Monte Carlo simulations for *in vitro* radiopharmaceutical experiments using the TOPAS toolkit

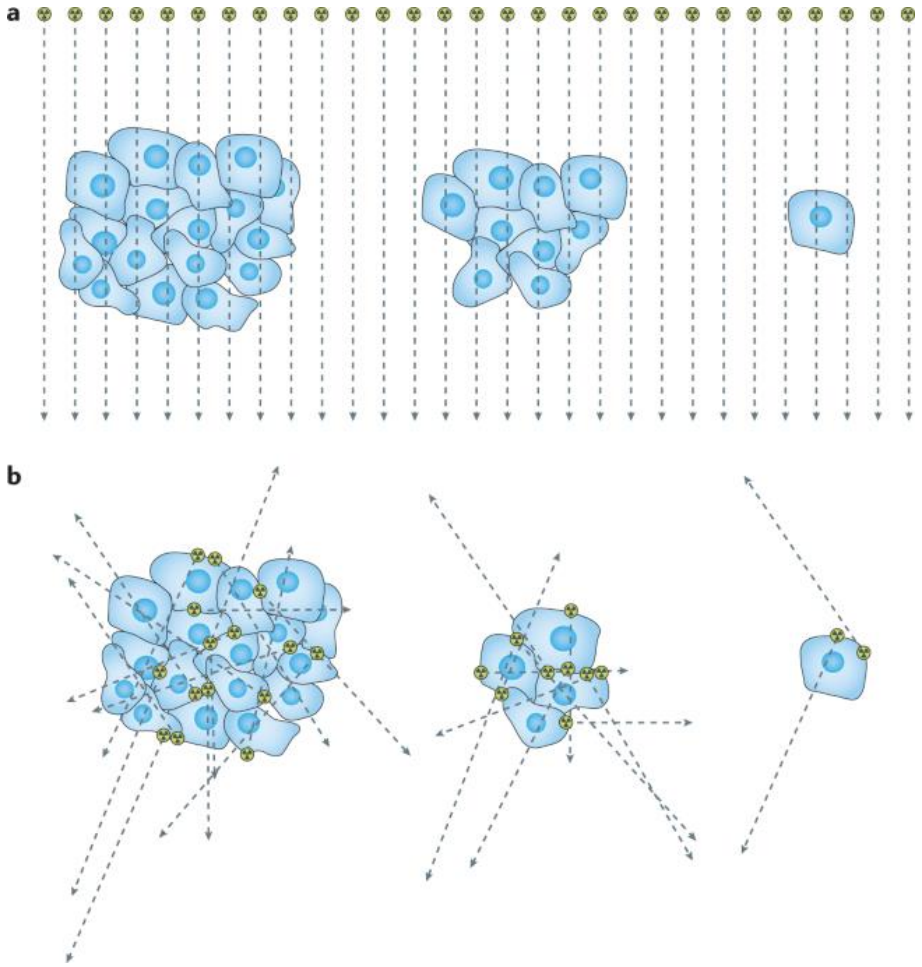
Daniel Suárez García[1*] , Miguel Antonio Cortés Giraldo[1] , Alejandro Bertolet[2]

IV Jornadas RSEF / IFIMED
November 30, 2023 – Sevilla

[1]Department of Atomic, Molecular and Nuclear Physics, University of Sevilla, Spain
[2]Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
**email: dsgarcia@us.es*

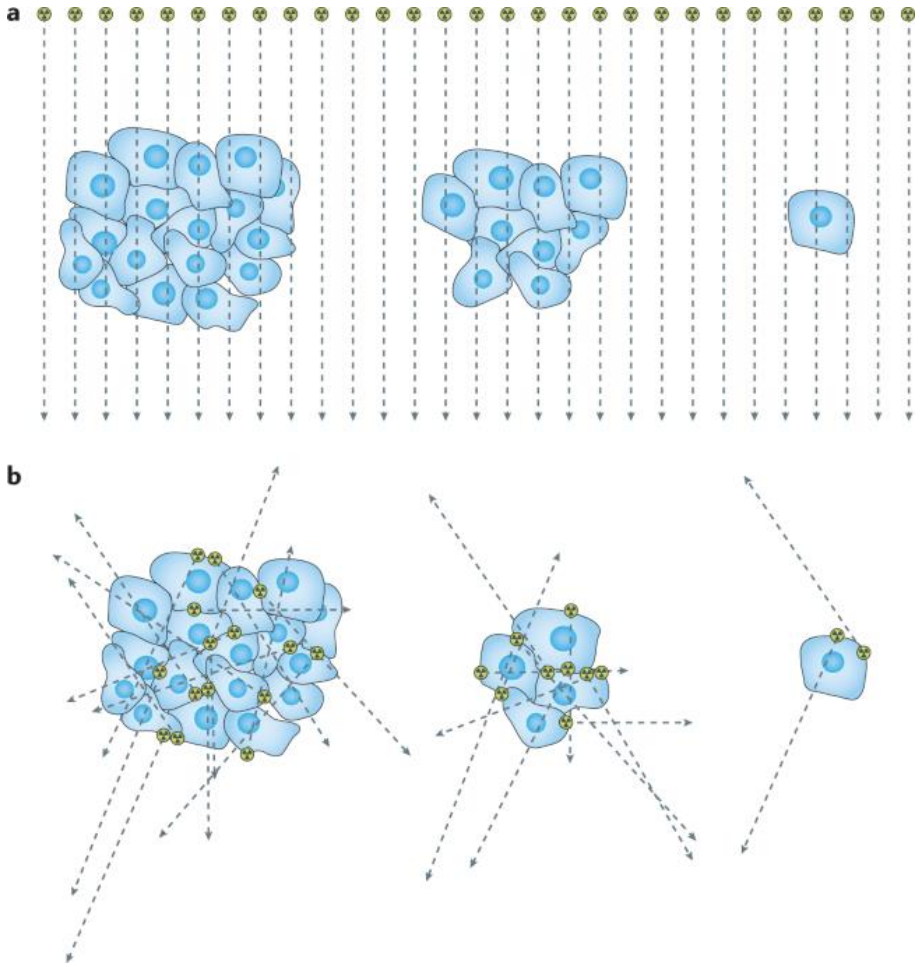
Radiopharmaceutical Therapy

Radiopharmaceutical therapy utilizes radiolabeled antibodies highly affine to antigens particularly expressed in tumor cell environments.



Radiopharmaceutical Therapy

Radiopharmaceutical therapy utilizes radiolabeled antibodies highly affine to antigens particularly expressed in tumor cell environments.

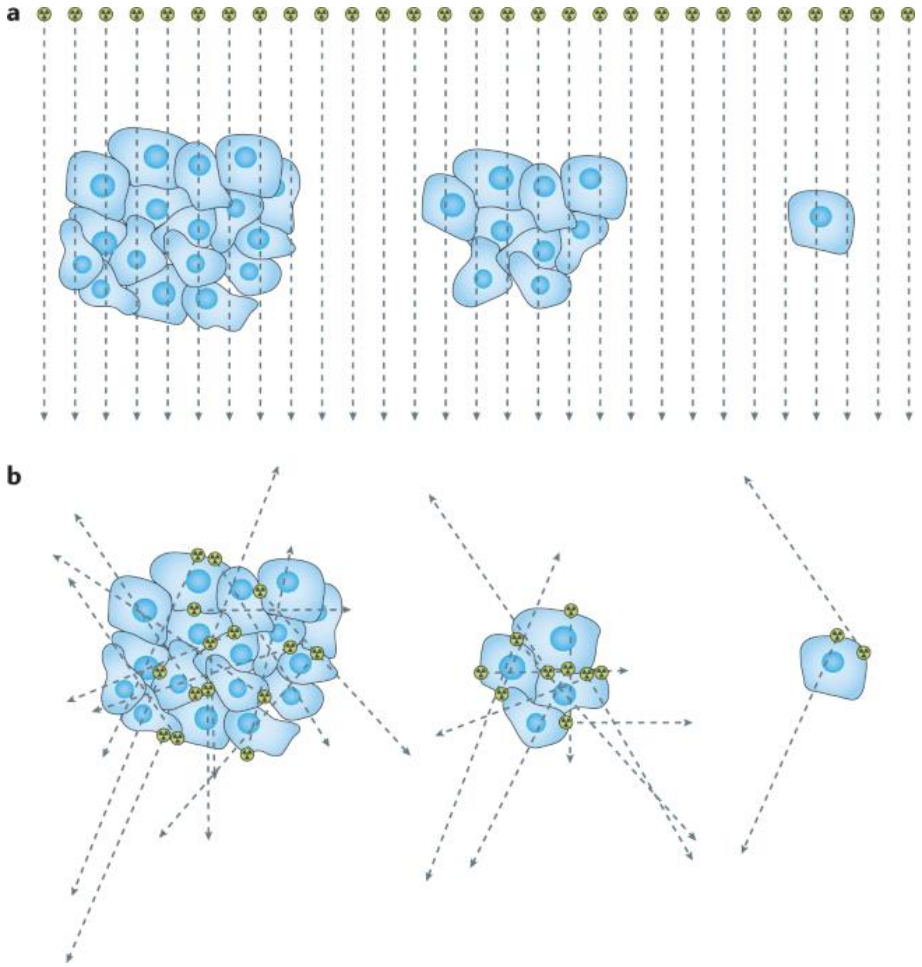


External beam therapy:

- Radiation beams from outside the body
- Exposes the surrounding healthy tissue
- Less invasive

Radiopharmaceutical Therapy

Radiopharmaceutical therapy utilizes radiolabeled antibodies highly affine to antigens particularly expressed in tumor cell environments.



