenomena is the Minimum Mutation Load (MML) model [1]. This model suggests that the variations in cell survival are the result of a tissue-level optimization process that, through cell-to-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 their own damage exceed the average.

The MML model is capable of accurately fitting experimental data from clonogenic assay studies as demonstrated by previous studies [1] and my own research in the previous semester.

However, the cellular environment during irradiation in clonogenic assay studies is quite different from real tissue. As the HRS/IRR phenomenon has been shown to be present in real tissues [2], [3], [4], it is important to run simulations that better replicate real tissues.

Biomolecular signaling, which is the proposed mechanism of the MML signal, is also not the only signaling pathway present in real tissues. Gap junctions [5] also play an important role, which presents the question whether the MML model could be adapted to account for that.

Description of research carried out in the current semester

During the semester, I continued the investigation of cell density's effect on the Minimum Mutation Load (MML) model cell survival curves [1].

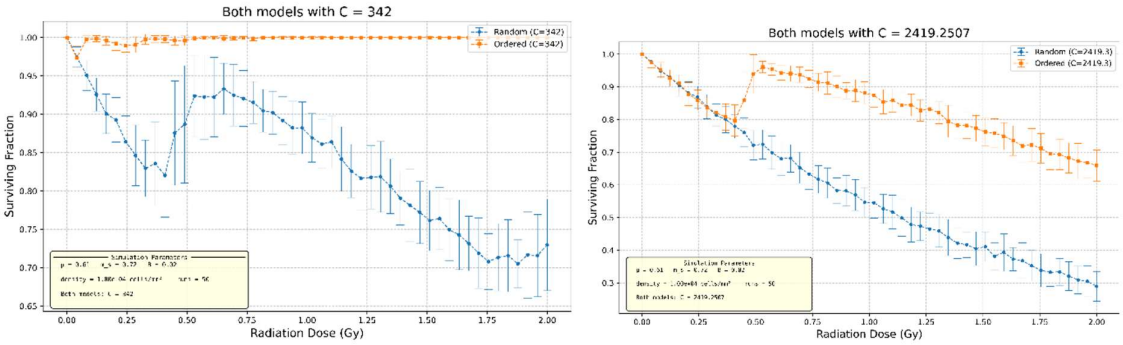
My first goal was to adapt the model to better represent a tissue-like structure, as opposed to the clonogenic assay setup used before. Cells were placed on a 2D hexagonal grid [6], representing cells like basal keratinocytes.

Cellular placement on the hexagonal grid still reproduced the survival curves of the MML model, which is to be expected as this only introduces a well-defined order of cell placement instead of the random cellular placement of previous implementations. My next task, therefore,

became the investigation of the effects of cell placement on the MML model. However, this introduced a point of biological ambiguity in the MML model. The environmental signal by which the cells decide their faith is defined as:

$$S_{biomolecule,i} = \frac{C_i}{C},$$

where C_i is signal felt by cell i from the environment, and C is a normalization factor, defined as the average signal felt by the cells, should every cell in the environment have 1 mutagenic damage. This normalization factor is both density and cell placement dependent. There is an argument to be made for this normalization factor to be kept at a fixed value across different cell placements and densities, which biologically would mean that each cell has an inherent sensitivity to this type of signal characteristic to its normal environment. Keeping the normalization fixed or adapting it to cell placement and/or density yields vastly different results.



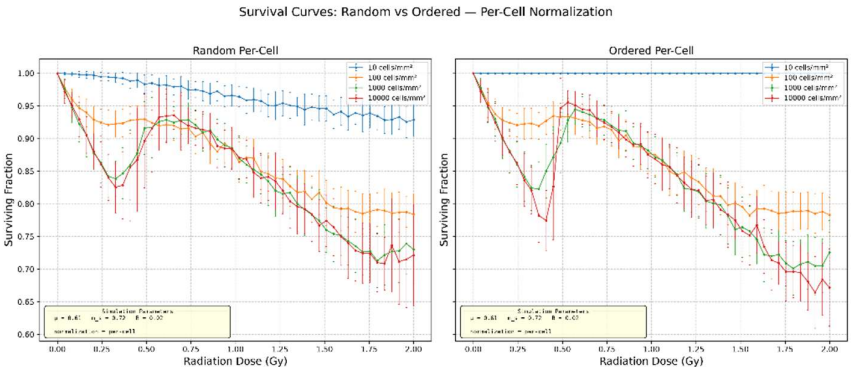
Recently, I started to work on a model change to address this ambiguity inspired by thermodynamics. As the signal detected by cells is dependent on the concentration of the signaling molecule [7] and concentration is an intensive property I redefined the signal to be evaluated as:

$$S_{biomolecule} = \frac{\sum_j G[i,j] \cdot damaga_j}{W[i]}$$

where $G[i,j]$ is the signal strength at cell i emitted from cell j and $W[i]$ is the normalization factor of cell i, where:

$$W[i] = \sum_j G[i,j]$$

This shows promising results by reproducing the survival curves of the MML model, while also eliminating the cell placement and density dependency of the model. This new normalization needs to be further investigated.



