



HAL
open science

Monte-Carlo modeling of intratumoral radionuclide distribution in TAT: comparison to experiment

Victor Levrage, Mario Alcocer-Ávila, Etienne Testa, Michaël Beuve, R. Delorme

► **To cite this version:**

Victor Levrage, Mario Alcocer-Ávila, Etienne Testa, Michaël Beuve, R. Delorme. Monte-Carlo modeling of intratumoral radionuclide distribution in TAT: comparison to experiment. 20th International Conference on the use of Computers in Radiation Therapy (ICCR), Jul 2024, Lyon, France. hal-04775900

HAL Id: hal-04775900

<https://hal.science/hal-04775900v1>

Submitted on 10 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Monte-Carlo modeling of intratumoral radionuclide distribution in TAT: comparison to experiment

Victor Levrague¹, Mario Alcocer-Ávila², Etienne Testa², Michaël Beuve², and Rachel Delorme¹

¹Univ. Grenoble Alpes, CNRS, Grenoble INP, LPSC-IN2P3, 38000 Grenoble, France

²IP2I, Université Claude Bernard Lyon 1, CNRS/IN2P3, 4 rue Enrico Fermi, 69622 Villeurbanne Cedex, France

Abstract In the context of predicting biological effects in Targeted Alpha Therapy, nano- and micro-dosimetry are essential because of the very heterogeneous dose deposition at cell level.

The NanOx [1] biophysical model has been developed and adapted to predict cell survivals to low energy ion irradiations. Combining CPOP to create complex spheroidal multicellular geometries and Geant4 to perform Monte-Carlo simulations, cell survivals can be calculated through NanOx algorithm for a given irradiation condition. This study's objectives are to investigate the impact of intratumoral radionuclide heterogeneities on mean cell survivals with our biophysical modeling chain, and to compare the results with the *in vitro* experiment of Neti et al. [2] and results obtained via the MIRDCell [3] tool.

The impact of a lognormal law on the initial activity per labeled cell, with varying shape factor, was evaluated, as well as the percentage of radiolabeled cells.

At 1% cell labeling, both MIRDCell and our model overestimate with several orders of magnitude cell survivals from the experiment. For 10% and 100% labeling, our simulation pipeline gave predictions with up to 0.89 R^2 for lognormal distributions.

This study highlights the consistency of our model's predictions with those of MIRDCell and the importance of considering realistic radionuclide distributions in calculations. However it also highlights the difficulty in reproducing as faithfully as possible experiments with limited controlled parameters.

1 Introduction

Targeted Alpha Therapy (TAT) is an emerging therapy, to treat localized cancers. It benefits from the short range of alpha particles emitted by specific alpha-emitter radionuclides, that are fixed to cancer sites with a biochemical vectors. Its recent rise is due to the improvements made in tumor targeting [4]. Being able to provide accurate dosimetry and predict part of the treatment efficacy would help clinicians in assessing the required injected activity for a patient. However, the short range of alpha particles (<100 μm , equivalent to a few cells) induces heterogeneity of dose deposition at the micrometric scale. A macroscopic dose would not be enough to predict cell survivals at the tumor scale.

Biophysical models, in the litterature, developed to calculate cell survivals to ion irradiation from nano and/or micro-dosimetry are validated for energies of hadrontherapy ($\sim 50\text{-}200$ MeV/n). Experimental data are scarce to parameterize and validate the biophysical model's predictions at the few MeV of TAT. To that aim, we are currently adapting the NanOx biophysical model [1] to such low energies. Formalism and its hypotheses were previously described, and prediction results were compared to those of the previous

formalism used for hadrontherapy applications to ensure auto-consistency and extension of the model's capabilities (article in submission process). In another study, we have explored the impact of intracellular distribution of radionuclides in TAT on several indexes like the nucleus physical dose or the Tumor Control Probability (article also in submission process). These studies were performed with a uniform intratumoral radionuclide distribution. This does not represent the variety of experimental cases. Moreover, there is a need for the biophysical model to be strengthened by experimental validations. The present study is dedicated to the comparison with the Neti et al. [2] experiment, that was chosen because their experimental parameters are given and controlled enough to be reproducible by simulation. The main objective of this study is to explore the impact of intratumoral distribution in TAT outcome predictions, and to compare the results with measures from the literature. Results will also be compared with the MIRDCell analytical-MC tool [3].