External beam therapy:

- Radiation beams from outside the body
- Exposes the surrounding healthy tissue
- Less invasive

Radiopharmaceutical therapy:

- Internalized radioactive substances
- Minimizes damage to healthy tissue
- Delivers a concentrated dose

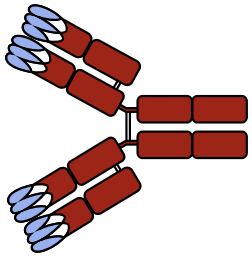
In vitro RPT experiments

Radionuclide

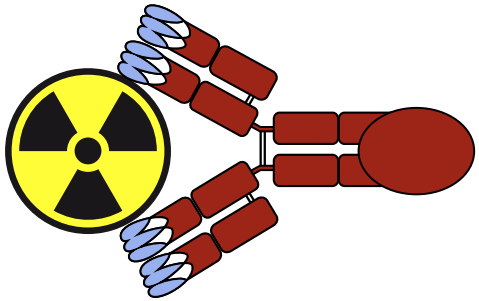
Chelate

+

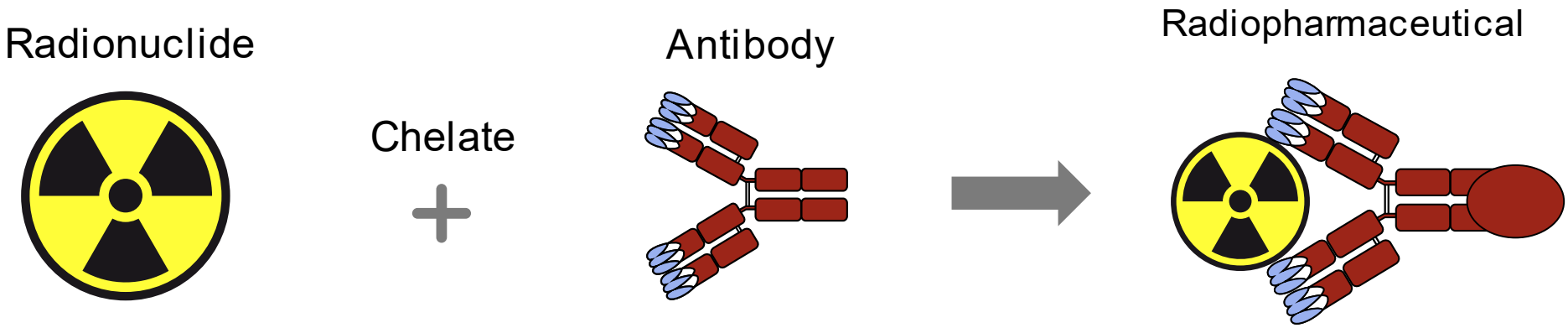
Antibody



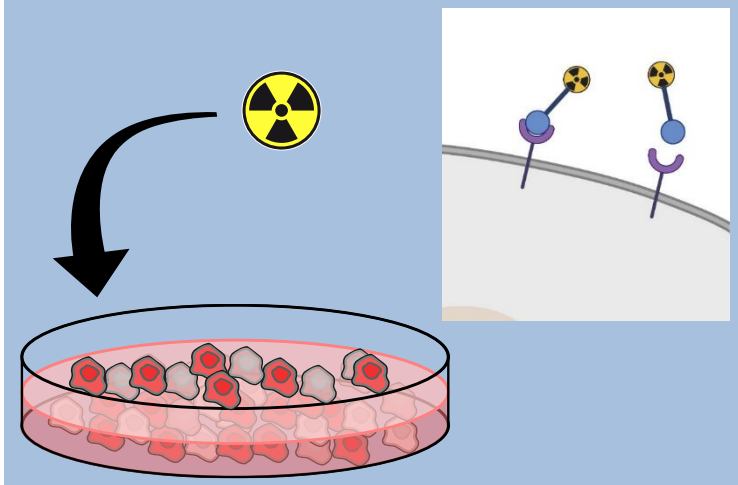
Radiopharmaceutical



In vitro RPT experiments

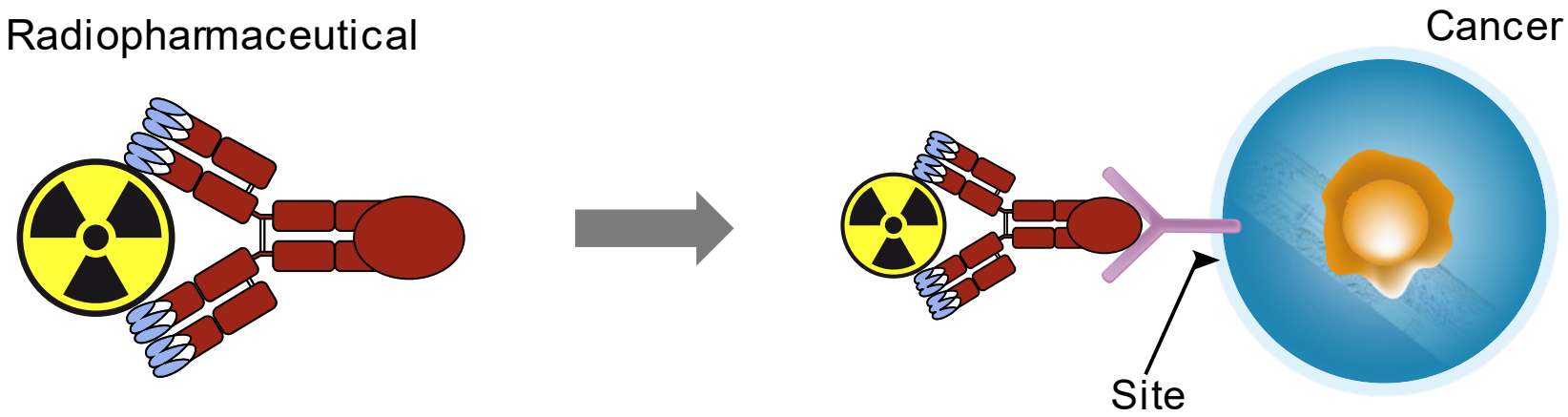


Stage 1: Injection

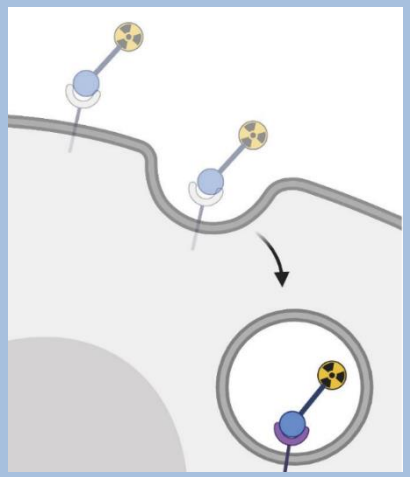


- Experiment initiates with the injection of the radiopharmaceutical into cell wells
- During this phase, the radionuclides are uniformly distributed across the medium
- After injection, they bind to cancer cells within the cell wells

In vitro RPT experiments



Stage 2: Internalization

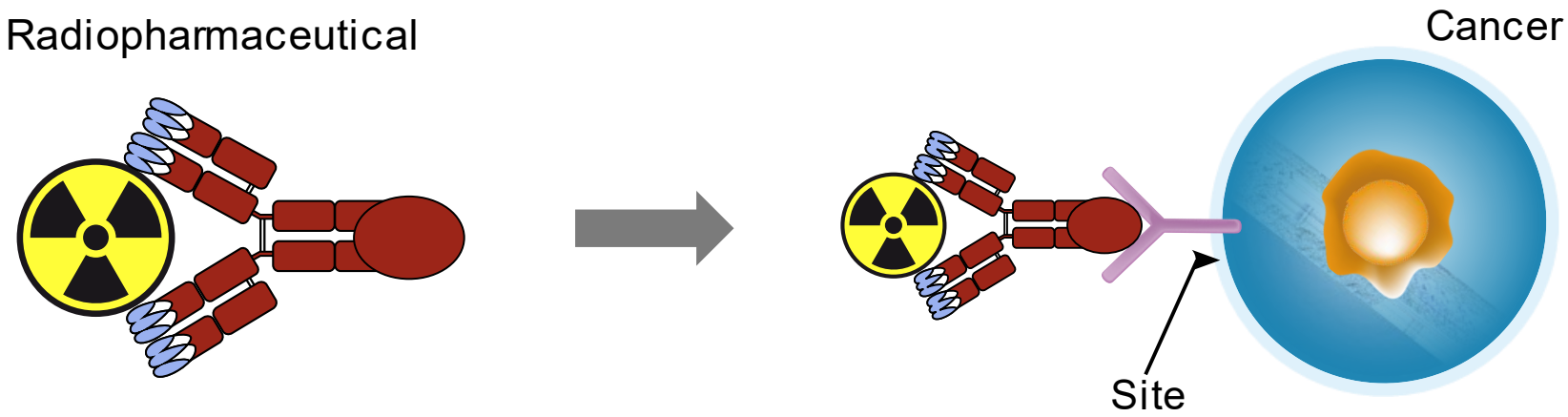


- Binding characterized by Kd

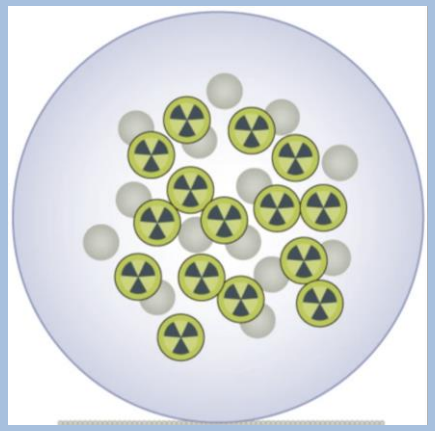
Kd: Concentration needed to have 50% of receptors bound

- Radiopharmaceuticals might internalize, i.e., pass through the membrane to the cytoplasm.

