Geant4 image-based cellular dosimetry for in-vitro Ag-111-irradiated LNCaP cells within the ISOLPHARM project

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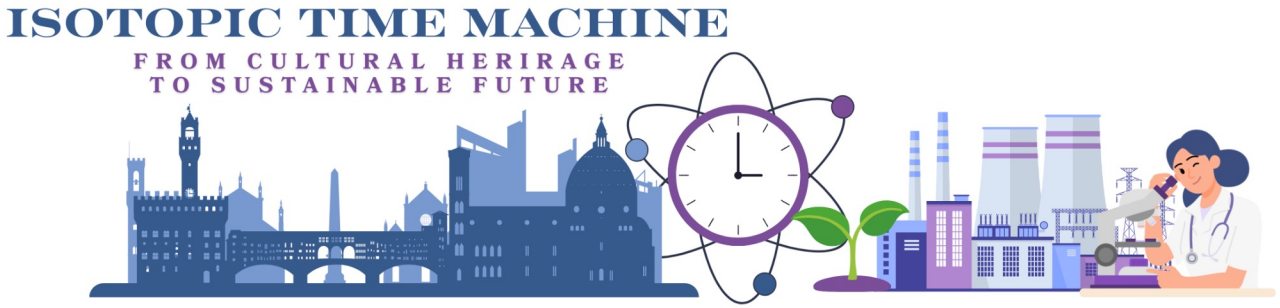

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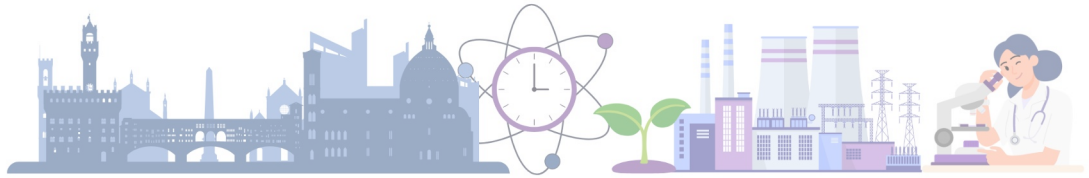

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- The ISOLPHARM project
- Motivation of the study
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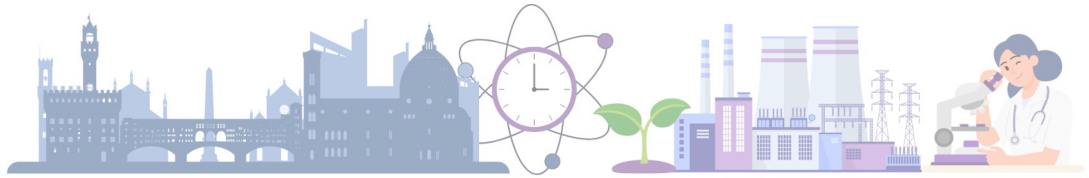
- Results
- Conclusions and future perspectives



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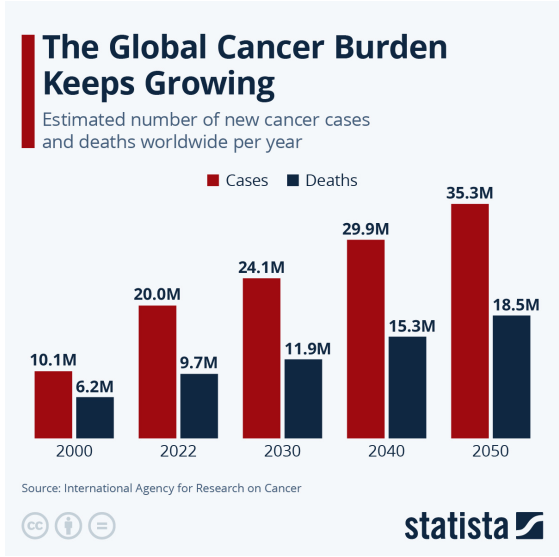
Targeted Radionuclide Therapy



- **Cancers** are the **second cause of death** after cardiovascular diseases

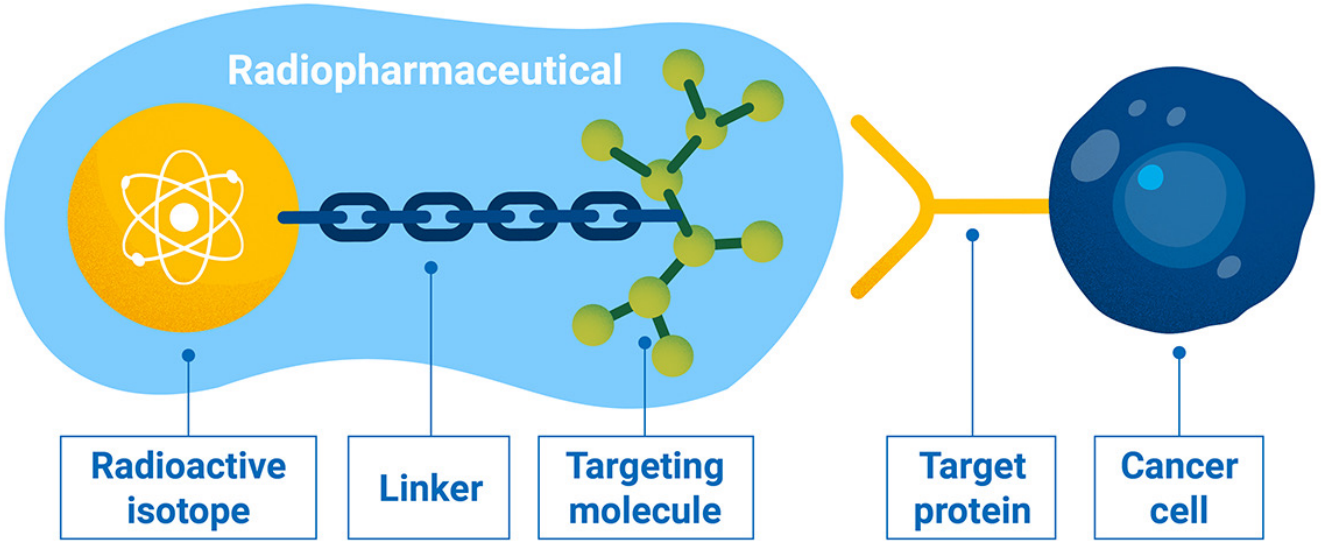
- There are many types of cancer treatment. One of them, **Targeted Radionuclide Therapy (TRNT)** is emerging as a promising approach

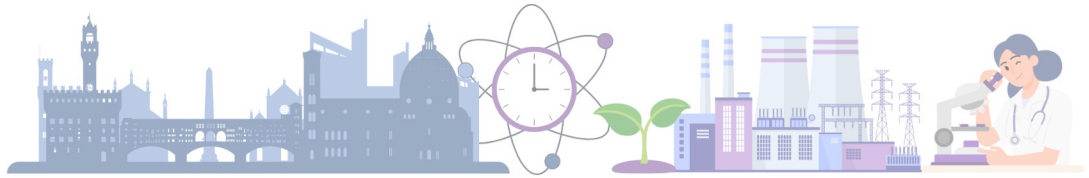
- TRNT employs a **systemic treatment using tumor type-specific biologic vectors labeled with a radionuclide** to treat cancerous cells, especially metastases and disseminated tumor cells that cannot be treated by External Beam Radiotherapy (EBRT)

Radiopharmaceuticals

- **Radiopharmaceuticals (RPs),** or medicinal radiocompounds, are a group of **pharmaceutical drugs containing radioactive isotopes** used in TRNT and as diagnostic agents.

- In therapeutic RPs, high-energy types of radiation with short range in tissue, such as alpha or beta particles, **destroy or weaken unwanted cells or tissues**, like tumours or overactive thyroid cells.





