Istituto Nazionale di Fisica Nucleare
LABORATORI NAZIONALI DI LEGNARO

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Laboratori Nazionali di Legnaro – INFN

WP4 - Updates on cellular dosimetry models and simulations

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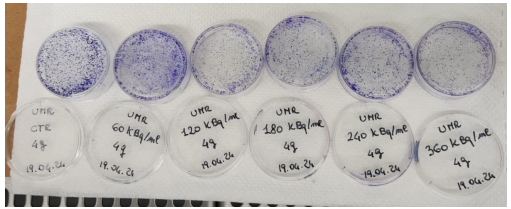
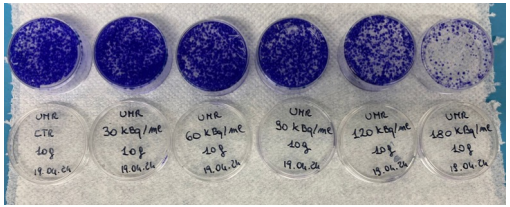
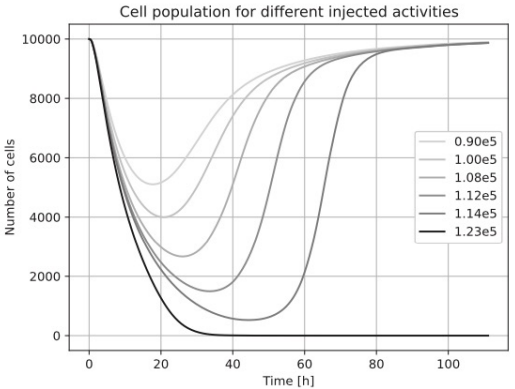
OUTLINE

- ***In vitro* experiment**
  - GEANT4 predictions
  - Codes comparison
  - Experiment preparation



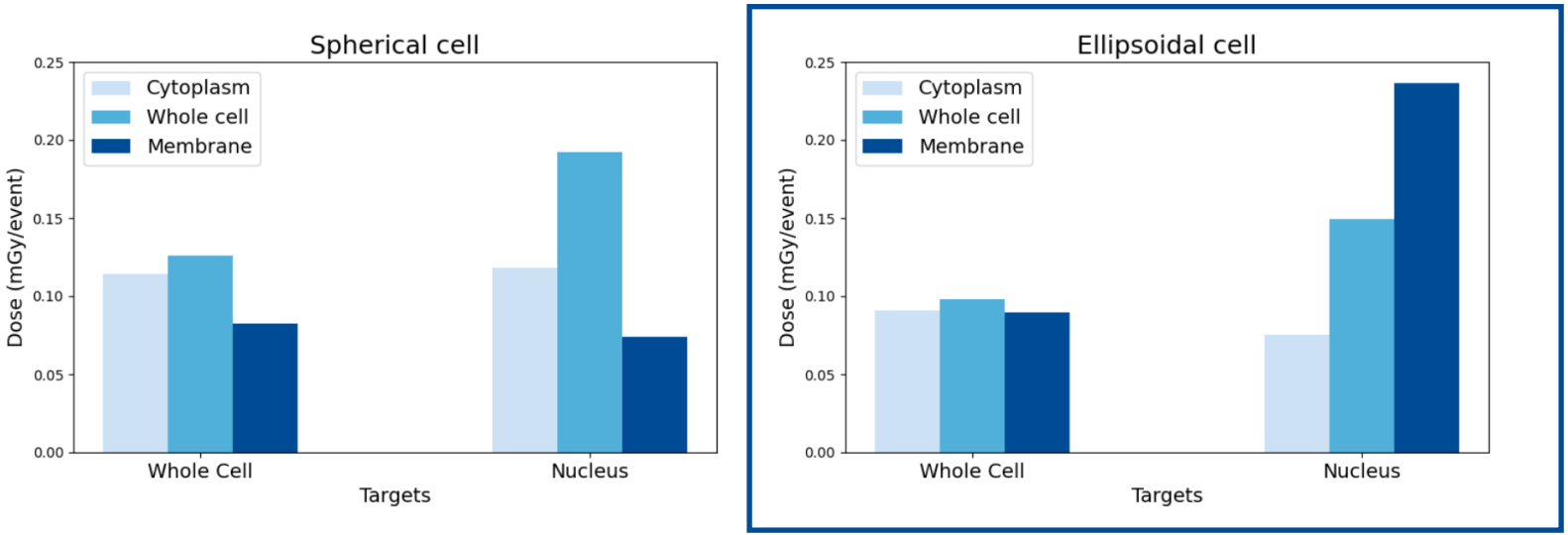


- **Model validation**
  - The model: motivation and assumptions
  - Data and Geant4-DNA predictions
  - Model validation
  - Future applications