In vitro RPT experiments

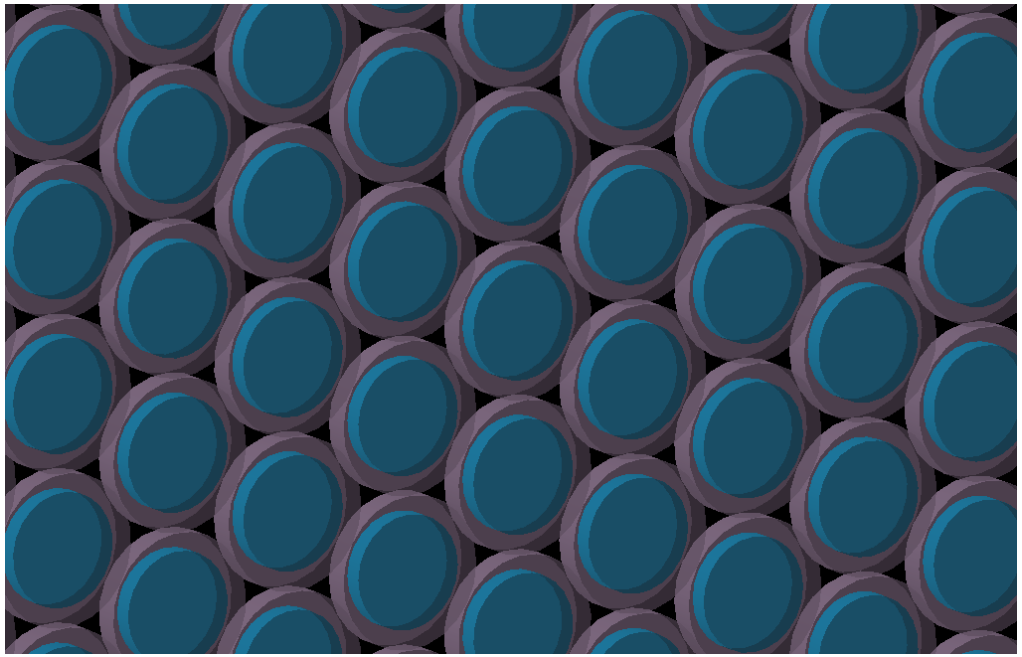


Stage 3: Already internalized

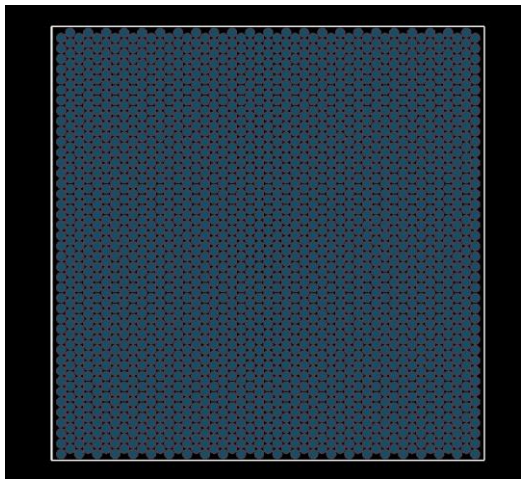


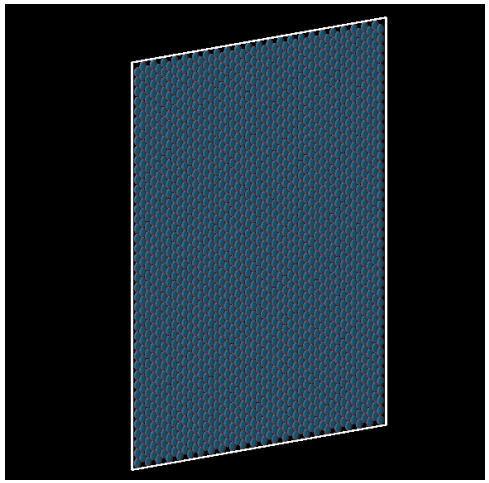
- Percentage of bound radiopharmaceutical internalizes into cytoplasm
- Radionuclide emits radiation directly from inside the cell

Geometry



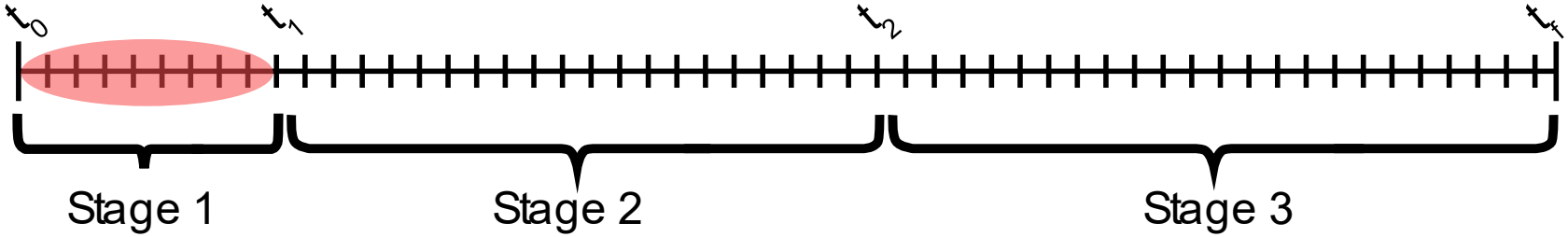
- Cell information
  - Cell radius and height
  - Nucleus radius and height

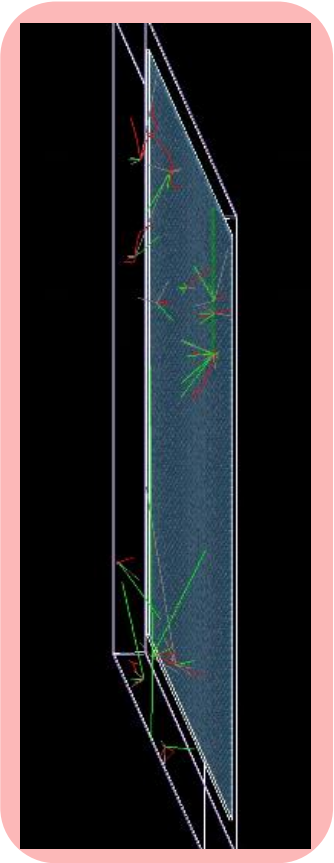




- Monolayer information
  - Monolayer dimension X, Y, Z

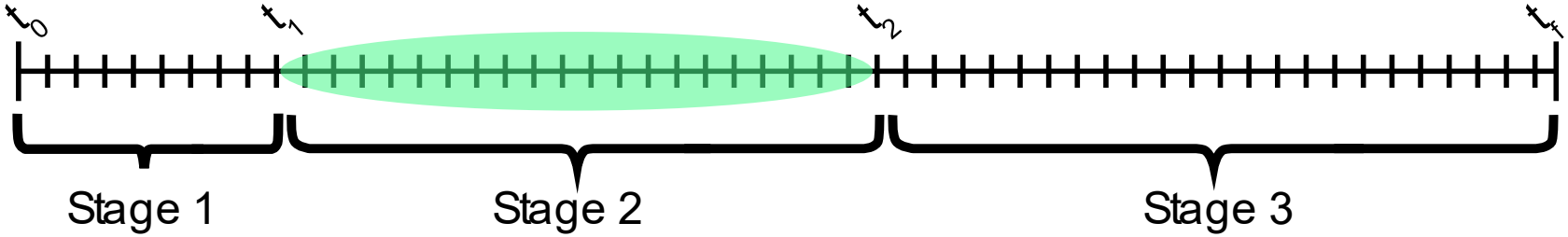
Actual time-structure

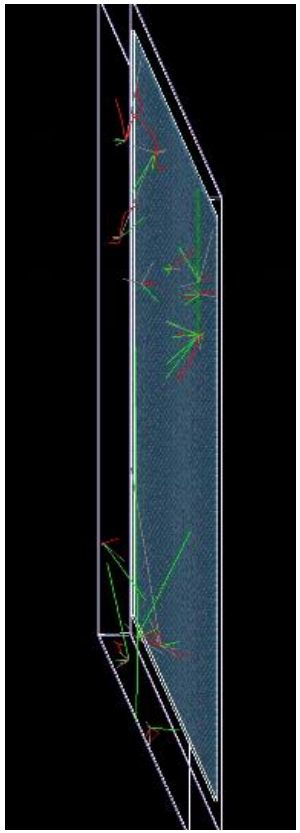


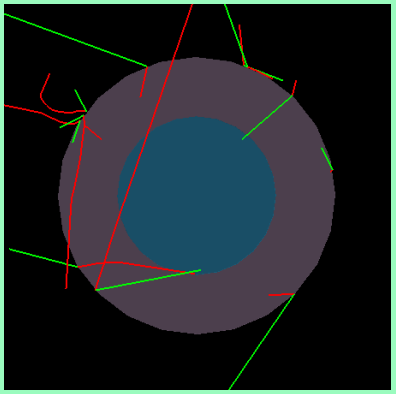


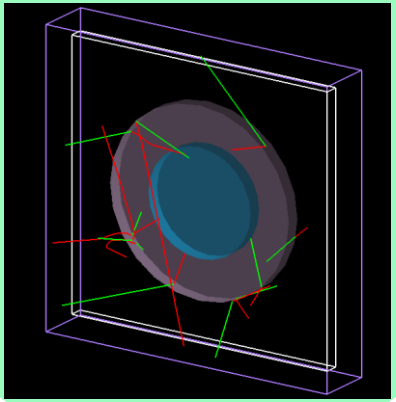
- Monolayer and cell geometry
- Radionuclide
- Initial activity
- Duration t_1
- Concentration (kBq/mL)
- Time step

Actual time-structure



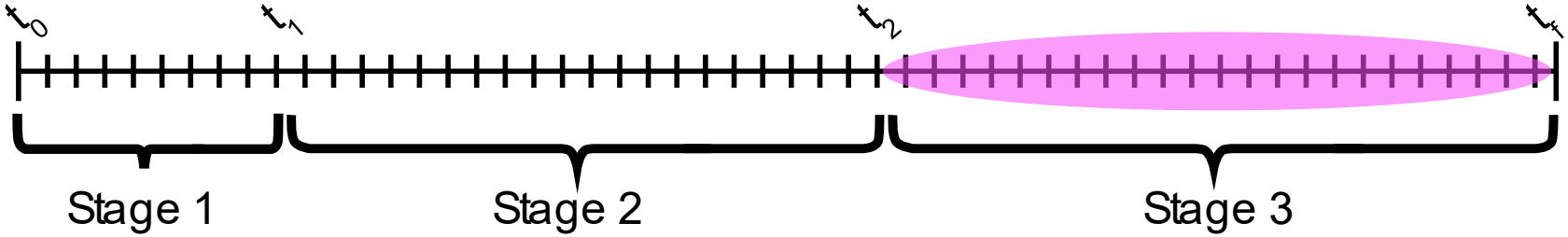


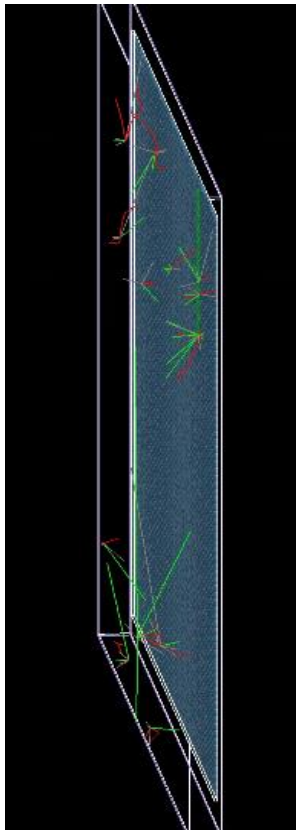


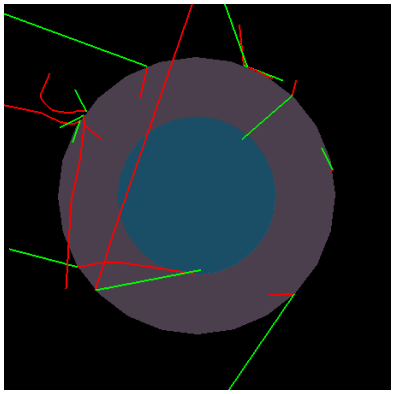


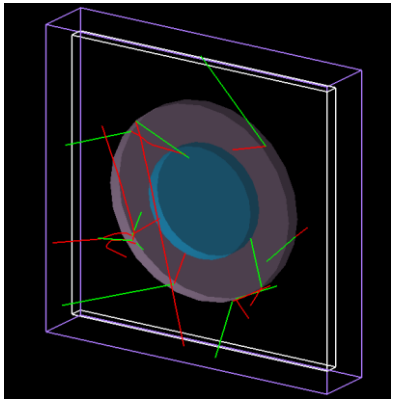
- Nº cells
- Nº sites/cell
- Parameter K_d
- Specific activity (kBq/mol)
- Duration t_2