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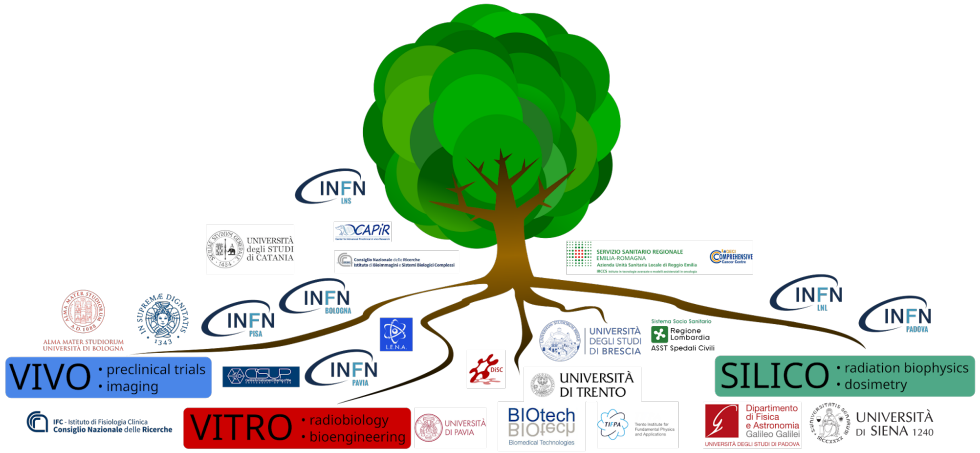
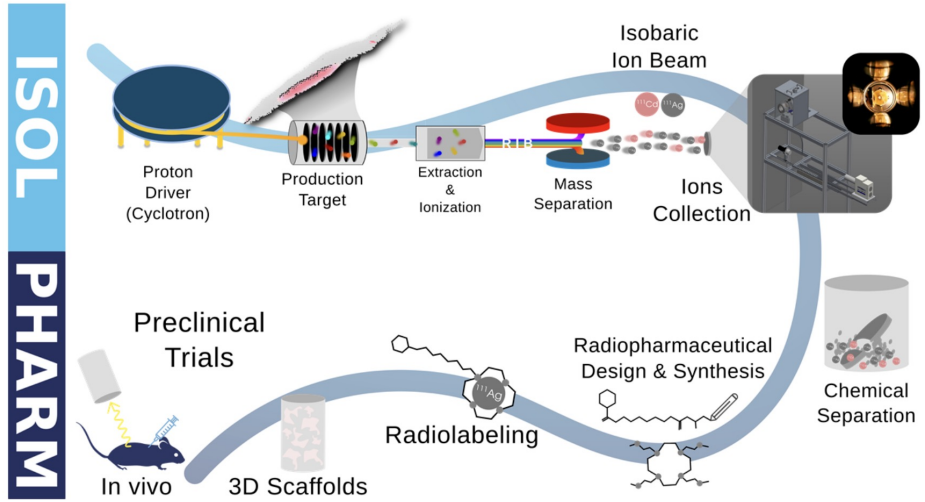
The ISOLPHARM project

- **ISOLPHARM** aims to develop **innovative RPs using nuclides produced via Isotope Separation OnLine (ISOL)** in the Selective Production of Exotic Species (SPES) facility, under commissioning at the Legnaro National Laboratories of the National Institute for Nuclear Physics (LNL-INFN)

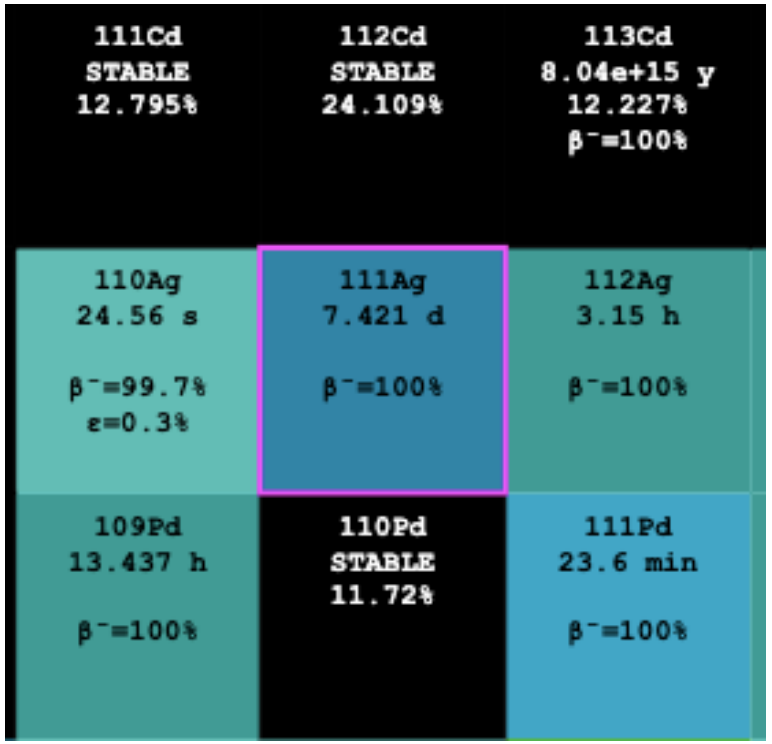
ISOLPHARM
SPES exotic beams for medicine

INFN
Istituto Nazionale di Fisica Nucleare



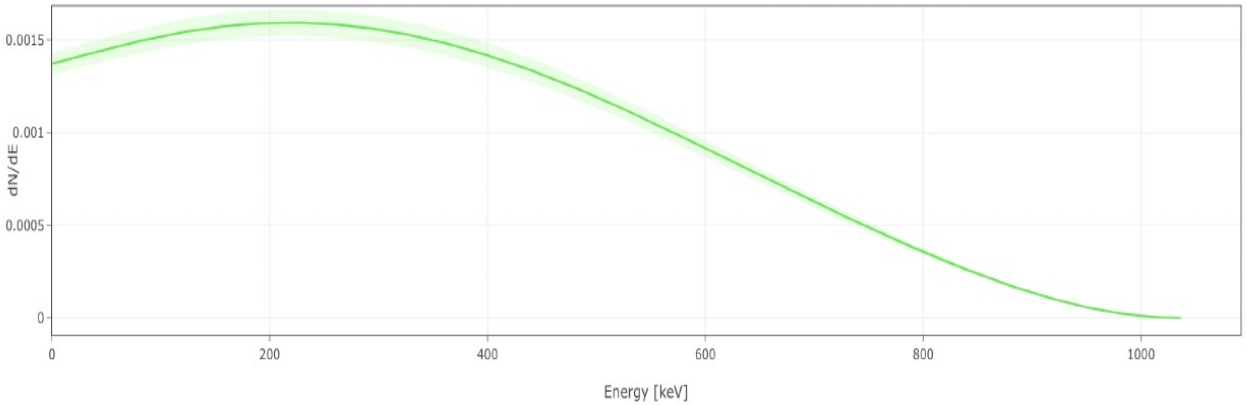


An innovative radionuclide: Ag-111



- **Ag-111** has several attractive properties for nuclear medical purposes

➢ $E_{\beta^-} = 360$ keV
➢ $E_\gamma = 245.40$ keV and 342.13 keV
➢ $t_{1/2} = 7.4$ days



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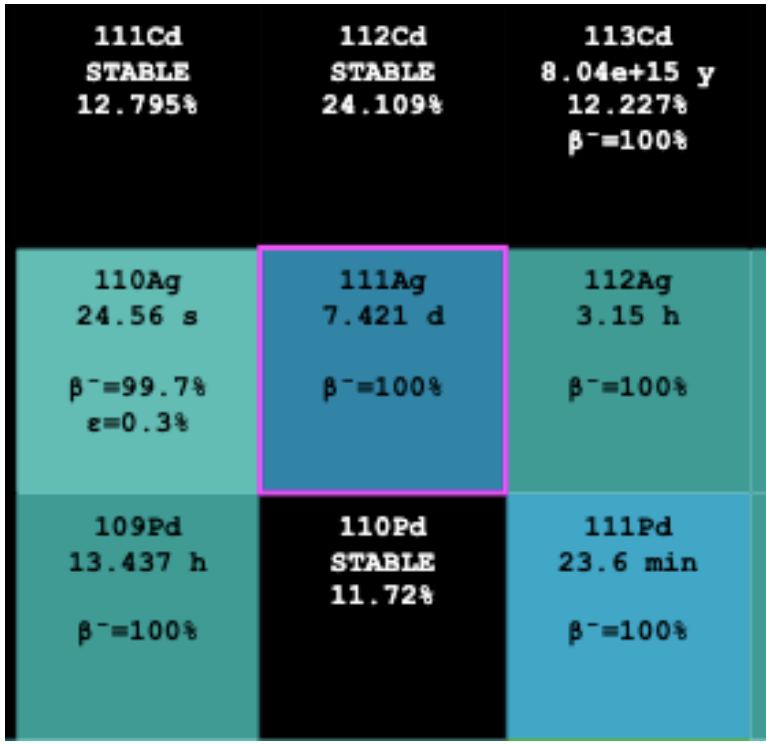
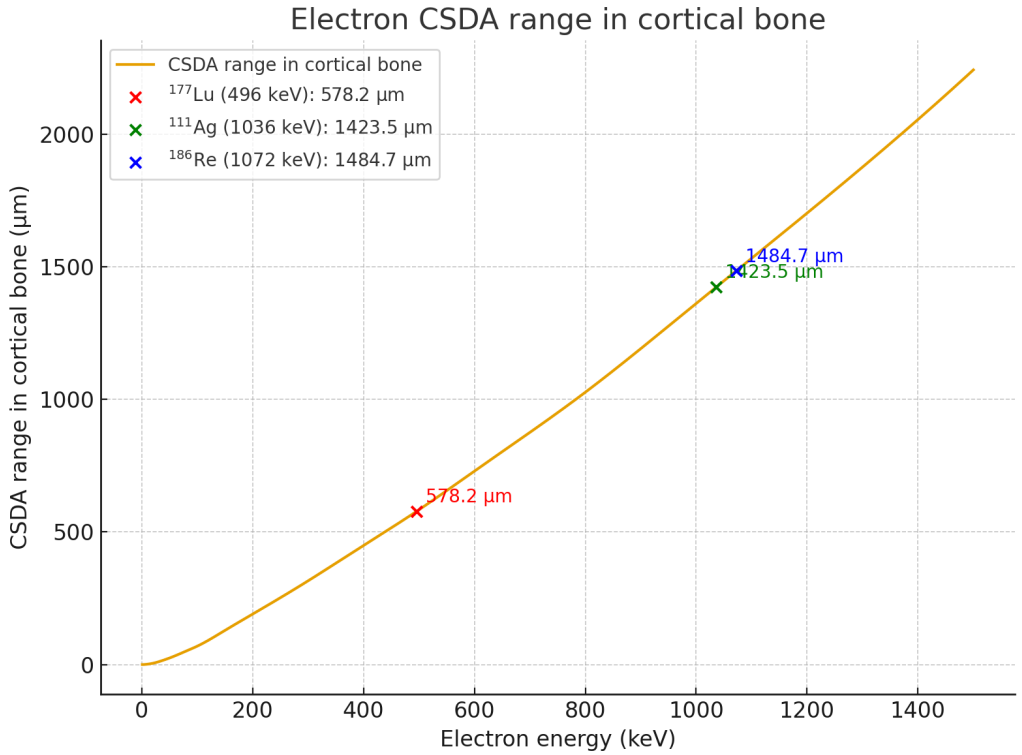