In vitro experiment

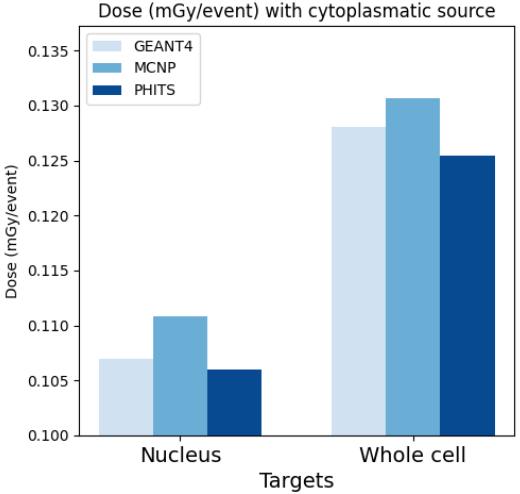
GEANT4 PREDICTIONS

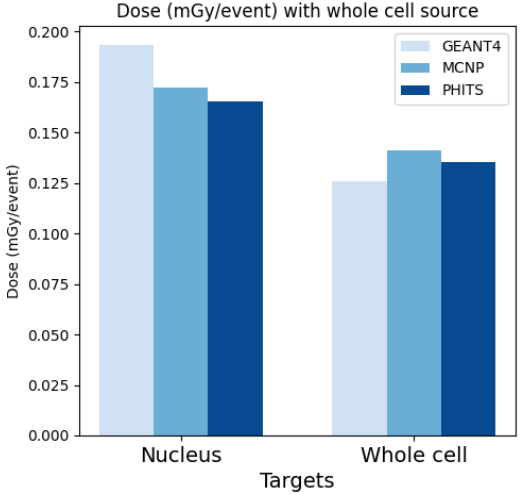


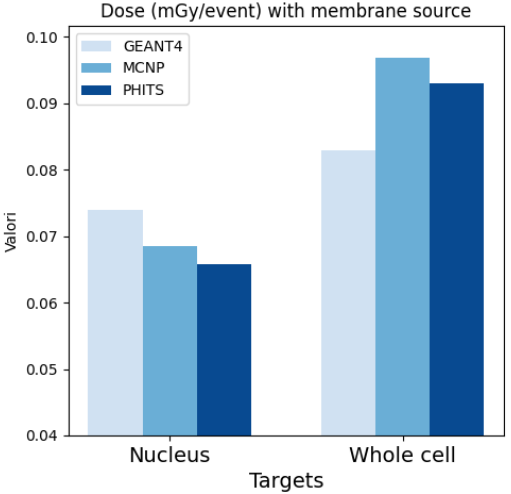
From Emma Reniero's Master thesis

The chosen configuration is the **ellipsoidal** one. In this geometry, the membrane source distribution gives the highest absorbed dose in the nucleus.