2 Materials and Methods

2.1 Multicellular irradiations

The multicellular irradiations were performed with CPOP [5]. CPOP is a layer on top of the Monte Carlo (MC) code Geant4, that allows the generation of complex multicellular geometries in which the particle tracking occurs. Due to its ability to allow flexible cell size and membrane deformation, compacted geometries can be used to reproduce as much as possible the different compaction level observed in *in vitro* or *in vivo* experiments.

Different degrees of intratumoral heterogeneity were considered in this study. Firstly, the percentage of radiolabeled cells was varied as 100%, 10% or 1%, meaning that only those cells contain alpha-emitter radionuclides. Secondly, the distribution of the initial activity per labeled cell (i.e. the number of alpha emitters) was investigated from a uniform to a lognormal law. Studies like Pasternack *et al.* [6] showed the importance of taking into account this type of distribution, to evaluate cell survivals. A lognormal law can be described with the mean activity per cell, and the shape parameter σ .

2.2 Cell survival calculations

Cell survival was chosen as the biological index in this study, due to the current knowledge on it and the model's abilities. The NanOx biophysical model was used to compute the cell survivals. This model has been developed for hadrontherapy applications, validated by comparison against experimental data and benchmarked to other biophysical models [1]. NanOx (like the other biophysical models) considers that only damage in a cell nucleus can induce cell death. A modified version of the NanOx formalism was used in this paper, to take into account the energy loss of ions in cell nuclei. This formalism relies on two main approximations, namely the "narrow track" and "charge equilibrium" approximations. The first one means that the secondary electrons emitted by ions are concentrated along the ion's trajectory at distances lower than 100 nm. Their tracking is therefore not required in the MC simulations. With the "charge equilibrium" approximation, all the energy transferred by the ion in the cell nucleus is deposited in it.

In MC simulations, any time an ion crosses a cell nucleus with an entrance energy E_i and an exit energy E_f , this can be converted into damage to the cell. These damage can be either lethal n_L , at the nanometer scale, or sublethal n_{SL} at the micrometric scale. Cell survival S is calculated as follows:

$$S = \exp(-n_L - n_{SL}) \quad (1)$$

2.3 Comparison to experimental data

In the experiment performed by Neti *et al.* [2], multicellular clusters of chinese hamster V79 lung fibroblast cells were created, by centrifugation. A defined percentage of cells were labeled with Po-210, a radionuclide that mainly emits a 5.3 MeV alpha particle. Clusters were made of millions of cells. For computing time and memory purposes, the cluster size has been reduced to 100 μm spheroid radius. According to the data given in the paper, the compaction level was $\sim 47\%$, and $\sim 22\%$ of radionuclides were internalized in nucleus, the rest remaining in the cytoplasm.

During the experiment, cells were irradiated in the centrifugation tube. The choice was made in this study to use a spheroidal geometry, to model a part of the cluster in the tube.

Three timelines could be defined: the activity uptake (0.5 h), the cluster maintenance (72 h) and the colony formation (96 h). Cells were maintained at a temperature that allowed them to stay in a cluster arrangement up to 72 h, without declining their ability to clone themselves [2]. After 72 h, cells were washed. As a result, radionuclides decays were supposed to be mainly happening during the cluster maintenance.

The parameters described in this paragraph were used for the following simulations. For 100, 10 and 1% cell labeling, the maximum activity per labeled cell were 0.1, 1 and 24 mBq. The default shape parameter of 2.0 for the lognormal

distribution was used to follow the recommendations of [3], and different values will be tested to investigate different distributions. The cell survivals were also compared with results obtained via the MIRDcell tool [3], with the same parameters. To compare our work to the results published in Neti *et al.*, a R^2 test for goodness of fit was performed, on logarithmic cell survivals.

2.4 Studied data and parameters

The different data in this study are the measures from Neti *et al.*, the calculations performed with MIRDCell and the ones from the CPOP - Geant4 - NanOx model (CGN). Simulation results will be compared between themselves, and against the experimental data. The studied parameters will be: the percentage of cell labeling, the type of activity distribution in cells (between uniform and lognormal), and the shape factor of a lognormal distribution. Results will be presented as a function of the mean injected activity per cell, calculated for a time of 94h. When the cluster activity is calculated, simulated activities are normalized to scale from the 2480 cells modeled to the $4 \cdot 10^6$ cells in the experiment.