- Ag-111 has several attractive properties for nuclear medical purposes

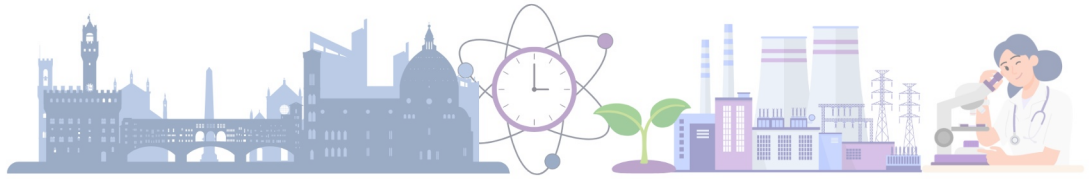
→ Suitable for TRT!

An innovative radionuclide: Ag-111



- Ag-111 has several attractive properties for nuclear medical purposes

  - Average tissue penetration = 1.8 mm, longer than the one of **Lu-177** , which could be sometimes **unsatisfactory** for the treatment of **bone metastases** (as confirmed by medical physicists from IRST D. Amadori, Meldola)



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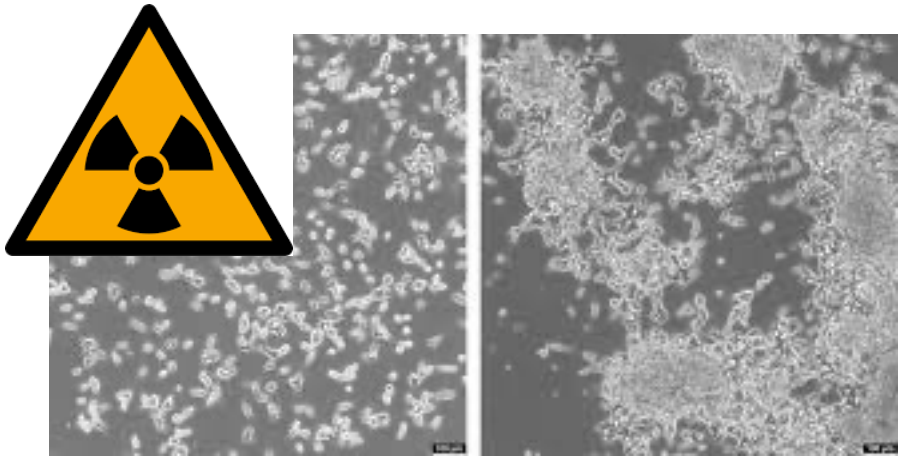
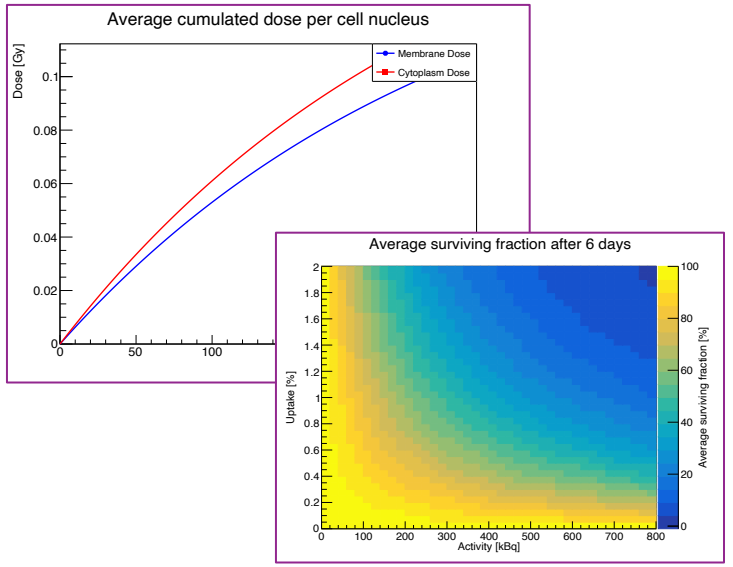
Objective

- ✓ **Estimation of the absorbed dose and of the survival fraction** of a cell culture irradiated with **Ag-111** through a microdosimetric model, which uses the **microscopic images** of the culture and **Geant4** Montecarlo toolkit



GEANT4
A SIMULATION TOOLKIT



Why?

- In order to complement and plan *in-vitro* experiments for the correct evaluation of the effectiveness of RPs one could use **microdosimetry calculations** to estimate the RBE of different nuclides

→ ***In-silico* computations** will be used as a screening tool for use prior to ***in-vitro* testing**

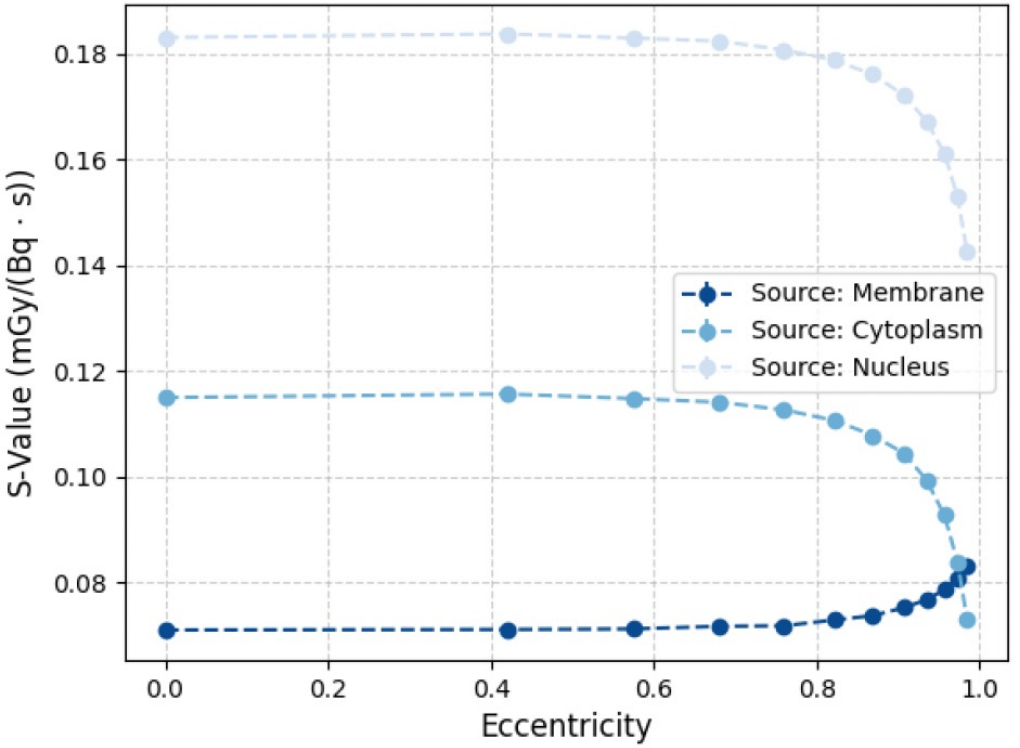
This study plays a key role in facilitating a **comparative assessment of the Ag-111 radionuclide against other radionuclides** used in radiotherapeutic applications

Dose and geometry

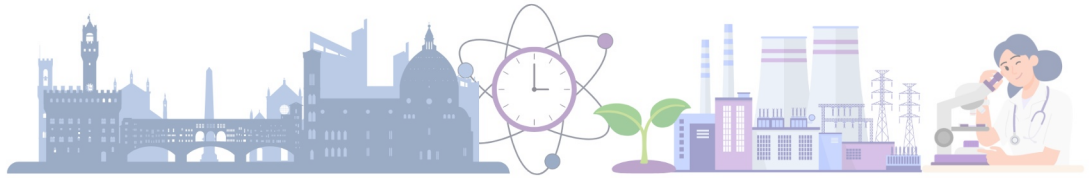
In *in-silico* computations:

- spherical models for non-spherical cell types can lead to errors in the dose estimate [1]
- dose calculations using a sample of identical cell sizes rather than a distribution of sizes can give large errors as well

→ The following computations are tailored **to handle the non-spherical cell geometry**, improving dose predictions



[1] A. Donzella et al. "Monte Carlo dosimetry of Ag-111 in simplified cell geometries in the framework of the ISOLPHARM project". In: Applied Radiation and Isotopes 225 (2025), p. 111979



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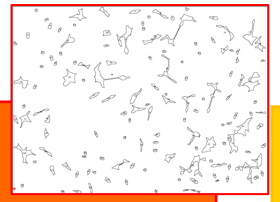
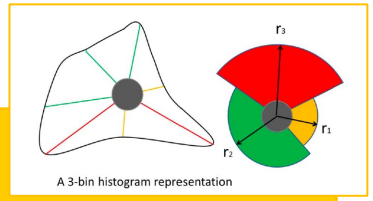
The algorithm

[2] T. L. Palmer et al. “Microdosimetry modeling with Auger emitters in generalized cell geometry”. In: Physics in Medicine & Biology 66.11 (June 2021)



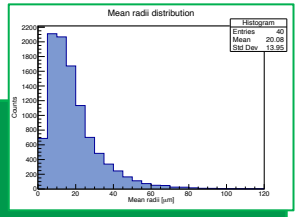
Phase I
Image study

- Cell → Probability Density Function (PDF)



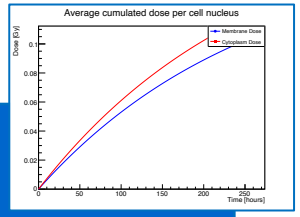
Phase II
Geometric model

- Wedge model
- Geant4 simulations
- Curve dose per event vs wedge radius



Phase III
Generation of cells

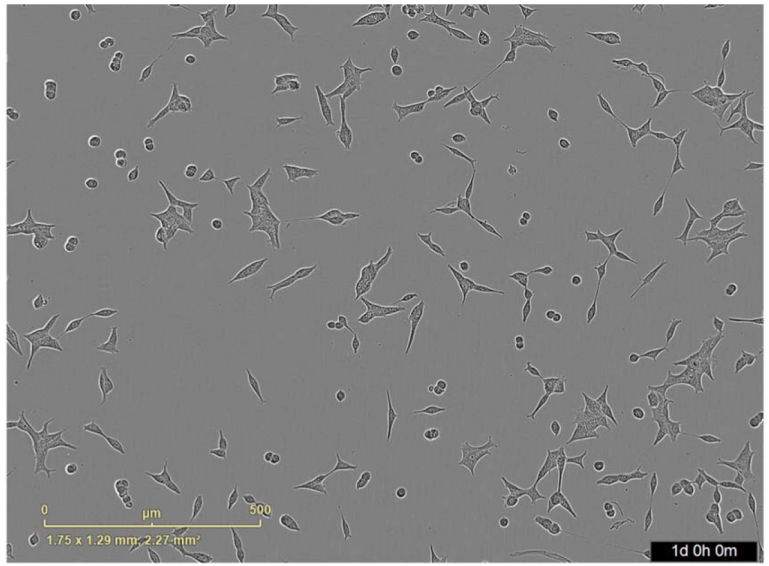
- Lognormal distribution of mean radii
- Bin → PDF



Phase IV
Dose & surviving fraction (SF)

- Activity association
- Dose & SF calculation

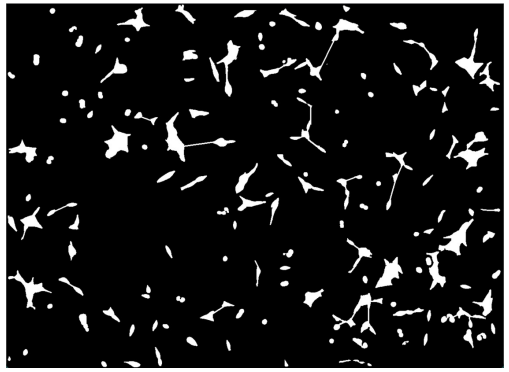
Image analysis with ImageJ



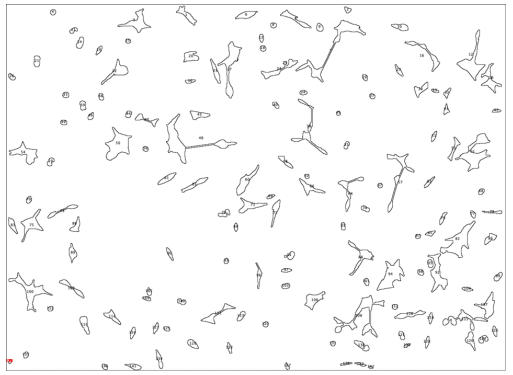
LNCaP cells
(Lymph Node Carcinoma of the Prostate)

(ImageJ logo)

1. Image thresholding



2. Cells segmentation

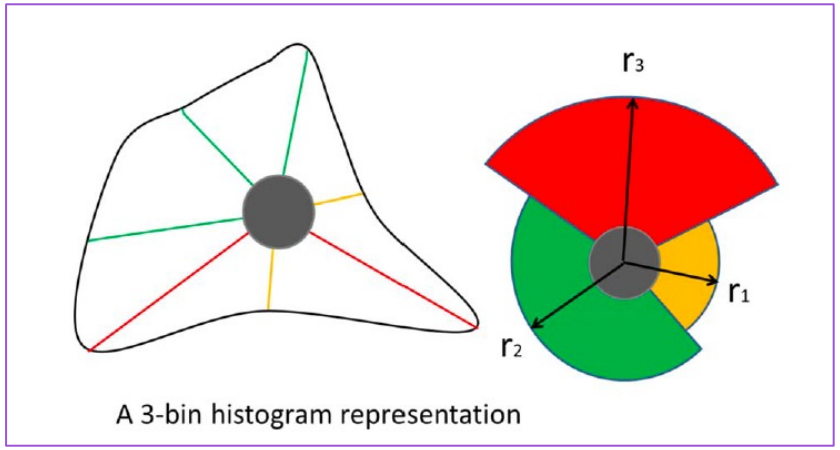


3. Cell radii analysis

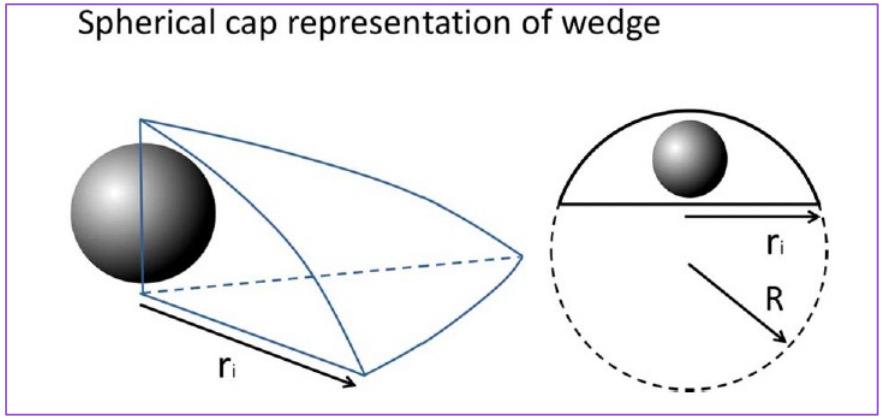
```
Cellula numero  1
r_ 1 = 8.5848  p_ 1 = 0.1429
r_ 2 = 12.4525  p_ 2 = 0.1571
r_ 3 = 16.3202  p_ 3 = 0.07143
r_ 4 = 20.1879  p_ 4 = 0.08571
r_ 5 = 24.0555  p_ 5 = 0.07143
r_ 6 = 27.9232  p_ 6 = 0.06429
r_ 7 = 31.7909  p_ 7 = 0.1
r_ 8 = 35.6586  p_ 8 = 0.1429
r_ 9 = 39.5263  p_ 9 = 0.1143
r_ 10 = 43.394  p_ 10 = 0.05
r_mean =  24.5176
*****************************
```

→ At the end every cell has its own radii PDF

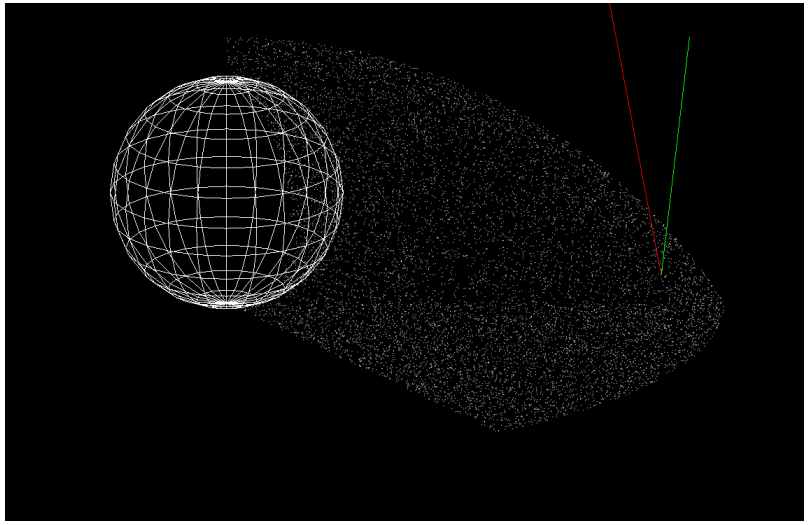
The wedge model



In 3 dimensions



In Geant4



Calculation of the absorbed dose (in the cell nucleus) per event for 100 different wedge radii