CODES COMPARISON



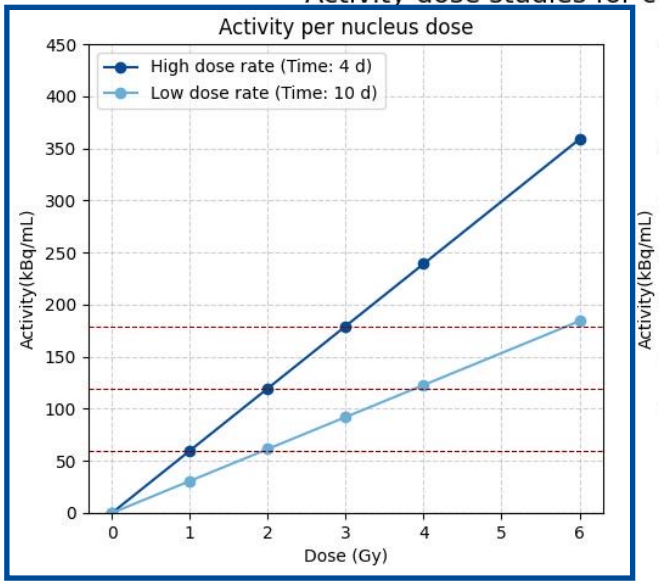


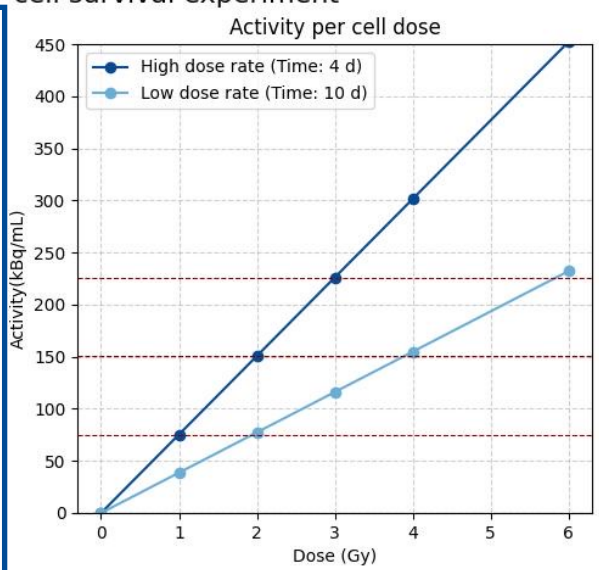


- The 3 MC codes give compatible results;
- Uncertainty lower than 5%.

EXPERIMENT PREPARATION

Activity-dose studies for cell survival experiment





- 2 dose rates;
- 5 different injected doses;
- 3 petri dishes for each dose.

→

Some doses are the same for the 2 dose rates

Model validation

THE MODEL: motivation

External beam radiotherapy

1. Dose rate per cell not dependent on cell population.
2. Uniform radiation cycles.
3. Exposure time shorter than biological processes.

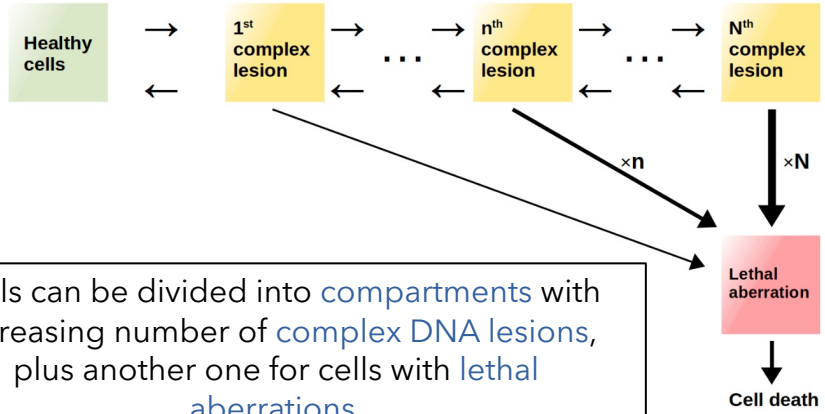
➢ Cell survival as a function of absorbed dose.

Targeted radionuclide therapy

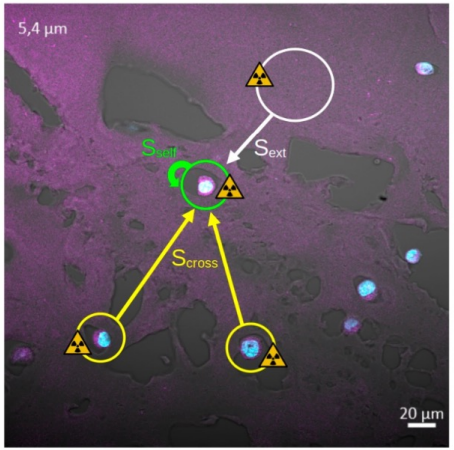
1. Dose rate per cell dependent on the amount of cell receptors.
2. Radiation decays in time.
3. Exposure time comparable with biological processes.

➢ Time-resolved cell survival and dose rate.

THE MODEL: assumptions



Cells can be divided into compartments with increasing number of complex DNA lesions, plus another one for cells with lethal aberrations.
Undamaged cells can reproduce.



- z_n: cells with n complex lesions, each one with repair rate ρ;
- Repair implies recovery of lethal aberration with probabilities $\mathbf{k_r + k_a = 1}$;
- Aberrant cells z_a die with rate η.