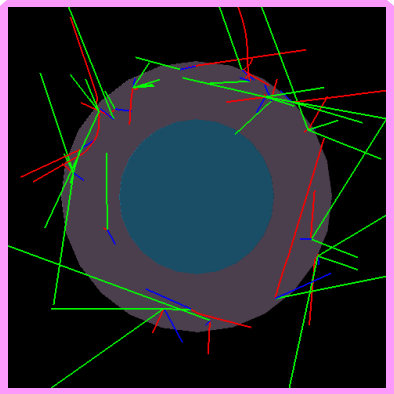
Actual time-structure

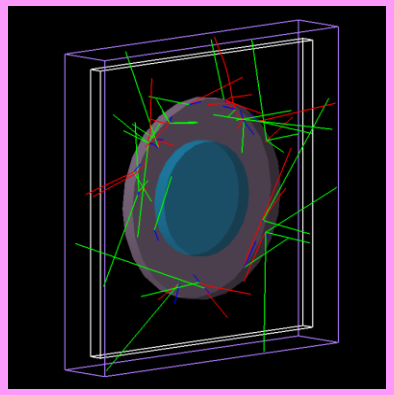






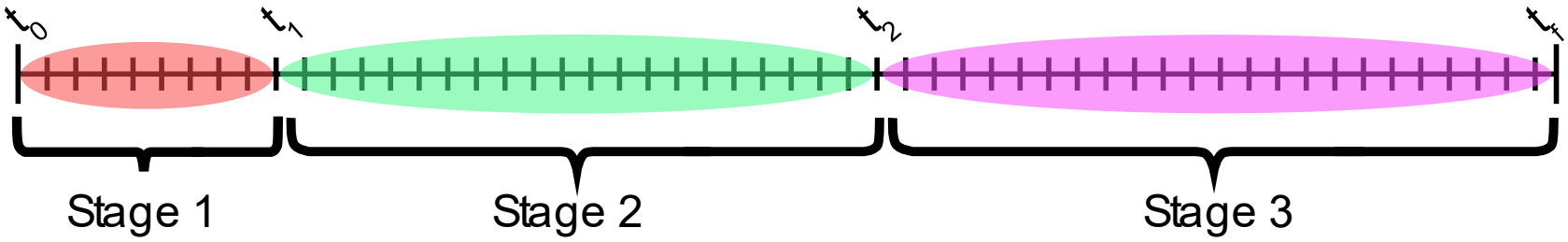


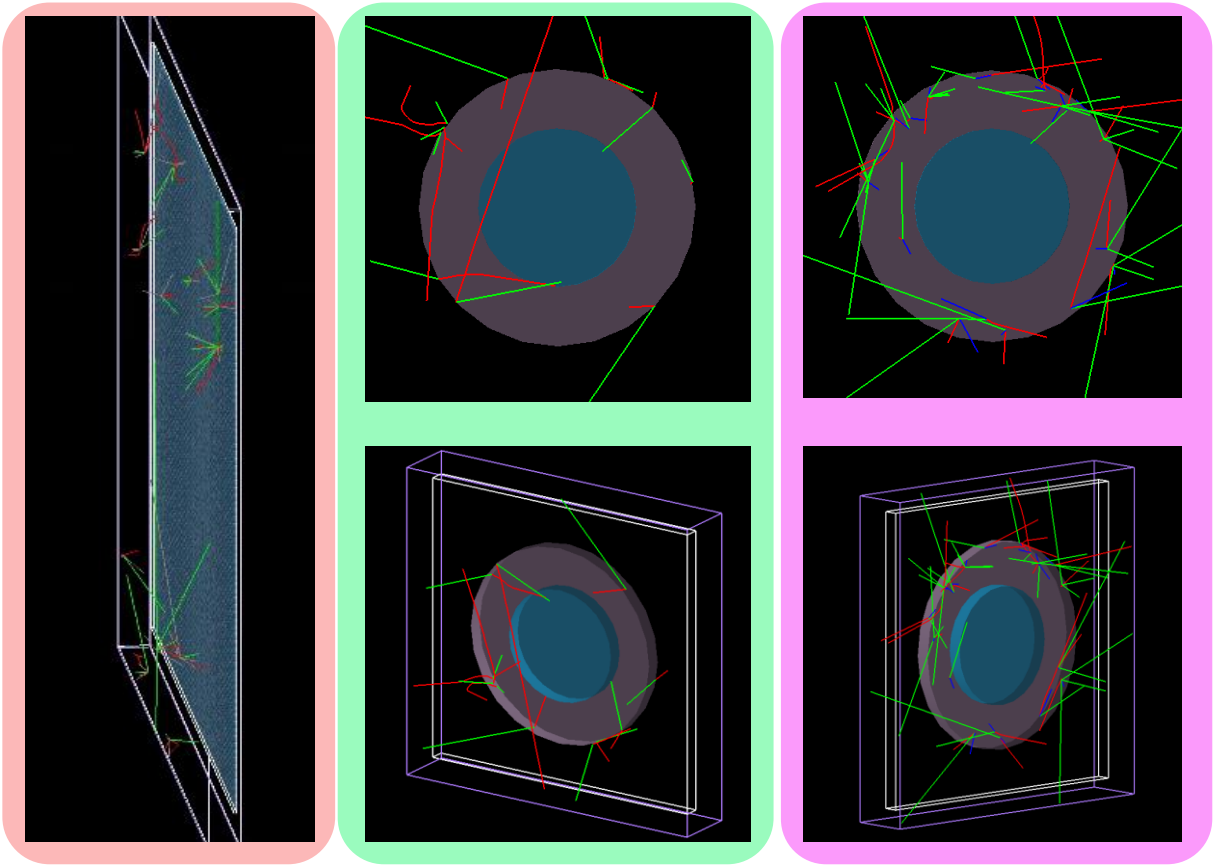




- Duration t_f
- Percentage internalized

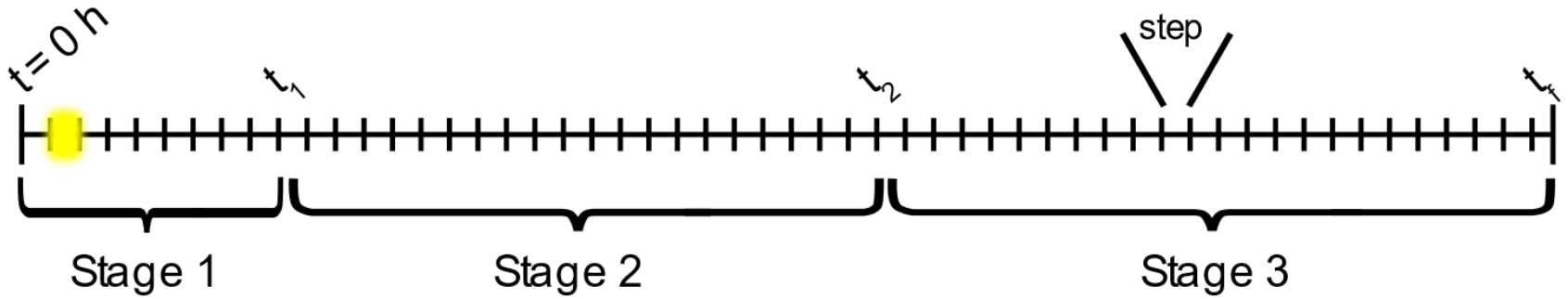
Actual time-structure





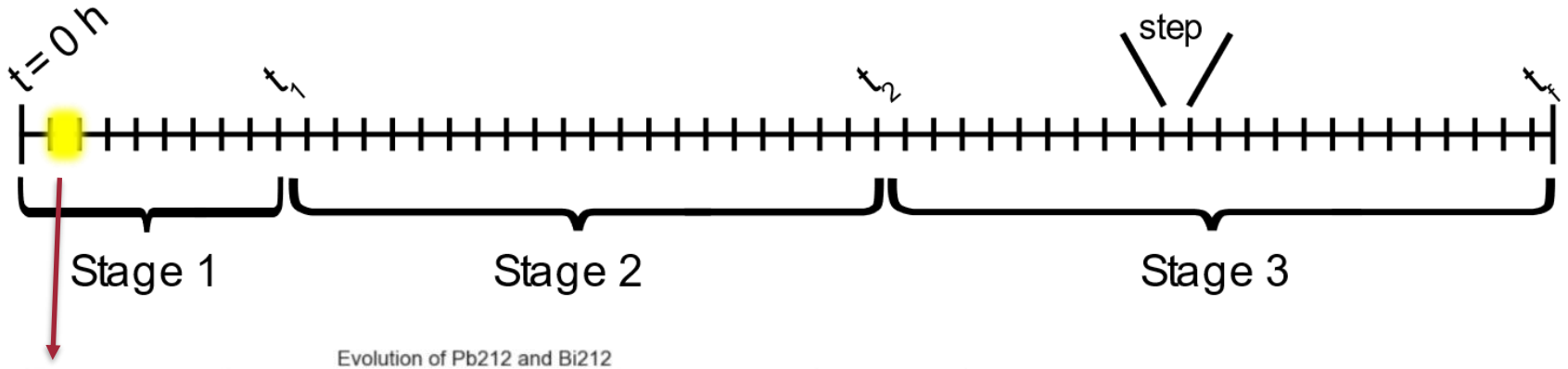
- Geometry
- Radionuclide
- Initial activity
- Duration each stage
- Concentration (kBq/mL)
- Time step
- Nº sites/cell
- Parameter K_d
- Specific activity (kBq/mol)
- Percentage internalized