The generation of cells

- Simulation of 10000 cells with different mean radii
- Lognormal distribution

- Every bin of the distribution is associated to a PDF (from image analysis)

```
Cellula numero  1
r_ 1 = 8.5848  p_ 1 = 0.1429
r_ 2 = 12.4525  p_ 2 = 0.1571
r_ 3 = 16.3202  p_ 3 = 0.07143
r_ 4 = 20.1879  p_ 4 = 0.08571
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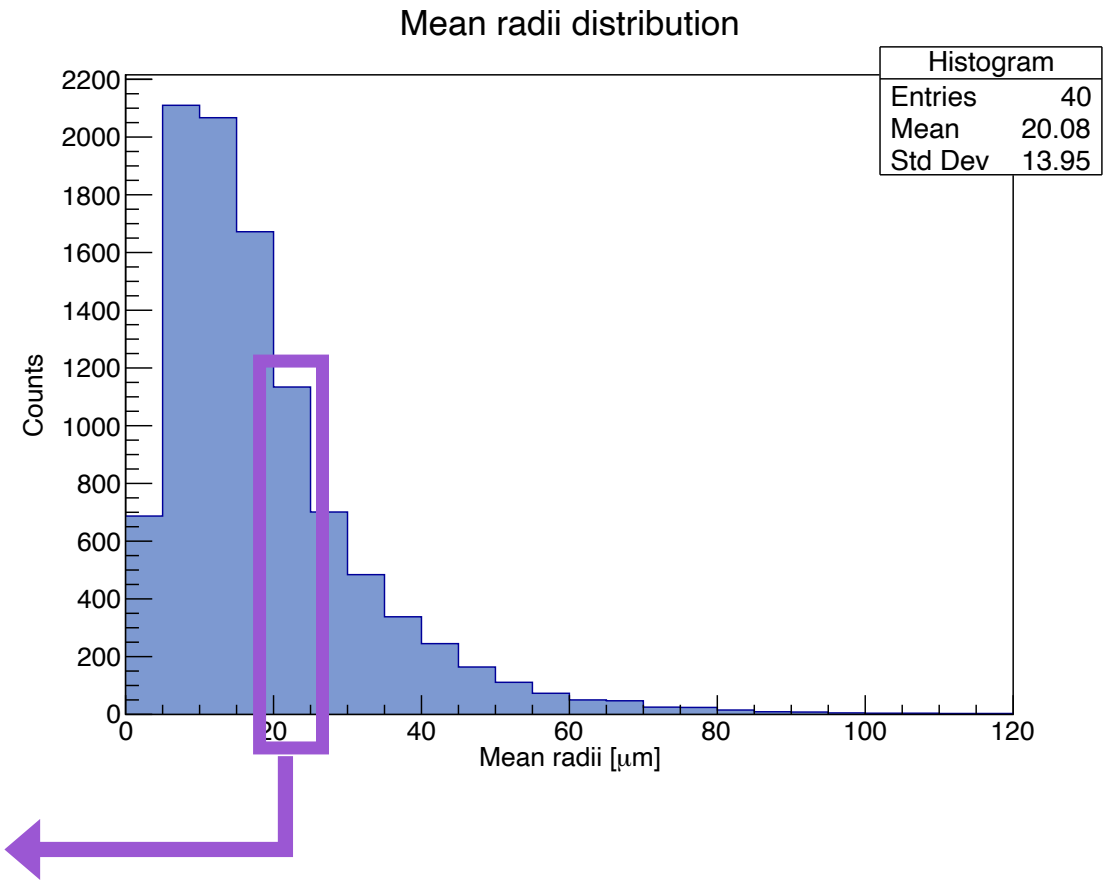
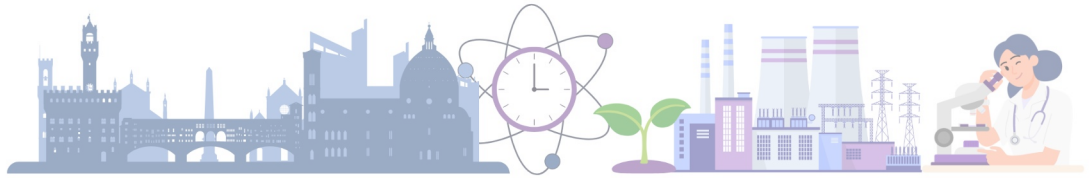




S-value calculations

- S-value: absorbed dose (in the cell nucleus) per nuclear decay

$$S_{\text{wedge}} = S(m \rightarrow n)(r_i) \cdot p_i + S(cy \rightarrow n)(r_i) \cdot p_i$$

- $S(m \rightarrow n)$: source: membrane; target: nucleus
- $S(cy \rightarrow n)$: source: cytoplasm; target: nucleus

S-value calculations

- S-value: absorbed dose (in the cell nucleus) per nuclear decay

$$S_{\text{wedge}}(r_i) = S(m \rightarrow n)(r_i) \cdot p_i + S(cy \rightarrow n)(r_i) \cdot p_i$$