3 Results

3.1 Impact of the distributions of initial activity per cell

Figure 1 shows the mean cell survival as a function of the mean initial activity per cell, with 10% cells radiolabeled. Are presented the experimental data from Neti *et al.*, and the prediction of our CGN model with an uniform and lognormal distribution of activity per cell. The measured mean cell survival is a fit given by the authors for their data. The shape factor (σ) of the lognormal law varied between 0.5 and 2.0. For a 2.0 lognormal shape factor, the CGN model overestimates cell survivals by up to 4 times higher than the experimental data. The lognormal distribution with σ equal to 1 stay within 2.5 times the cell survivals from the uniform distribution, ~ 10 times lower than the lognormal with $\sigma = 2.0$.

For the 0.5, 1 and 2.0 shape factor, the R^2 , compared to the experimental data, are respectively equal to 0.55, 0.89 and 0.23. It is equal to 0.44 for the uniform distribution.

Figure 2 represents the mean cell survival as a function of the mean activity per cell, with 100% of cells labeled with radionuclides. With MIRDcell and our CGN model, results with both uniform and lognormal radionuclide distribution are presented. Results are presented with a 2σ error, for the rest of the study.

In this logarithmic representation, the experimental mean cell survival in the Neti experiment follows a linear law with a slope of ~ -0.993 , and starts to "saturate" with increasing cell activity.

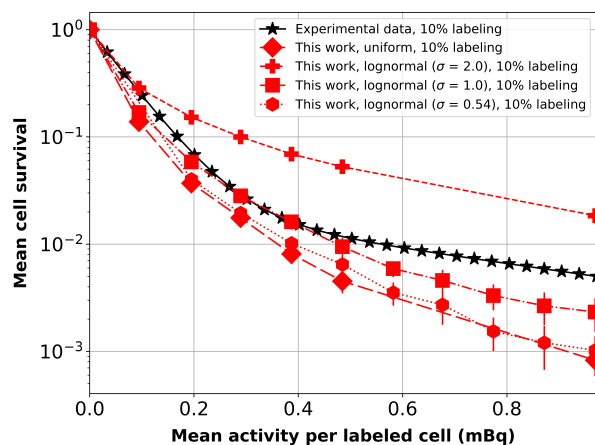


Figure 1: Mean cell survival calculated as a function of the mean activity in each cell, with 10% cells radiolabeled. Experimental data from Neti *et al.* [2] are in stars (solid line). Data calculated with the CGN model distributed via a lognormal law with a shape factor of 2.0, 1.0 and 0.54 are, respectively in plus signs (dashed), squares (dashdotted), hexagons (dotted). The simulations with a uniform distribution are in diamonds, with long dashes.

For lognormal distributions, MIRDcell mean survivals are 2 to 6 times higher than survivals from the CGN model. For both models (MIRDcell and CGN), applying a lognormal distribution to the number of radionuclides in cells, increases the cell survival. For example, for the CGN results, differences can go from 10-fold differences at 0.015 mBq per cell to more than 100-fold above 0.030 mBq per cell. For the CGN results, the R^2 , compared to measured data, are 0.28 (lognormal distribution), and -47.6 (uniform distribution). For MIRDcell, R^2 are 0.78 (lognormal distribution), and -17.8 (uniform distribution)

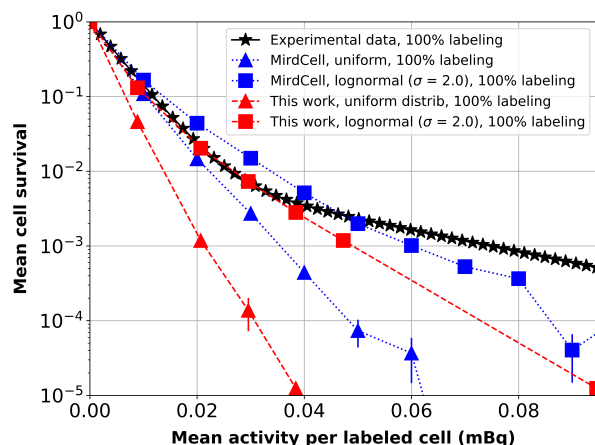


Figure 2: Mean cell survival calculated as a function of the mean activity in each cell, with all cells labeled with radionuclides. Experimental data from Neti *et al.* [2] are in stars (solid line). Simulation data with a uniform distribution are in triangle, those with a lognormal one are in squares. MIRDcell data are plotted in dotted lines, and CGN in dashed lines.