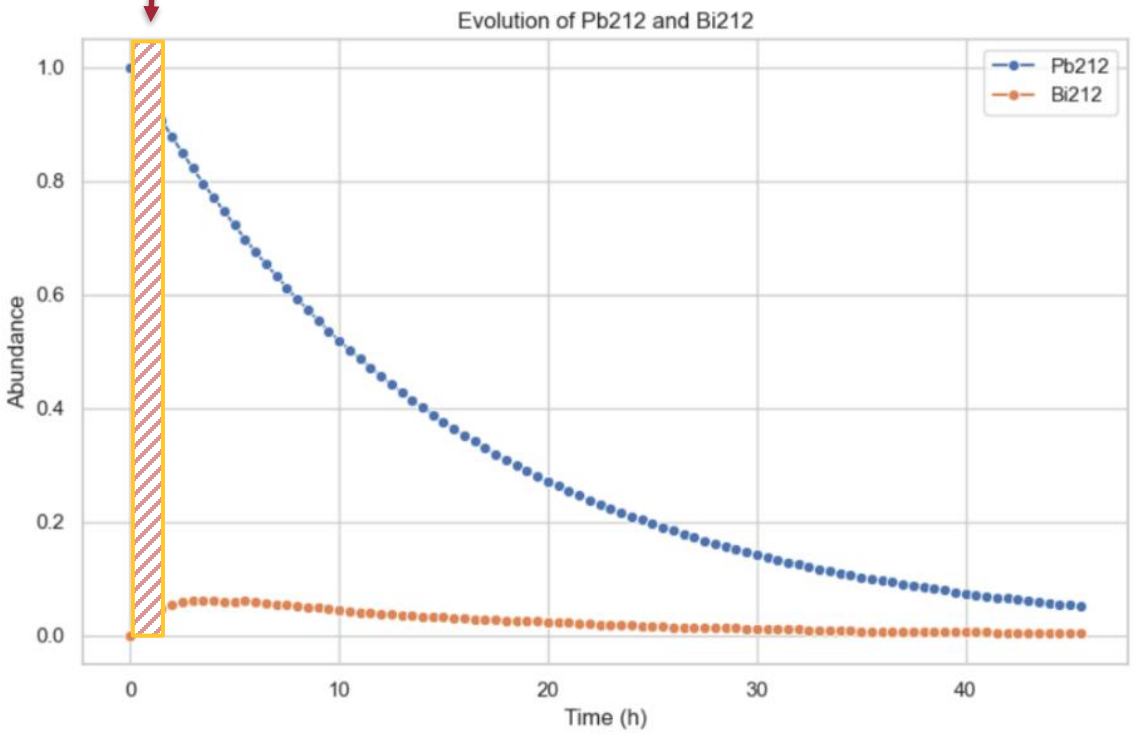
Actual time-structure



- The number of decays simulated is calculated step by step

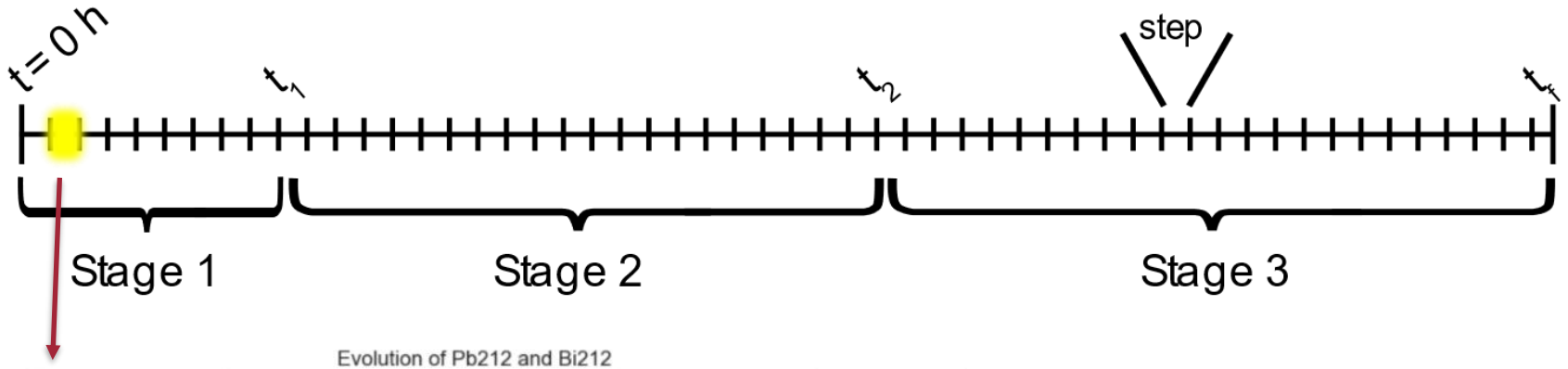
Actual time-structure

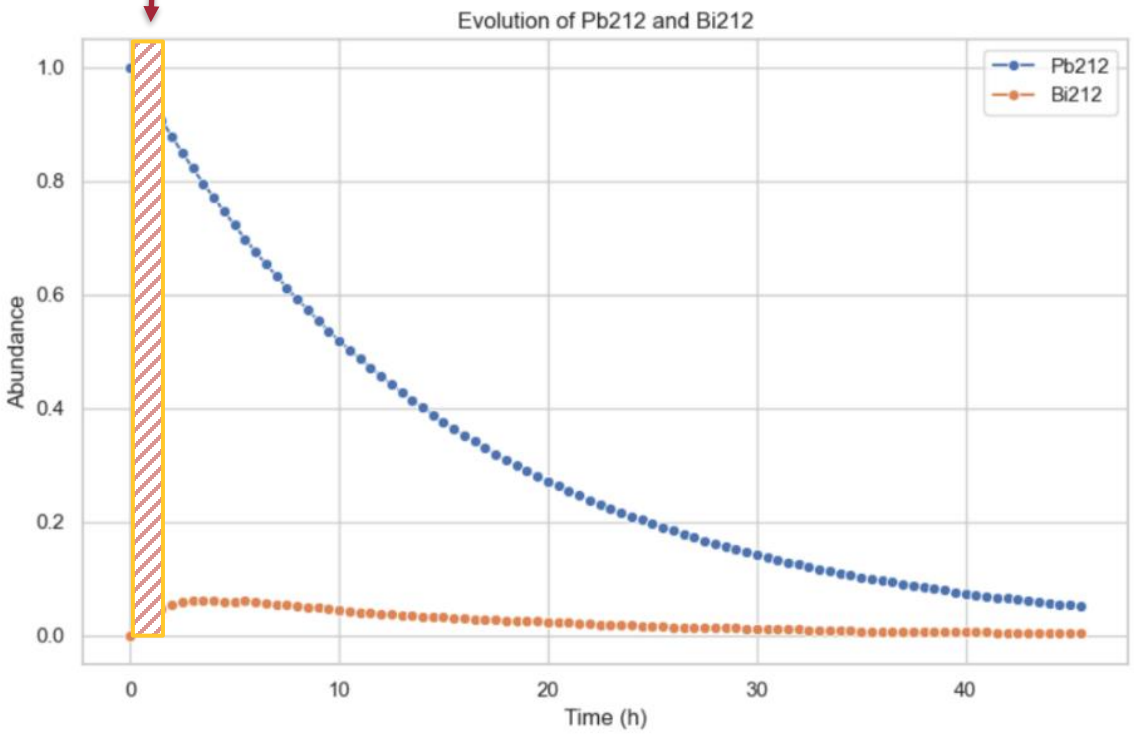




- The number of decays simulated is calculated step by step

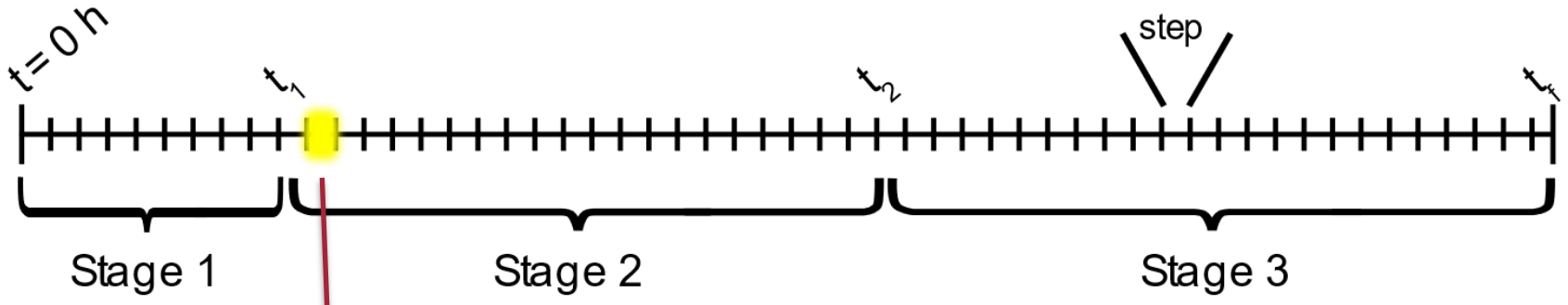
Actual time-structure

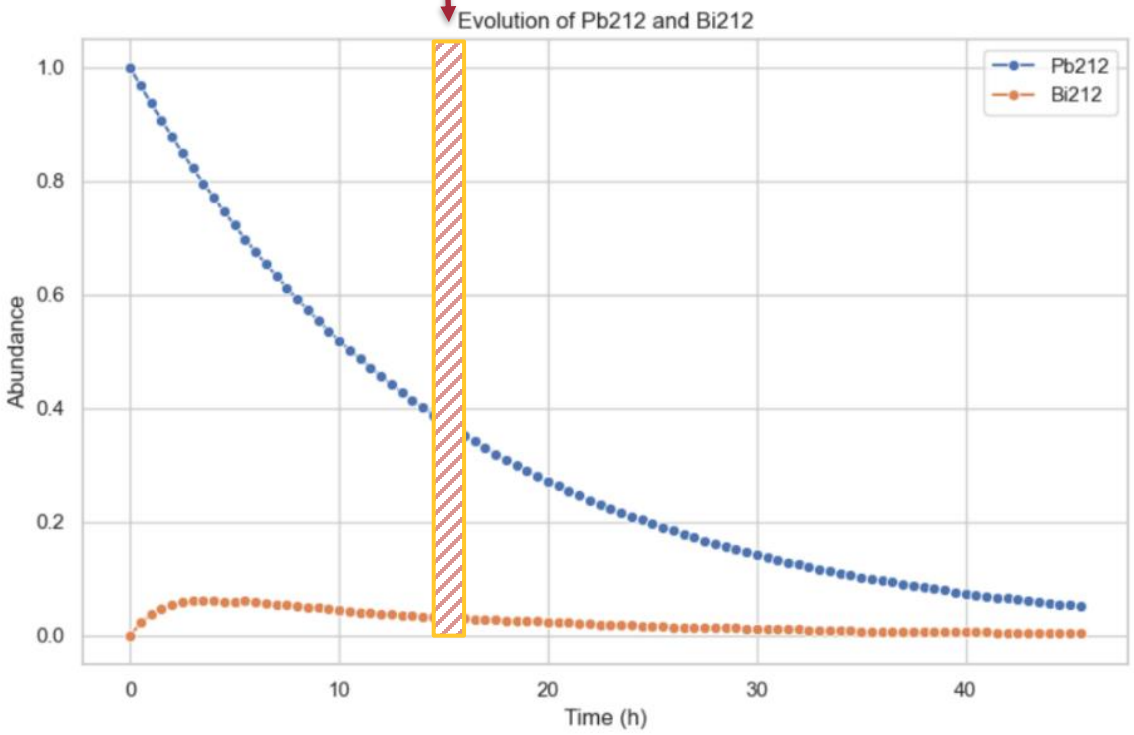




- The number of decays simulated is calculated step by step
- The particles are weighted considering the number of decays of this step