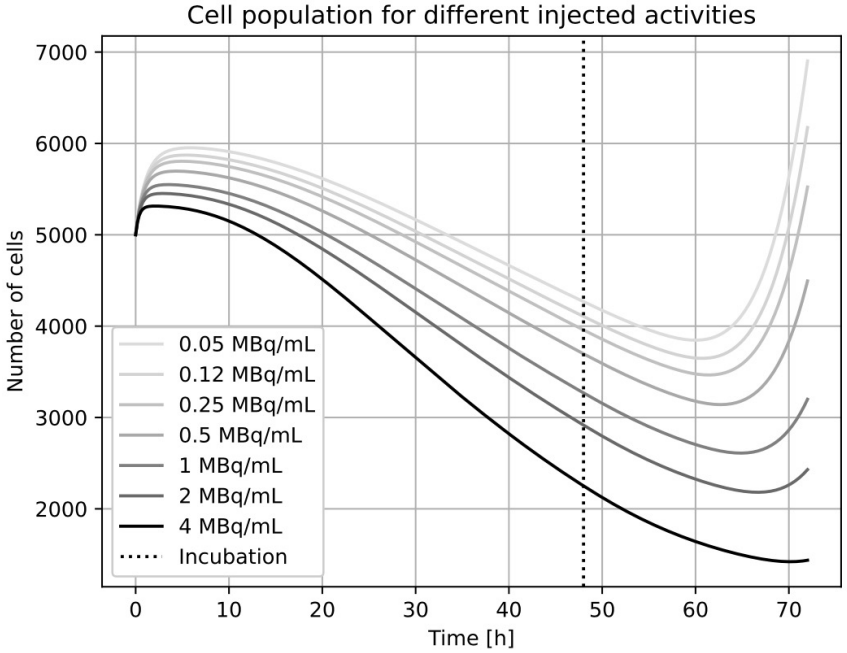
DNA damage will have 3 components:

- Self-absorbed;
- Crossfire;
- Culture medium.

DATA PREDICTION

Ref.: joint measurement of **clonogenic survival** and **uptake** using ^{125}I-loaded antibodies [Pouget et al. (2008)].

- A-431 and SK-OV-3 cells irradiated for 48 h.
- Model curve minimum (minus the aberrating cells at the same time) associated to the surviving fraction.

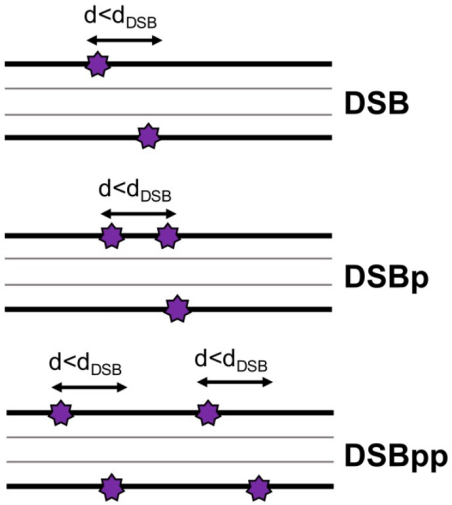


GEANT4-DNA PREDICTIONS

The δ parameter in the model represents the number of lesions per dose unit.

$\delta = (9.7 \pm 0.9)\ \mathrm{Gy}^{-1}$

Estimated by running 10^5 decay events of ^{125}I in a simplified ellipsoidal human cell geometry and counting DSB+ and DSB++.



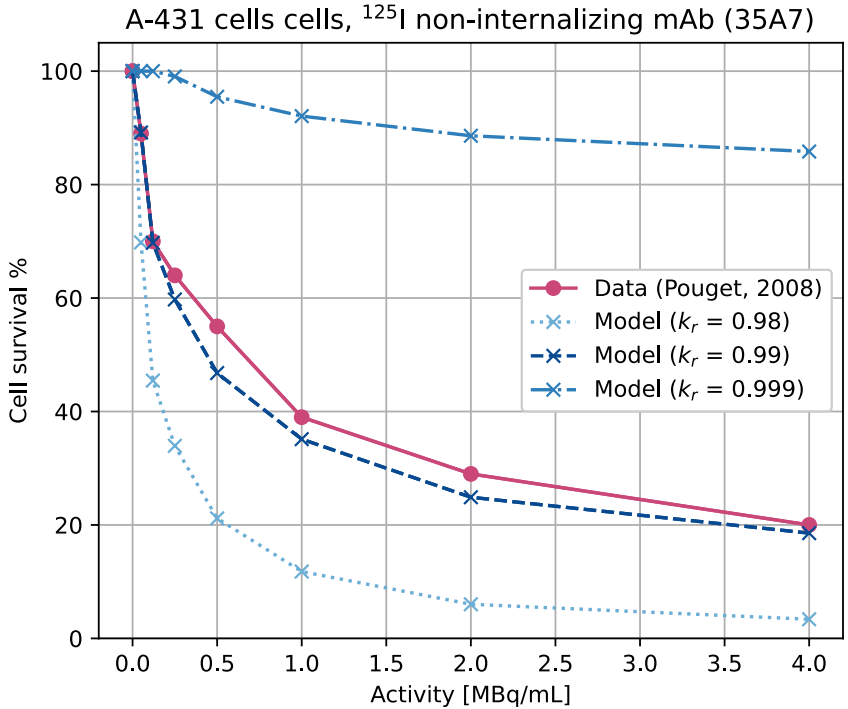
- **DSB+**: at least one DSB and an additional lesion within d_{dsb} = 10 bp;
- **DSB++**: at least two DSBs within 100 bp.