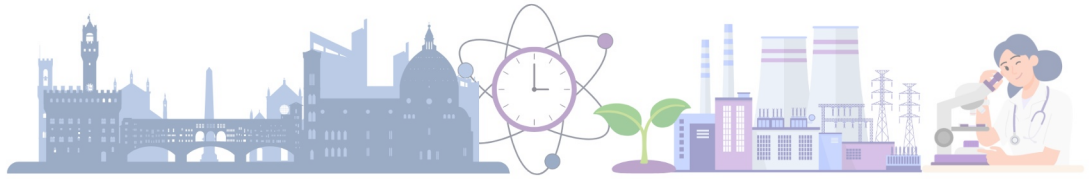
Dependence of S on radius r_i

S-value calculations

- S-value: absorbed dose (in the cell nucleus) per nuclear decay

$$S_{\text{wedge}}(r_i) = S(m \rightarrow n)(r_i) \cdot p_i + S(cy \rightarrow n)(r_i) \cdot p_i$$

Probability of the radius r_i



S-value calculations

- S-value: absorbed dose (in the cell nucleus) per nuclear decay

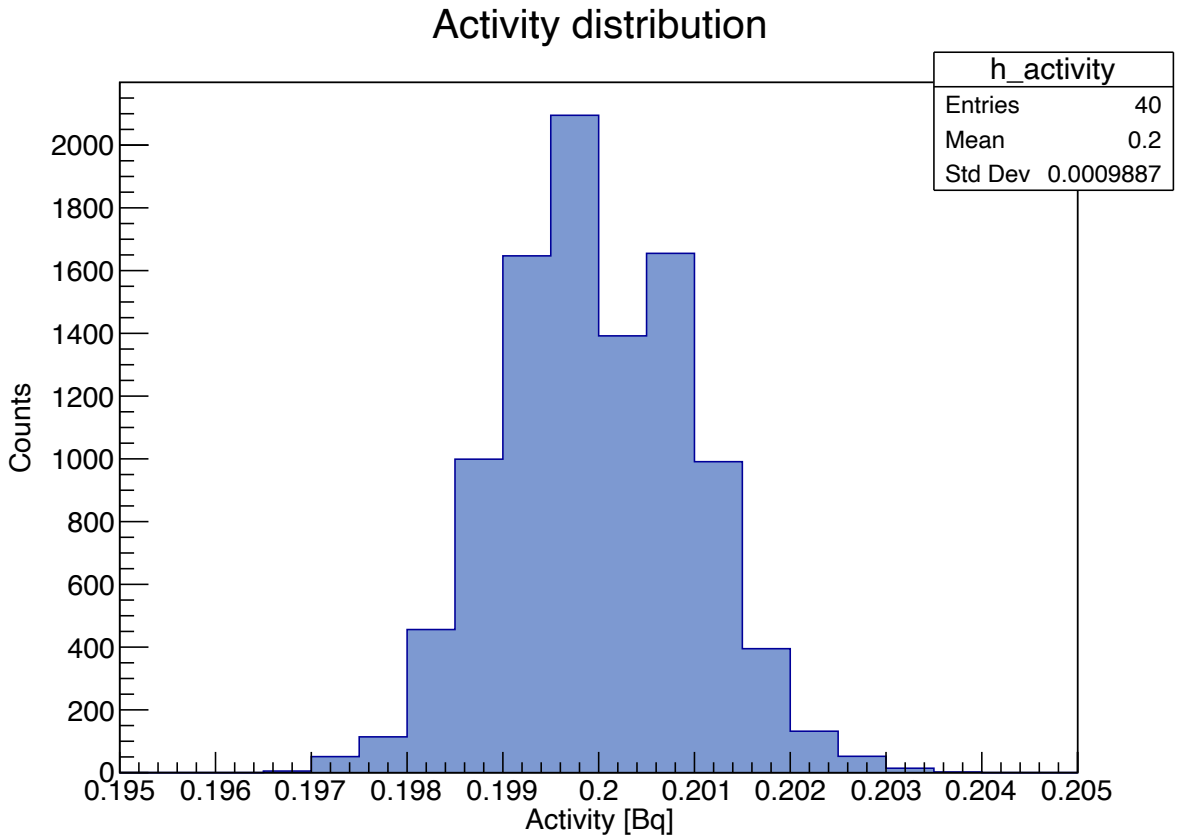
$$S_{tot} = \sum_{i}^{\#wedges} S(m \rightarrow n)\,(r_i) \cdot p_i + S(cy \rightarrow n)(r_i) \cdot p_i$$

Activity association

- The activity is assigned randomly to each cell using a lognormal distribution

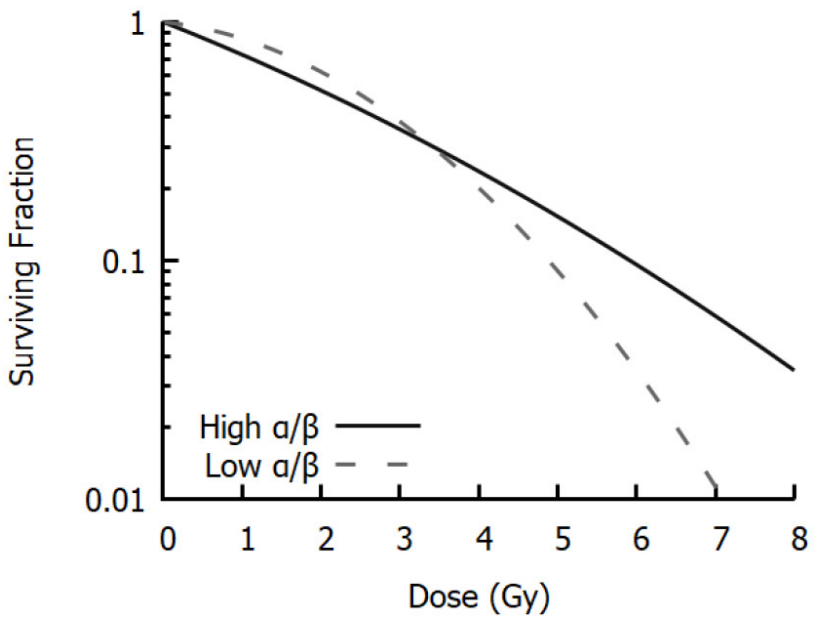
Hypothesis

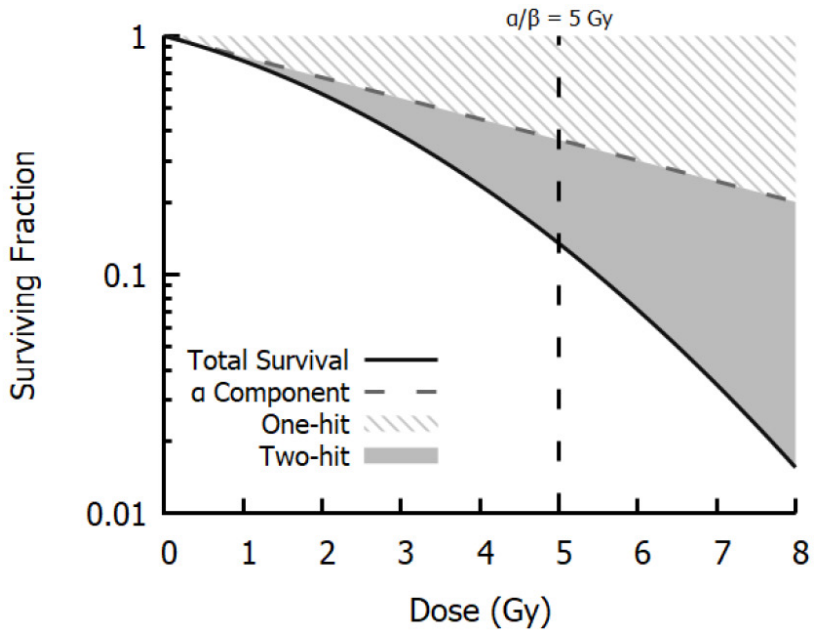
1. Applied activity: 100 kBq
2. Uptake: 2%
3. In the cytoplasm: 60%
4. In the membrane: 40%

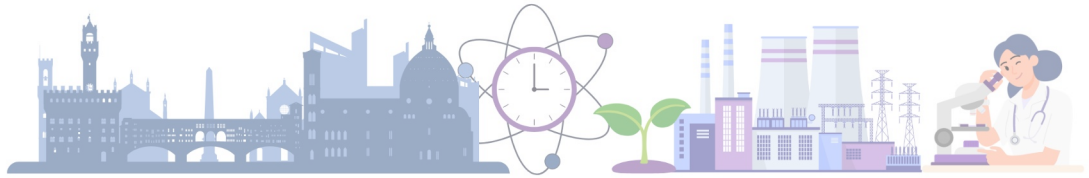


Surviving fraction calculations

- The Linear Quadratic (LQ) model is used: $P = e^{-\alpha D - \beta D^2}$