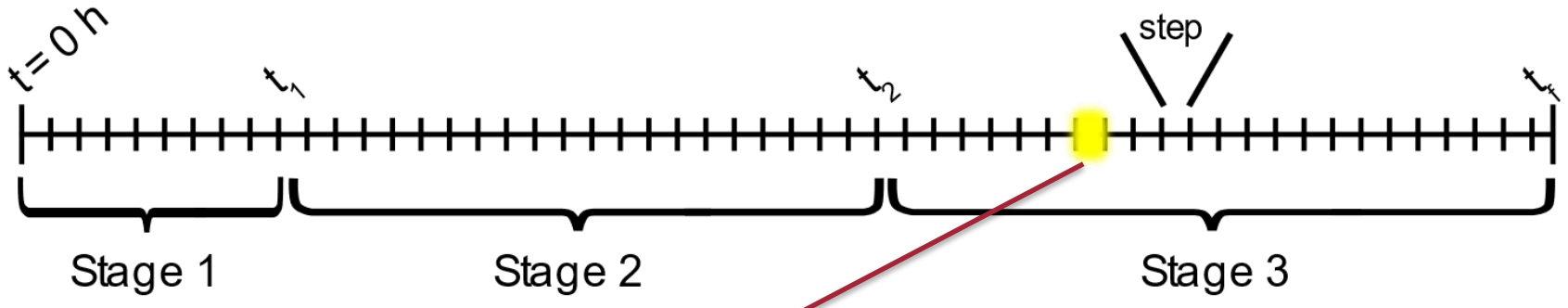
Actual time-structure

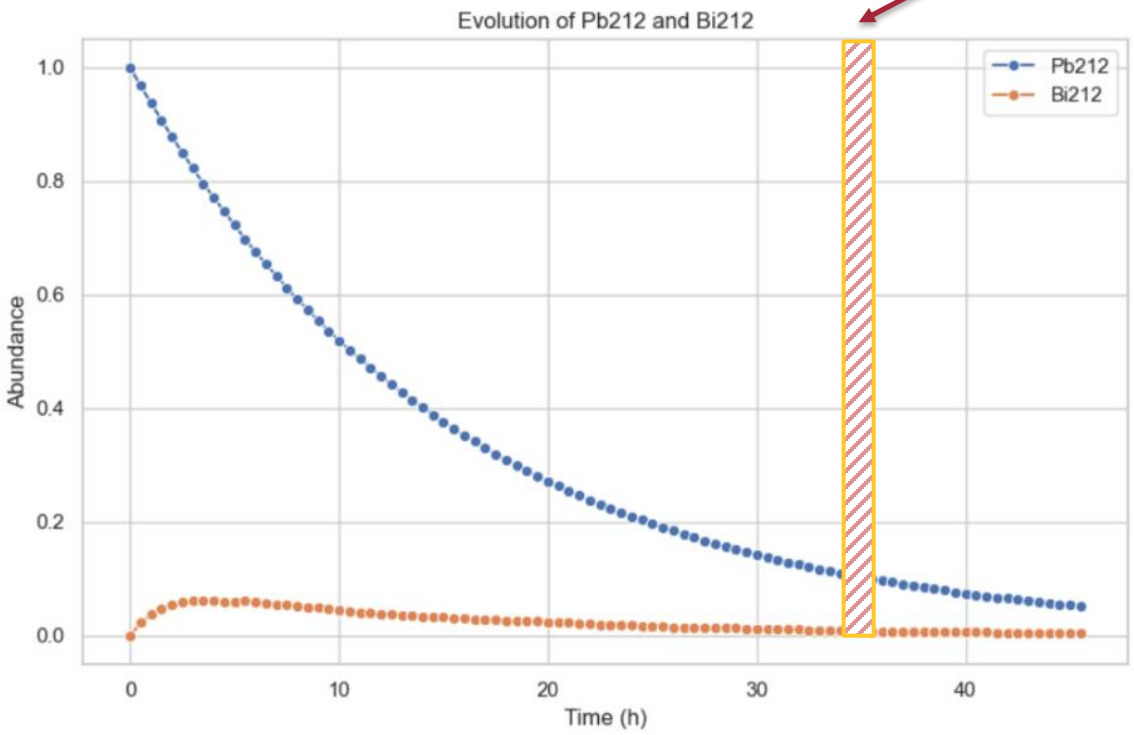




- The number of decays simulated is calculated step by step
- The particles are weighted considering the number of decays of this step

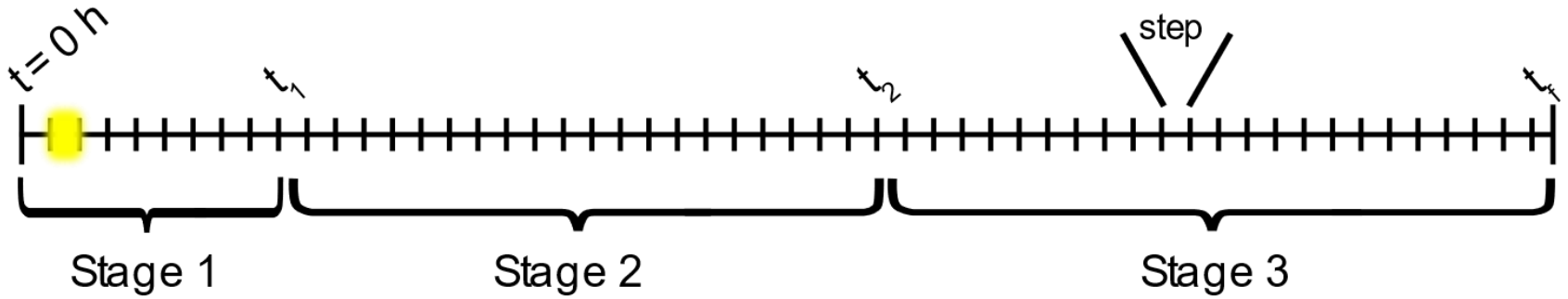
Actual time-structure

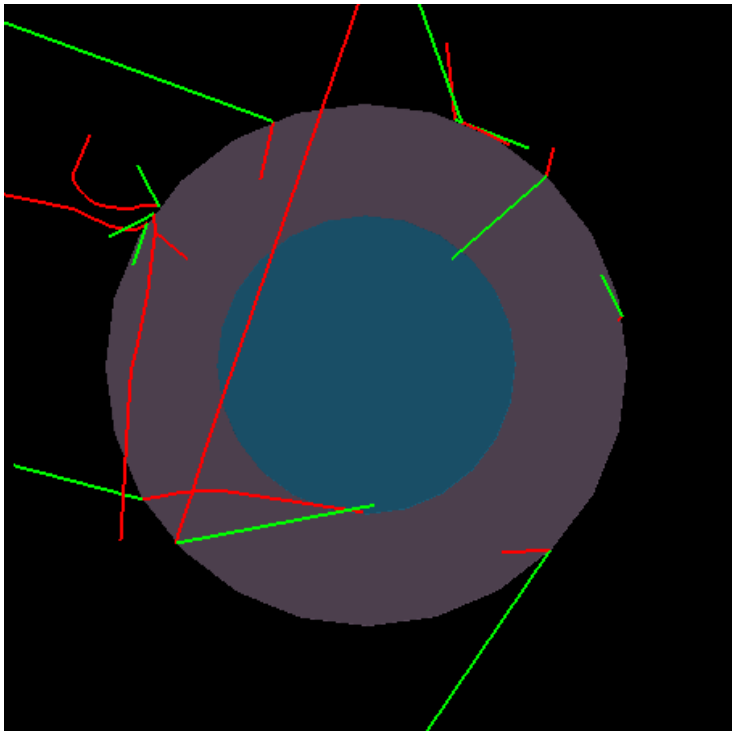




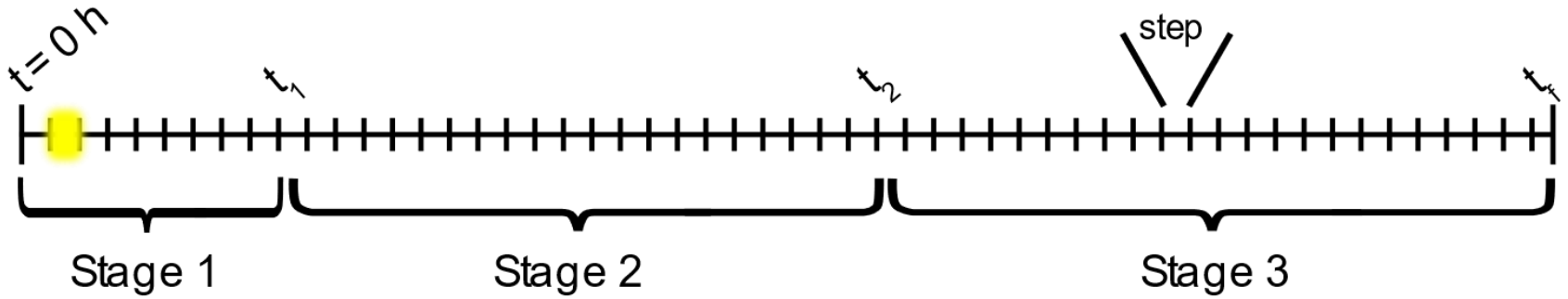
- The number of decays simulated is calculated step by step
- The particles are weighted considering the number of decays of this step