The algorithm of the **moleculardna** example was used. [Chatzipapas et al. (2023); Sakata et al. (2020)]

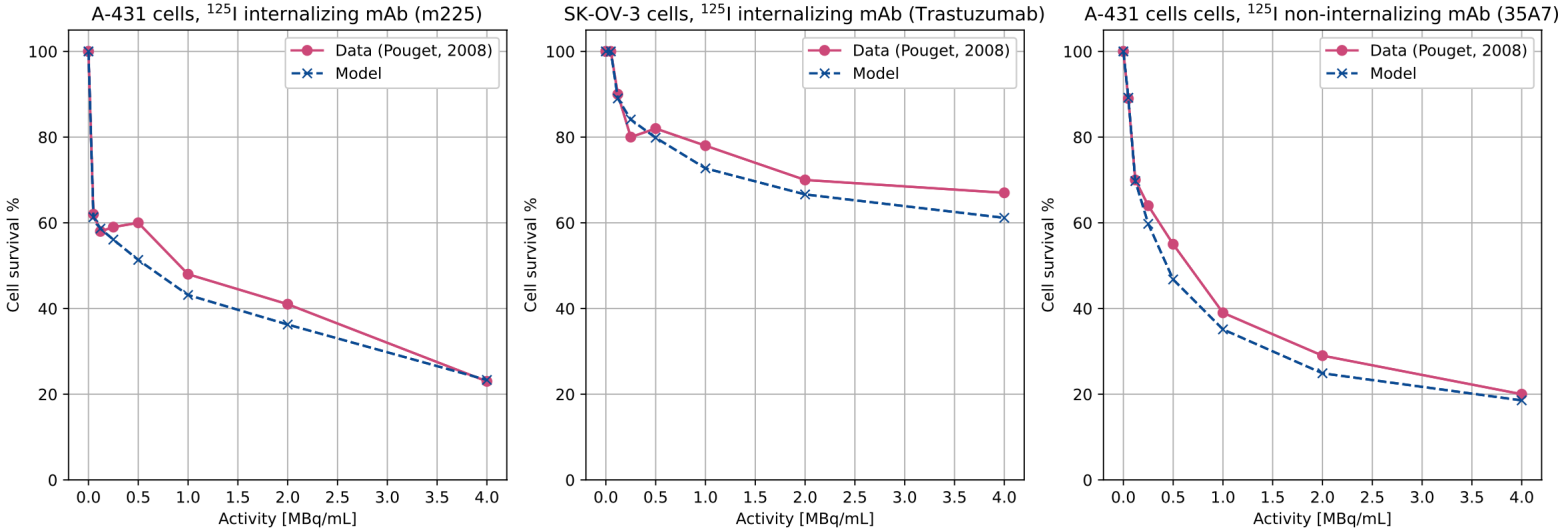
MODEL VALIDATION: k_r variation

- The model was applied considering the parameters given in the article.
- δ was chosen as described in the previous slide.
- $\mathbf{k_r}$ (i.e. the correct repair probability of a damage) is varied in order to get the best agreement between model outcomes and data.

  The slope of the model curve is very sensitive to slight variations of k_r.



MODEL VALIDATION



- **kr = 0.99** reproduced the measured slopes.
- Discrepancies < 10%.

FUTURE APPLICATIONS

- In July more dose points will be added to the high dose rate (4 days) test.
  - **Which dose points will we consider?**
- In September the low dose rate (10 days) test will be redone due to the overpopulation of cells observed in the latest experiment. Moreover, a clonogenic assay will be performed.

- Validate the model with ^{111}Ag
- Study the possible effect of low-dose hyper-radiosensitivity on ρ and k_r.

Thank you for your kind attention