- A cell is marked alive if $\xi < P$, for $\xi \in [0, 1]$
- The average survival probability is then: N_{alive}/N_{cells}







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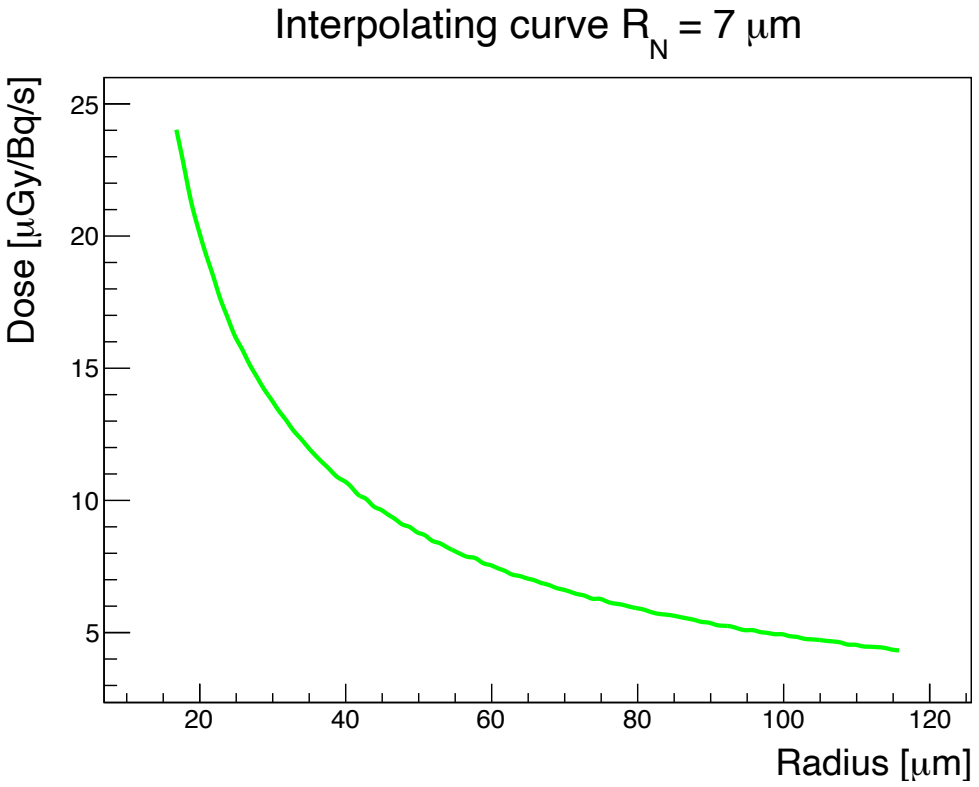
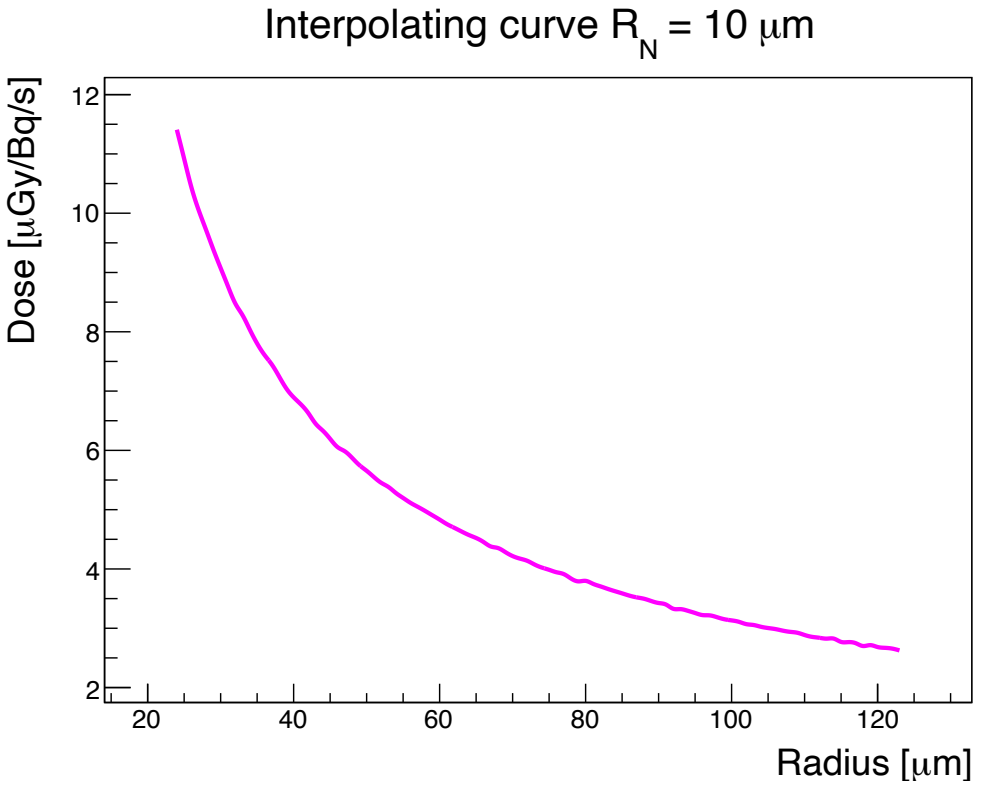
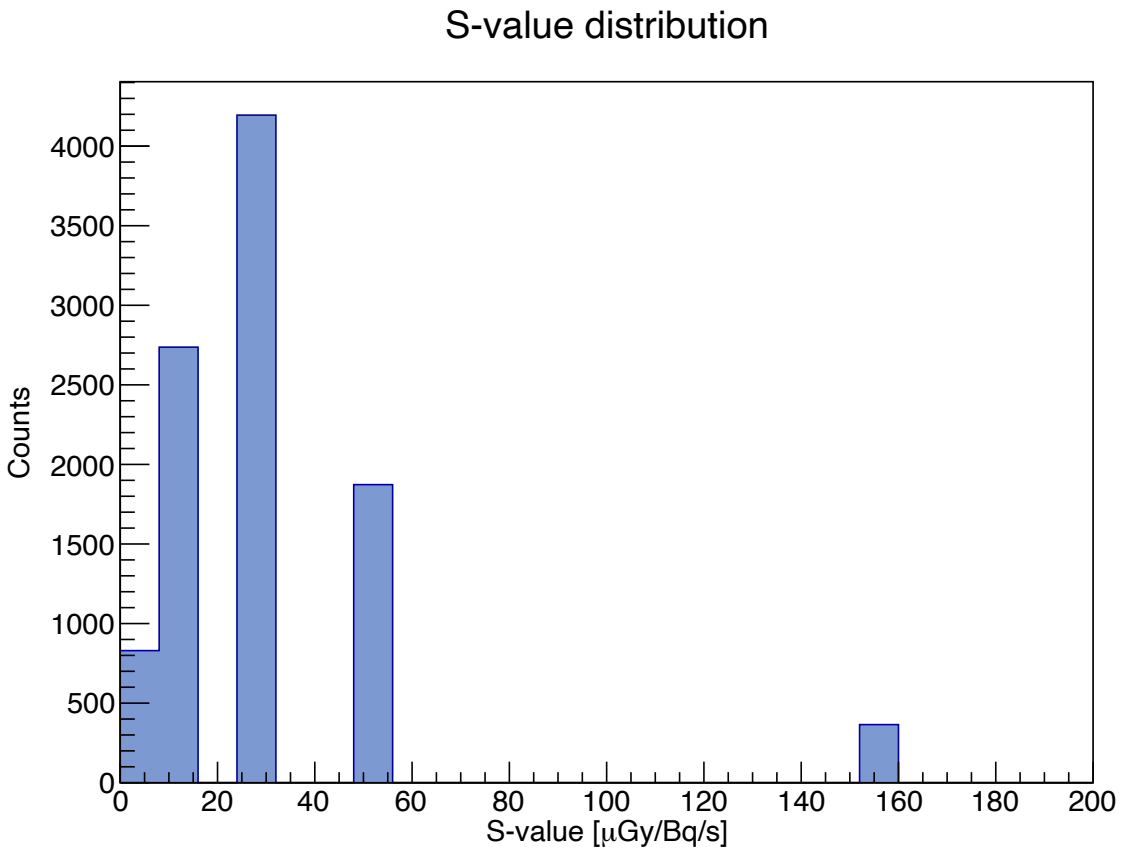
S-value curves



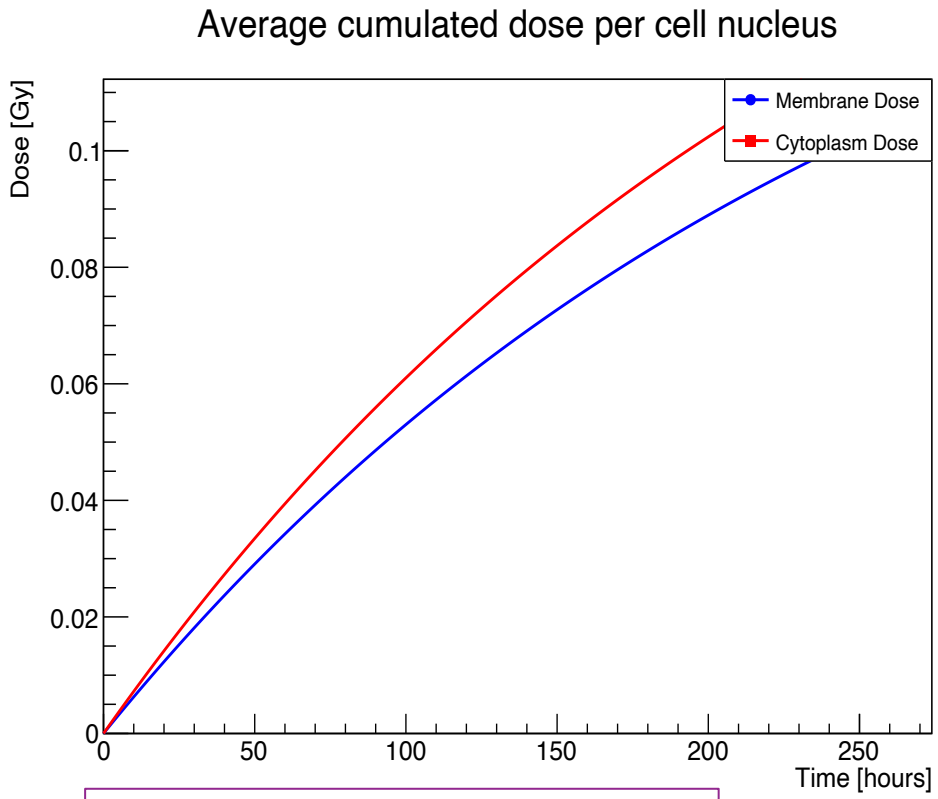


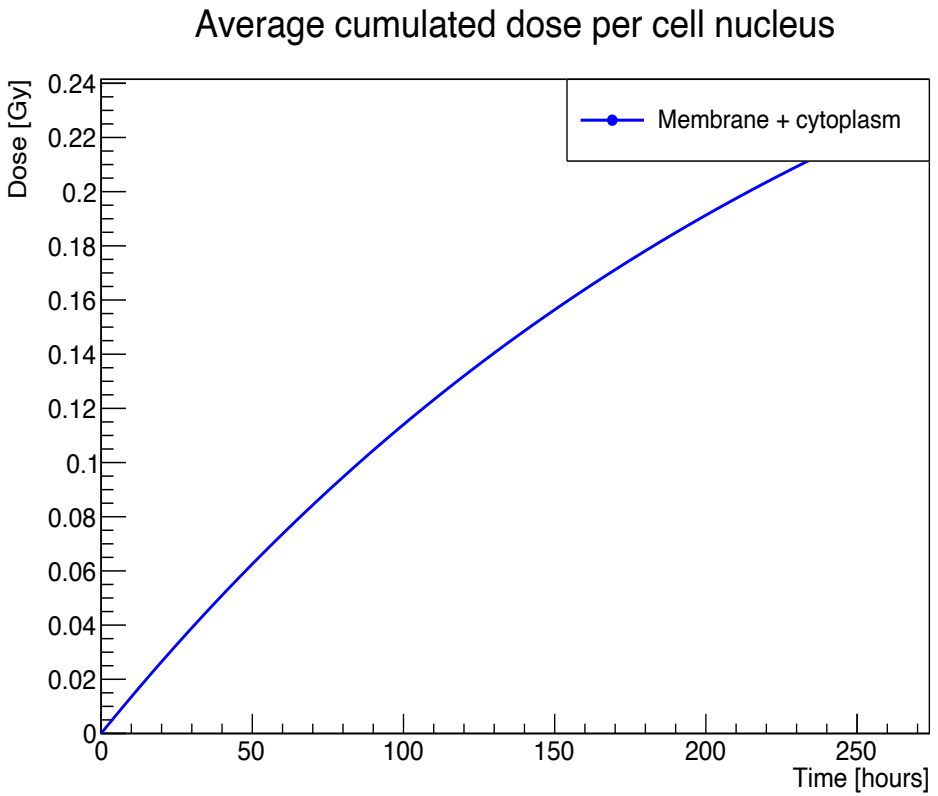
S-value distribution



Large span of dose values mainly due to the varying cell geometry

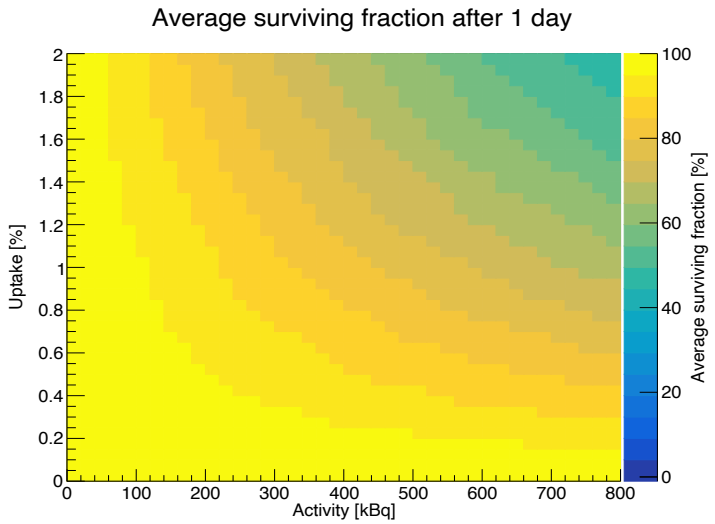
Absorbed dose VS time

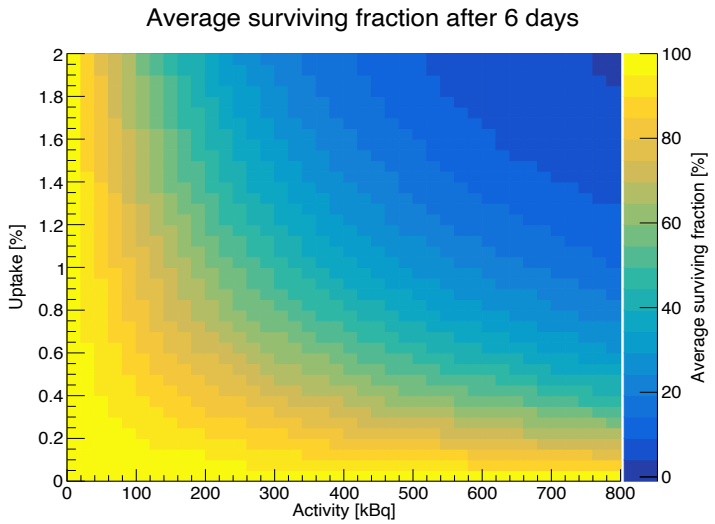


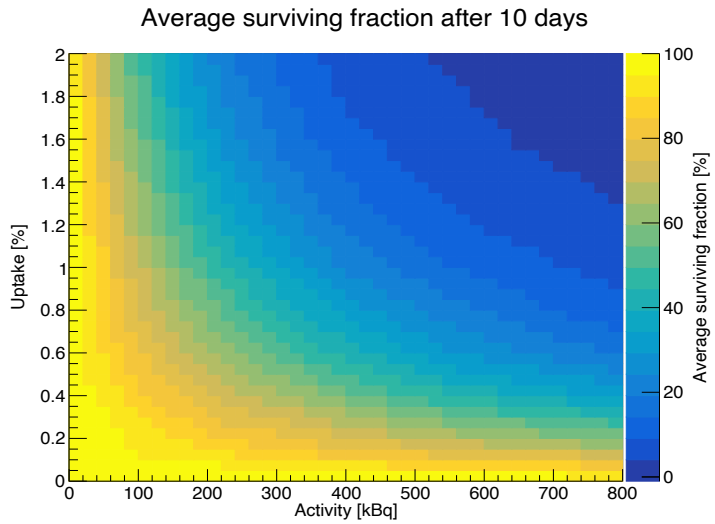


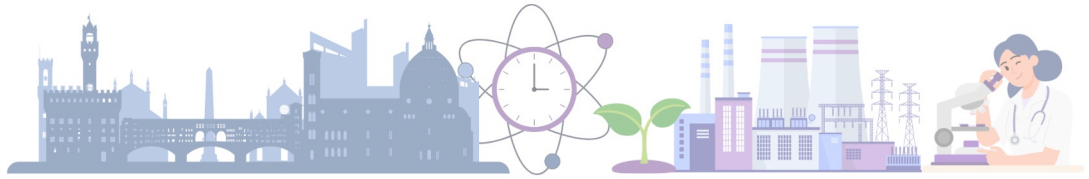
The applied activity is **100 kBq**

SF VS applied activity VS cellular uptake









Contents

- Scientific background
- The ISOLPHARM project
- Motivation of the study
- Geant4 image-based cell dosimetry
- Results