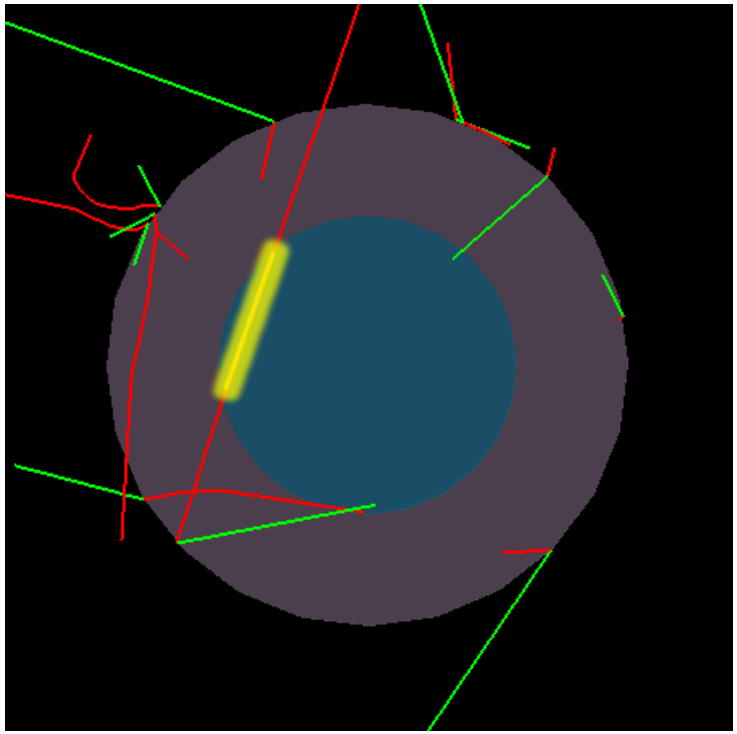
Scorer + time-structure



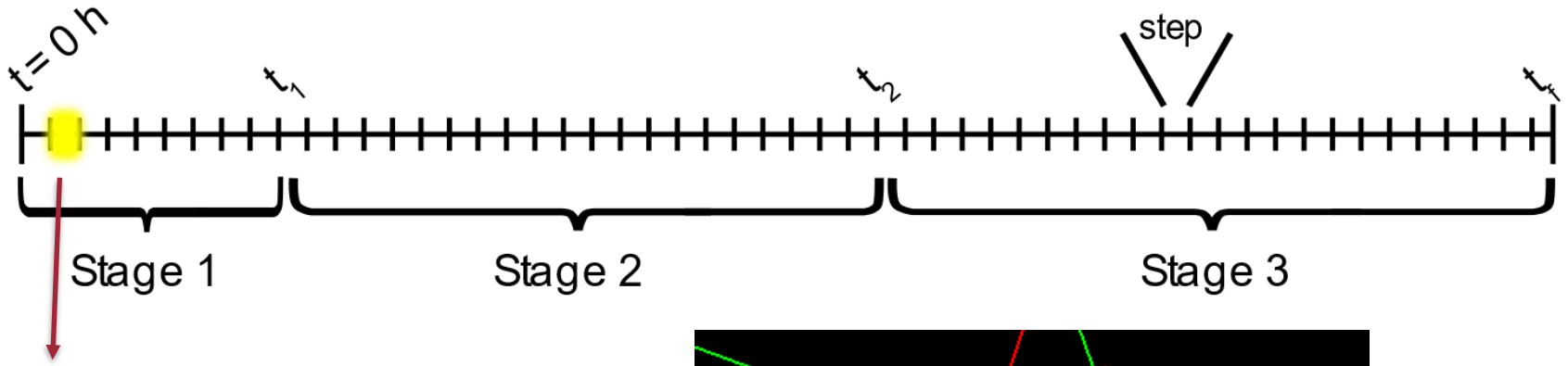


Scorer + time-structure

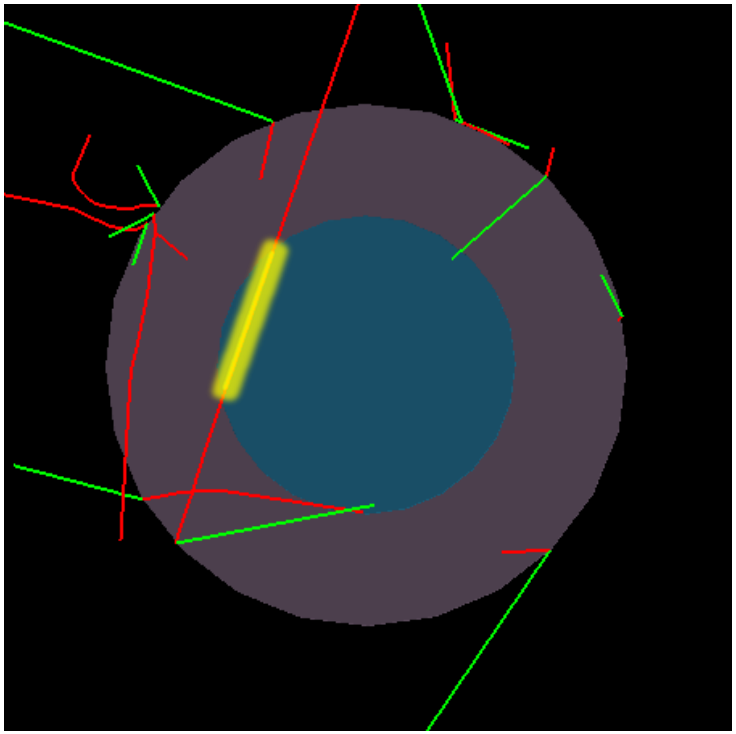




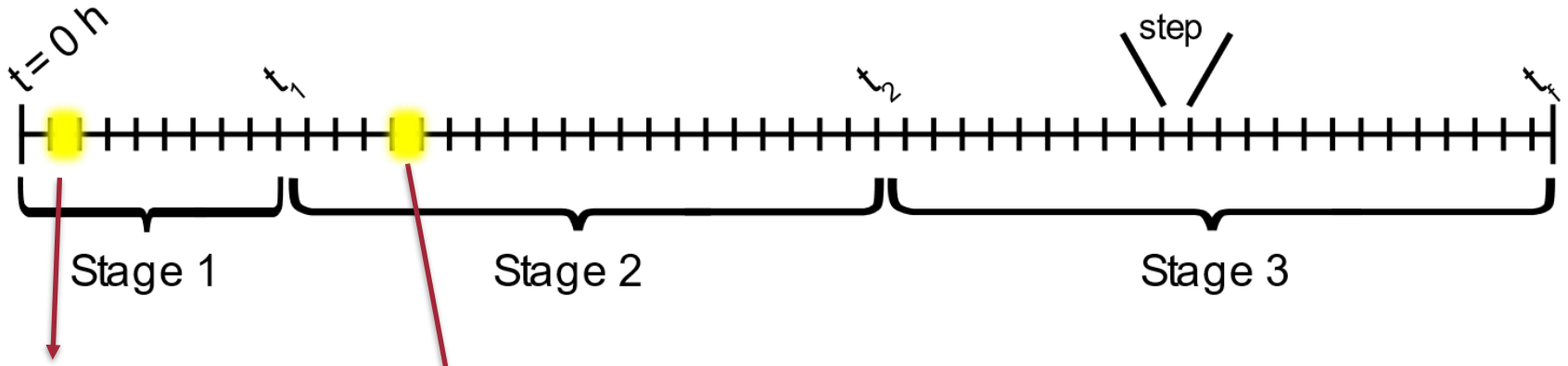
Scorer + time-structure



Nucleus	Dose (Gy)
2	0.02
….	….
654	0.1



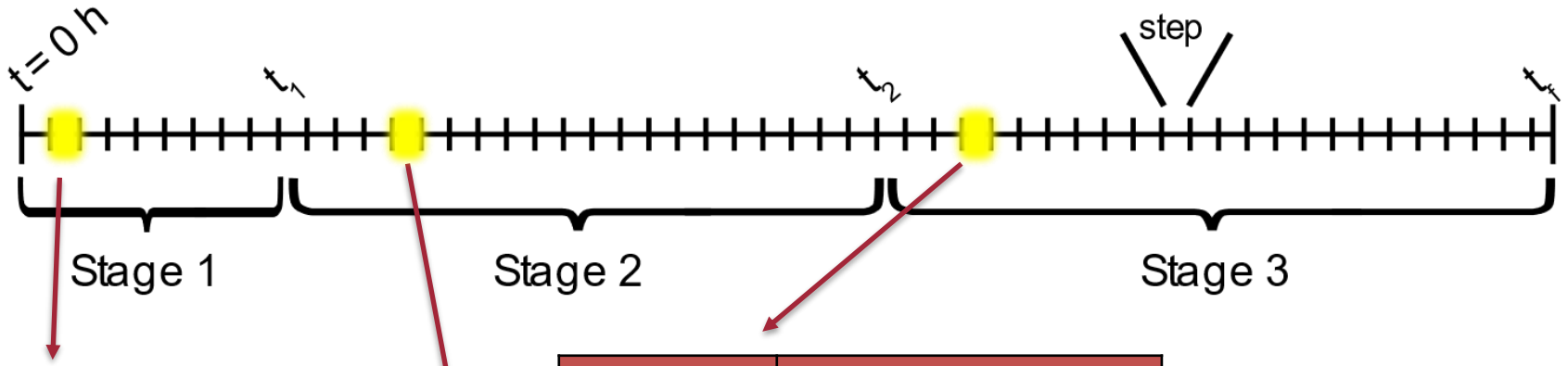
Scorer + time-structure



Nucleus	Dose (Gy)
2	0.02
….	….
654	0.1

Nucleus	Dose (Gy)
2	0.02
….	….
654	0.23

Scorer + time-structure

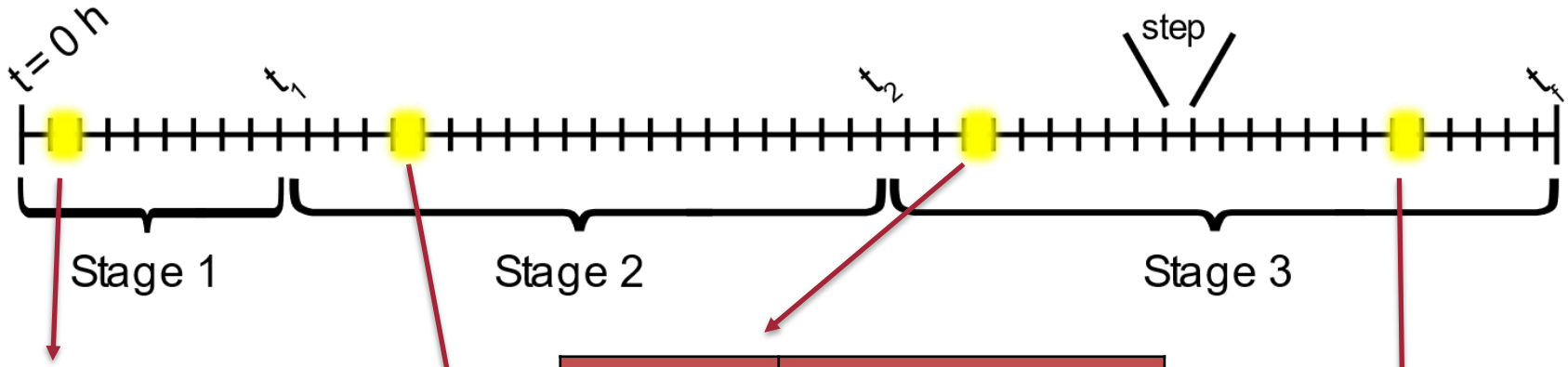


Nucleus	Dose (Gy)
2	0.02
….	….
654	0.1

Nucleus	Dose (Gy)
16	0.3
….	….
2876	0.09

Nucleus	Dose (Gy)
2	0.02
….	….
654	0.23

Scorer + time-structure



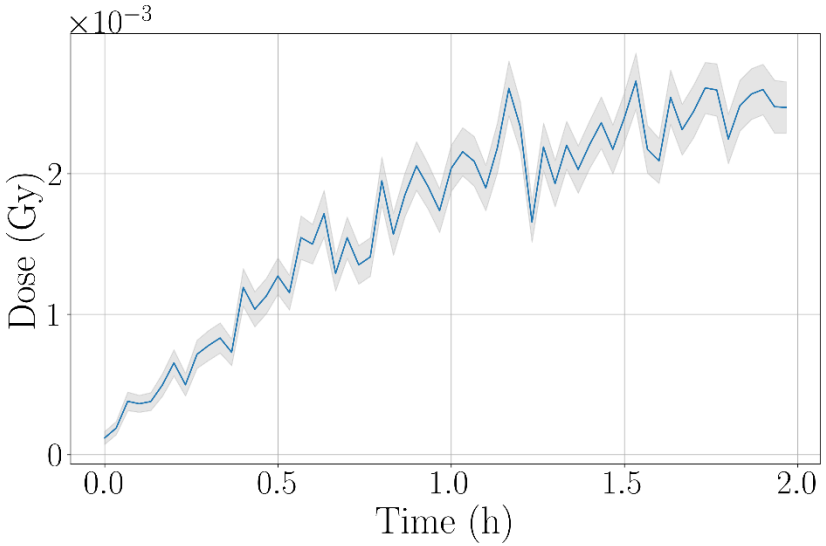
Nucleus	Dose (Gy)
2	0.02
….	….
654	0.1

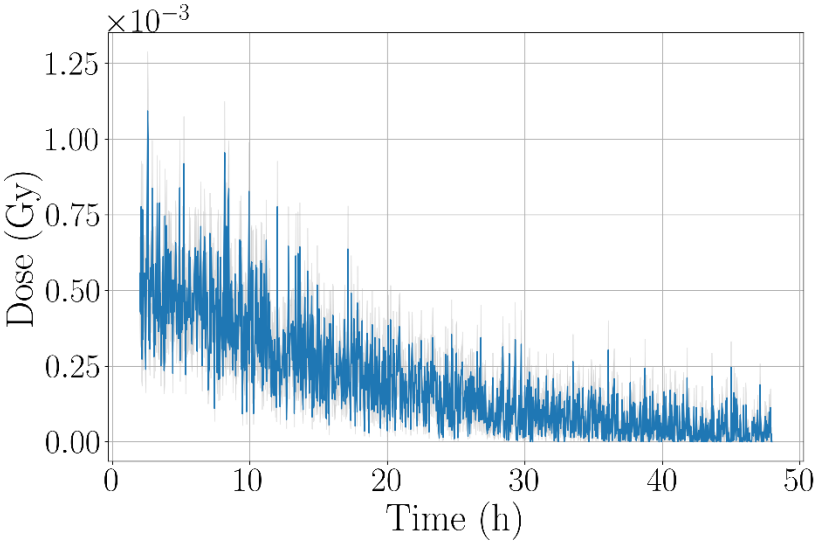
Nucleus	Dose (Gy)
16	0.3
….	….
2876	0.09

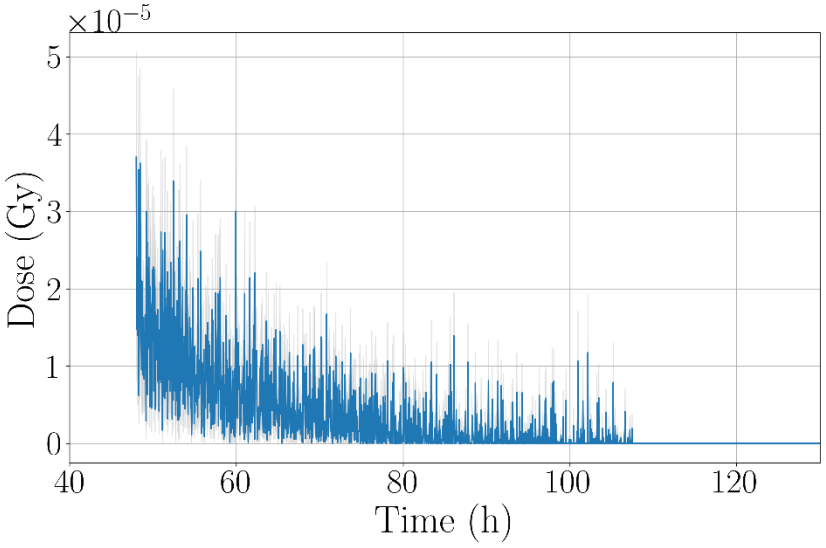
Nucleus	Dose (Gy)
2	0.02
….	….
654	0.23

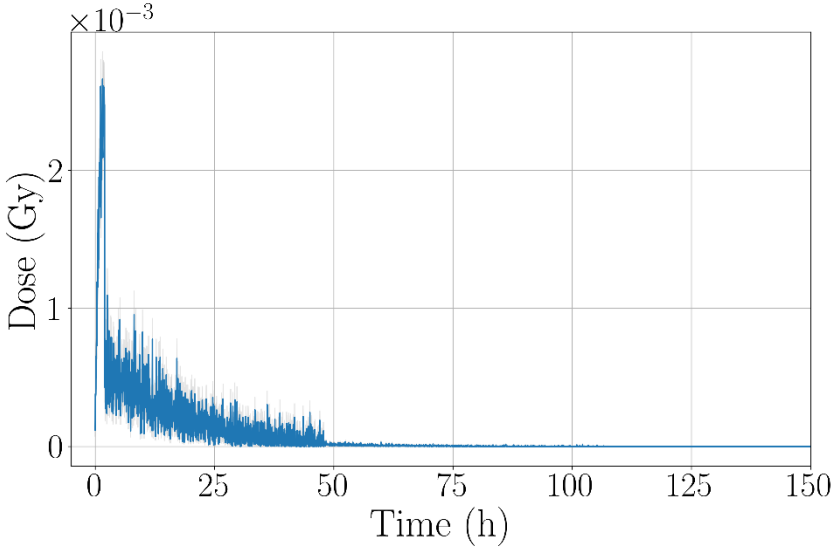
Nucleus	Dose (Gy)