3.2 Impact of the percentage of cell labeling

Figure 3 shows the mean cell survival as a function as the total cluster activity in kBq.

For the same total cluster activity, cell survival differences range from ~ 2 at 0.04 kBq to 10-folds at 0.39 kBq. The lower the % of radiolabeling, the higher the mean cell survival. In the experimental data, survivals at 1 and 10% cell labeling are similar. For MIRDcell and CGN, differences can go up 20-fold.

Looking at the 1% cell radiolabeling, the R^2 , compared to experimental data, with MIRDcell are -4.61 (lognormal distribution) and -3.63 (uniform distribution). With NanOx, they are -4.47 (lognormal distribution) and -3.51 (uniform distribution).

The minimum of mean cell survival obtained with our model is 0.183 ± 0.007 . For the Neti experiment, the minimum is equal to $1.7 \cdot 10^{-4}$, for the same activity per labeled cell.

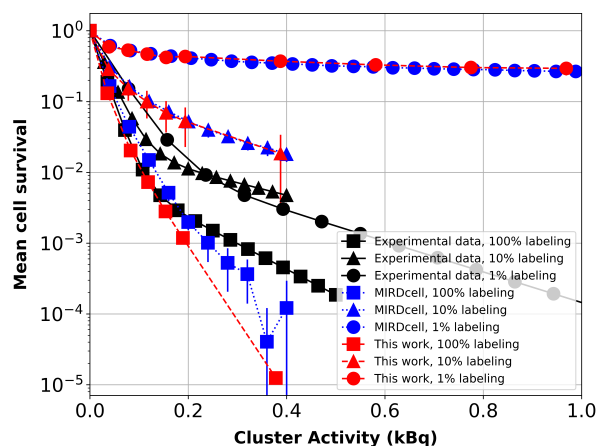


Figure 3: Mean cell survivals as a function of the total cluster activity (kBq). The measures from Neti *et al.* (solid lines), and calculations performed with the MIRDcell (dotted lines) and CGN (dashed lines) are presented. All calculations were done with a lognormal distribution on the number of radionuclides per labeled cell, with a shape factor of 2.0. Neti *et al.* data are a fit given by the authors on their experimental data. Data at 100, 10 and 1% cell labeling are, respectively, in squares, triangles and circles.

4 Discussion

This study confirms that applying a lognormal distribution seems to have a major impact in cell survivals assessment, as previously shown in the literature. A lognormal distribution could be creating some areas with lower radionuclide concentration. Even though, alpha particles can cross $\sim 40 \mu\text{m}$, it is not enough to irradiate entirely a cluster of $100 \mu\text{m}$ radius. Under the activities observed, there is never a complete saturation because the emptier areas will eventually get irradiated by fixed radionuclides in this area or nearby, if a majority of cells are radiolabeled.

The shape parameter of a lognormal law can be defined as potential variations allowed for the distribution. When it tends towards zero, the distribution becomes closer to an uniform one and cell survivals get lower, as observed in Figure 1 and confirmed by experiments in the literature [6]. To model *in vitro* experiments, it appears mandatory to have measured the shape factor beforehand to set up the simulations with a lognormal distribution on the number of radionuclide per labeled cell. Considering only an uniform distribution of radionuclides could explain an overkilling in cell predictions.

The lower cell survivals when a lognormal law is applied can be associated to an overkill effect. Adding more radionuclides to a cell zone that is already mostly dead will not have an important effect on cell killing. The untouched cells will keep increasing the mean cell survival.

Results between MIRDcell and our model have similar orders of magnitude. The differences can be explained with the NanOx being closer to the physical reality. In particular, the (α, β) coefficients for cell survival calculations are constant in MIRDcell, while varying as a function of the energy in NanOx. Furthermore, the NanOx model was built to be flexible and easily enhanced.