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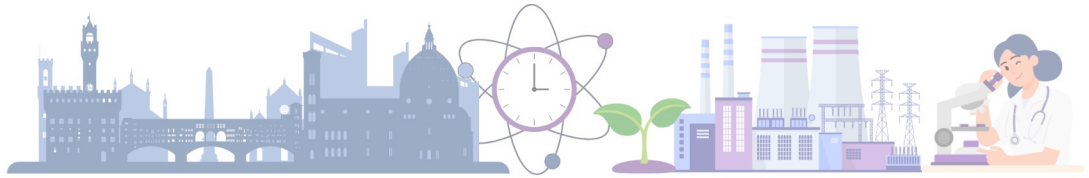
Conclusions and future perspectives

- ✓ Estimation of the absorbed dose and of the survival fraction with the microdosimetric algorithm developed → it could be used as **comparative assessment of Ag-111 against other radionuclides**

- ✓ The analysis took into account the irregular cell geometries, as traditional spherical cell models can lead to significant errors

→ In any case, a validation of the microdosimetric model results through future experiments with internalized Ag-111 is needed

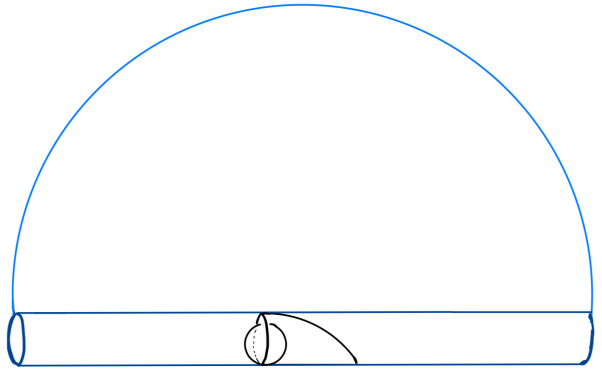


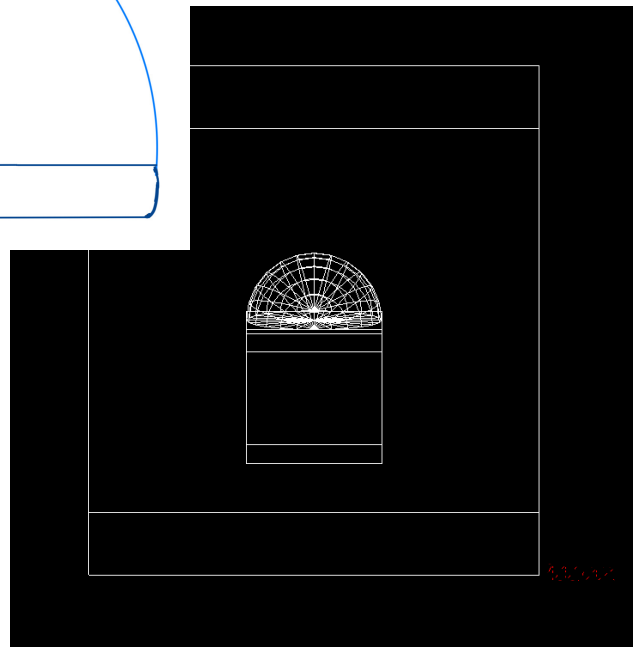
Thanks for your kind attention!

☺

Environmental and cross dose

- Emisphere (water) of radius 3 mm
- Cylinder (water) of height ~15 µm
- Box (polystyrene) of height 1 mm
- Box (steel) of height 5 mm





Geometry	S-value [pGy/Bq/s·mL]
Hemisphere	24.597
Cylinder	1.1364