534	0.32
….	….
6471	0.17

TOPAS tool: Dose-rate vs time

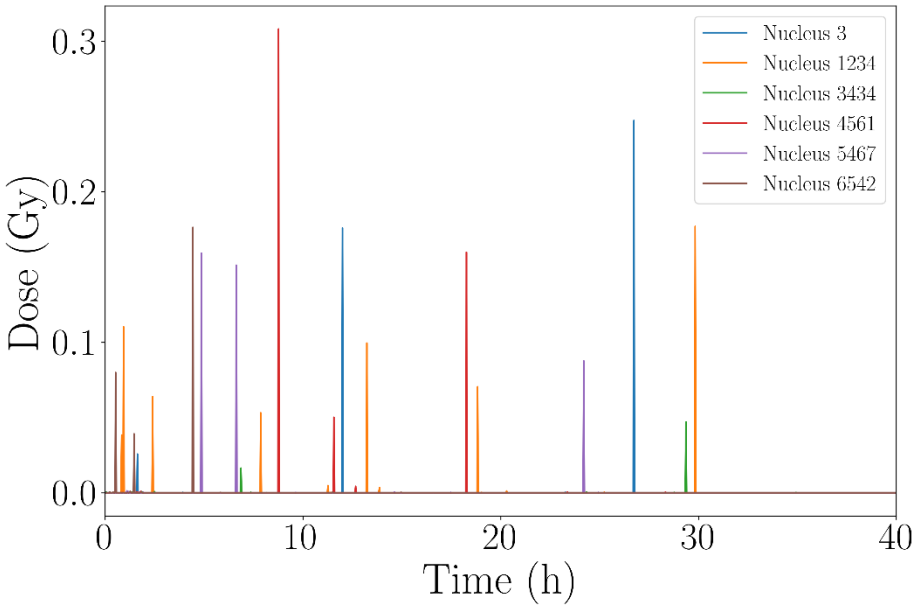


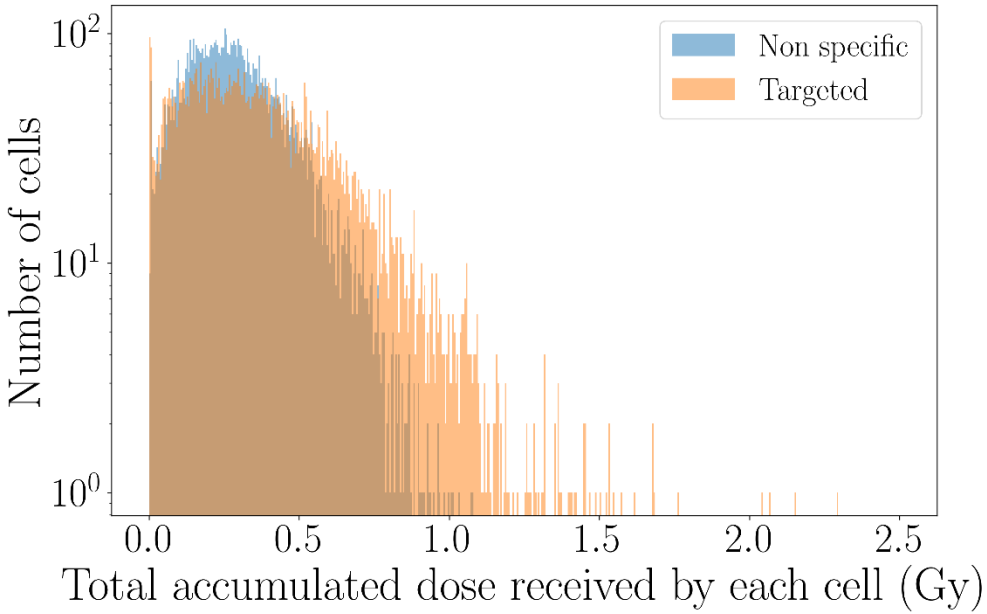






TOPAS tool: Microdosimetry





Conclusions

- We have developed a computational tool to recreate *in vitro* radiopharmaceutical experiments. To our knowledge, it is the first time that:
  - An **actual time-structure** for the dose is calculated
  - All emissions from **all the decay products** are considered, ordered in the **right time and abundance**
  - It is considered the dose received **by each nucleus individually**

Future…

- To extend the tool to 3D geometries would provide capability to simulate experiment with tumor spheres.
- To implement a biological model to obtain directly the survival fraction depending on the dose delivered.

Acknowledgments

This work was funded in part by Grant PID2021-098117-B-C21/ MCIN/AEI/10.13039/501100011033/ERDF, EU and by Grant NIH R00 CA267560.