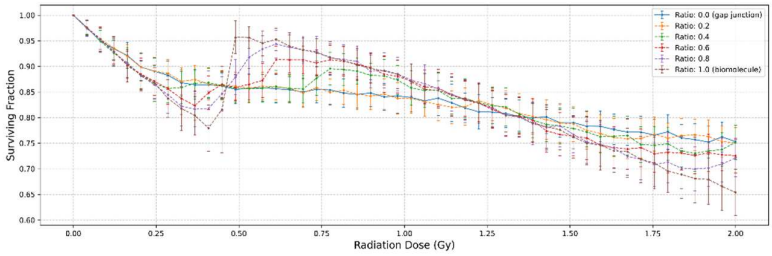
Another topic I was working on is regarding the communication pathways of intercellular signaling. In the MML model the assumption is that the damage response signal is carried by biomolecules in the intercellular environment, however cells also communicate through gap junctions [5]. Therefore, I adapted the model to represent it as well, with the following considerations:

- Cells only communicate with their immediate neighbors through gap junctions.
- Cells evaluate the average of their neighbor's damage when deciding whether to survive or commit to apoptosis

This resulted in survival curves with much less pronounced HRS minimum and IRR maximums. I then investigated the possibility of the signal being transmitted through both communication channels, with the assumption that the final evaluated signal value comes from the linear combination of the two signals

$$S = \varepsilon \cdot S_{biomolecule} + (1 - \varepsilon) \cdot S_{gap\ junction},$$

where ε is the signal contribution ratio. In the future I will be working on exploring ways to unify the two types (biomolecule, gap junction) signaling pathways.



Publications

I have one manuscript in draft to be submitted by end of August:

- Márton Juhász, Szabolcs Polgár, Balázs G. Madas *"The effects of cells density on low-dose hyper-radiosensitivity and increased radioresistance."*

Studies in current semester

During the semester, I completed the following ELTE classes:

- New results in machine learning (FIZ/3/092)
- Nuclear Environmental Protection (KÖR-2/20)

I also attended the *Interdisciplinary Radiation Research* training course between April 13-24. The first week was held online and the second in person in Munich.

Conferences in current semester

During the semester I attended the following conferences:

- IEEE Central European AI Summit (2026 March 19–21)
- HUN-REN AI Symposium (2026 May 21-22)

Other activities

- Professional activity: AI Ambassador of HUN-REN Centre for Energy Research

References

[1] S. Polgár and B. Madas, 'Minimising mutation load as a mechanism for low-dose hyper-radiosensitivity and induced radioresistance', May 16, 2025, *In Review*. doi: 10.21203/rs.3.rs-6674497/v1.

[2] J. Harney *et al.*, 'The evaluation of low dose hyper-radiosensitivity in normal human skin', *Radiother. Oncol.*, vol. 70, no. 3, pp. 319–329, Mar. 2004, doi: 10.1016/j.radonc.2004.01.015.

[3] I. Turesson *et al.*, 'A low-dose hypersensitive keratinocyte loss in response to fractionated radiotherapy is associated with growth arrest and apoptosis', *Radiother. Oncol.*, vol. 94, no. 1, pp. 90–101, Jan. 2010, doi: 10.1016/j.radonc.2009.10.007.

[4] C. Di Dio *et al.*, 'In vivo study of the radioadaptive response and low-dose hyper-radiosensitivity for chromosome breaks induced by gamma rays in wild-type Drosophila melanogaster larval neuroblasts: Dose and dose rate dependence', *PLOS One*, vol. 20, no. 6, p. e0325608, Jun. 2025, doi: 10.1371/journal.pone.0325608.

[5] S. Talukdar, L. Emdad, S. K. Das, and P. B. Fisher, 'GAP junctions: multifaceted regulators of neuronal differentiation', *Tissue Barriers*, vol. 10, no. 1, p. 1982349, Jan. 2022, doi: 10.1080/21688370.2021.1982349.

[6] D. L. Chao, J. T. Eck, D. E. Brash, C. C. Maley, and E. G. Luebeck, 'Preneoplastic lesion growth driven by the death of adjacent normal stem cells', *Proc. Natl. Acad. Sci.*, vol. 105, no. 39, pp. 15034–15039, Sep. 2008, doi: 10.1073/pnas.0802211105.

[7] M. S. Salahudeen and P. S. Nishtala, 'An overview of pharmacodynamic modelling, ligand-binding approach and its application in clinical practice', *Saudi Pharm. J.*, vol. 25, no. 2, pp. 165–175, Feb. 2017, doi: 10.1016/j.jsps.2016.07.002.