At 100% cell labeling, according to the R^2 goodness of fit test, the simulations with a lognormal distribution at $\sigma = 2.0$ are fitting better the experimental data. The negative R^2 from the uniform distribution means that the prediction is worse than using the average horizontal value. Except for MIRDcell under 0.05 mBq per cell, models tend to overestimate cell death. Especially, the saturation of cell survivals in the Neti et al. experiment is not well reproduced, and the explanation is not straightforward. Several hypotheses are under investigation like cellular protection could be happening, as well as reparation effects.

To explain why cell survivals at 1% radiobeling are off the charts compared to Neti et al. experiments, regardless of the model used, multiple paths are guessed. Firstly, as pointed in the reference article [2], bystander could be a non-considered effect that increases cell death. Adding bystander damage to the model is an option to understand if this path is enough to explain the differences. Secondly, experimental uncertainties not taken into account in this paper could induce some deviations. For example, radionuclides could diffuse in the cluster and alpha particles emitted could hit more cells than in our simulations.

The saturation in our simulations could be explained by a geometric effect, where all cells that could be hit by helium ions are already dead, and increasing the dose would only kill those already dead cells. Moreover, the washes made to remove radionuclides from cells could not be optimal and cells could be still irradiated during the clonogenic assays,

which this study doesn't take into account.

The Geant4 simulations were performed only in spheroid configurations. But, in the Neti et al. experiment, the geometry changes after 72 h, with cells still being irradiated. The impact of this geometry change has yet to be evaluated.

The effect of the percentage of radiolabeling heterogeneity, major in our simulations, is slim between the 10 and 1% Neti et al. experiments, although significantly different at 100% labeling. A comprehensive study of the impact of this type of heterogeneity on cell survivals or other physical and biological indexes will be done in the future.

This study underlines the difficulty of working with experimental data of low energy ion irradiation. Even with the multitude of controlled parameters in the Neti et al. experiment, many uncertainties restrain the perfect reproduction of it. However, the flexibility of our simulation pipeline allows the user to adapt to many complex irradiation configurations.

5 Conclusion

This ongoing study is a first validation step of the CGN pipeline for TAT. To model and predict properly *in vitro* experiments, one has to consider the intratumoral distribution of radionuclides in cells and, at best, to have it first measured depending on the vector. On top of that, knowing the ability for the targeting vector to fix to cells, i.e. the percentage of radiolabeling is mandatory to avoid errors up to several orders of magnitude.

The results given by our pipeline, using an intratumoral distribution of radionuclides is promising, although gaps have to be overcome, like the lack of saturation in our cell survivals for high radiolabeling and the severe underkilling at low radiolabeling.

References

- [1] C. Monini, G. Alphonse, C. Rodriguez-Lafrasse, et al. "Comparison of biophysical models with experimental data for three cell lines in response to irradiation with monoenergetic ions". *Physics and Imaging in Radiation Oncology* 12 (Oct. 2019), pp. 17–21.
- [2] P. V. S. V. Neti and R. W. Howell. "Biological response to nonuniform distributions of ^{210}Po in multicellular clusters". *Radiation research* 168.3 (2007), pp. 332–340.
- [3] S. Katugampola, J. Wang, A. Rosen, et al. "MIRD Pamphlet No. 27: MIRDcell V3, a revised software tool for multicellular dosimetry and bioeffect modeling". *Journal of Nuclear Medicine* 63.9 (2022), pp. 1441–1449.
- [4] A.-M. Tsimberidou. "Targeted therapy in cancer". *Cancer chemotherapy and pharmacology* 76.6 (2015). Publisher: Springer, pp. 1113–1132.
- [5] L. Maigne, A. Delsol, G. Fois, et al. "CPOP: An open source C++ cell POPulation modeler for radiation biology applications". *en. Physica Medica* 89 (Sept. 2021), pp. 41–50.
- [6] J. B. Pasternack, J. D. Domogauer, A. Khullar, et al. "The advantage of antibody cocktails for targeted alpha therapy depends on specific activity". *Journal of Nuclear Medicine* 55.12 (2014). Publisher: Soc Nuclear Med, pp. 2012–2019.