The MC simulation of WIDMApp: an innovative approach for individual dose monitoring in Molecular Radiotherapy

C. Mancini-Terracciano, B. Cassano, F. Collamati, G. Iaccarino, R. Mirabelli, S. Morganti, F. Nicolanti, E. Solfaroli Camillocci, A. Soriani, R. Faccini

Istituto Nazionale di Fisica Nucleare

Contact: francesca.nicolanti@uniroma1.it

Molecular Radio-Therapy

- MRT dose distribution depends on:
  - Pharmaceutical biokinetics
  - Competition with supportive drugs

→ Uptake and clearance vary among individuals

- The state of the art monitoring is done with a few SPECTs

→ Low accuracy (uncertainty > 30%)

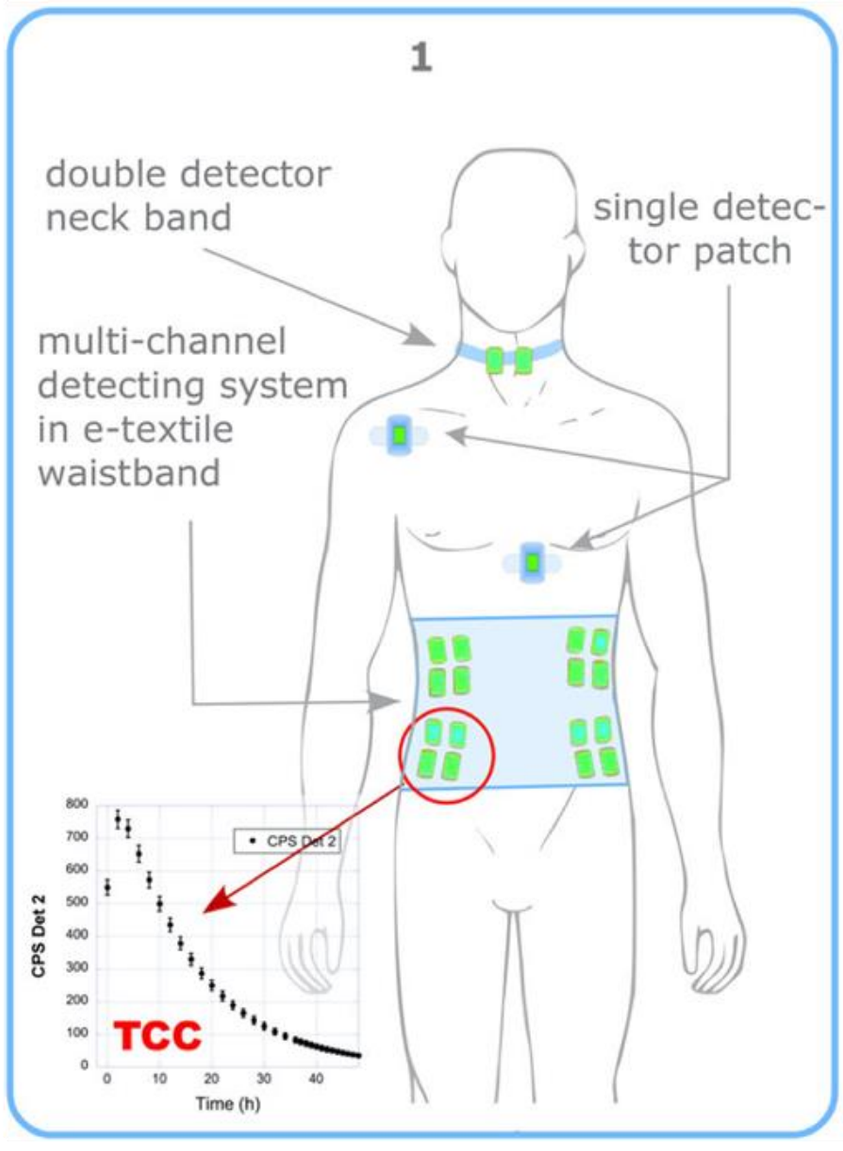
↓

Dose limited by organs at risk dose knowledge

The WIDMApp approach

Wearable Individual Dose Monitoring Apparatus

WIDMApp aims to provide **a <u>continuos</u> real-time measurement** of radiopharmaceutical accumulation and transit in MRT treatments.



Detector system

The WIDMApp approach

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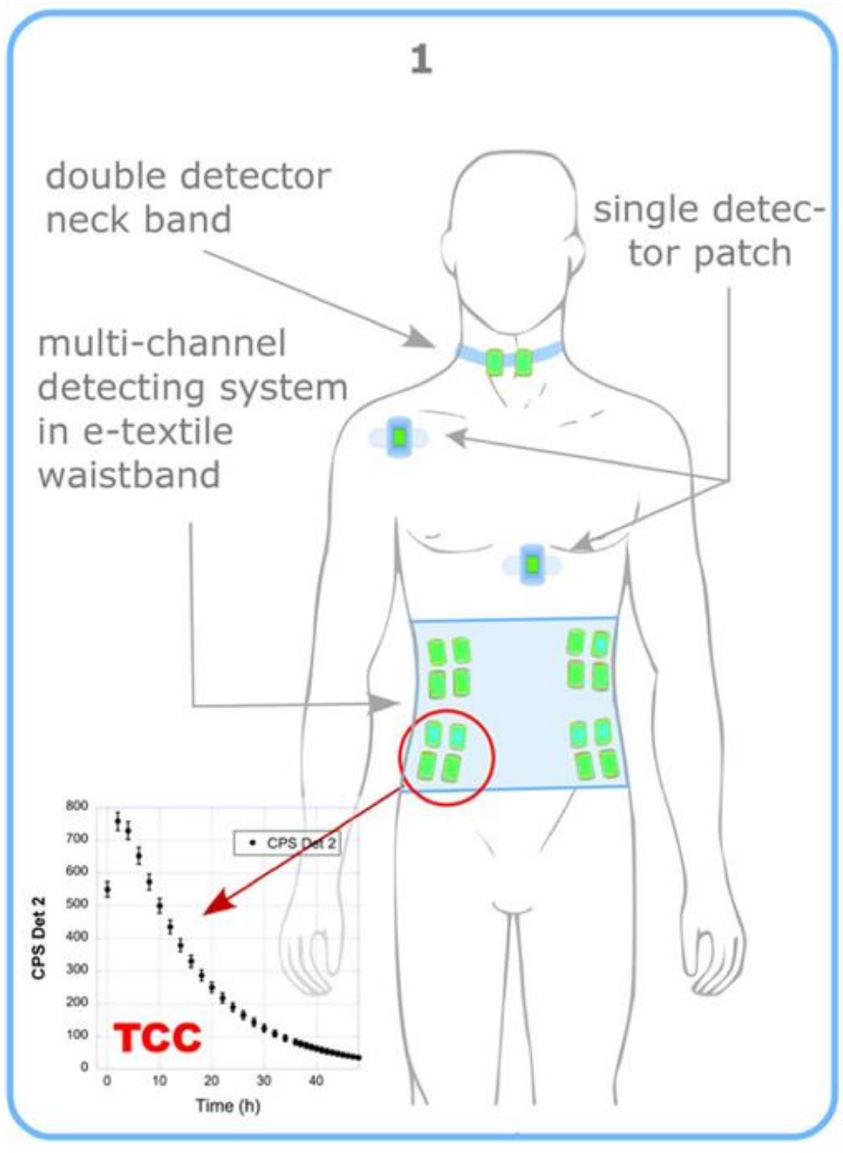
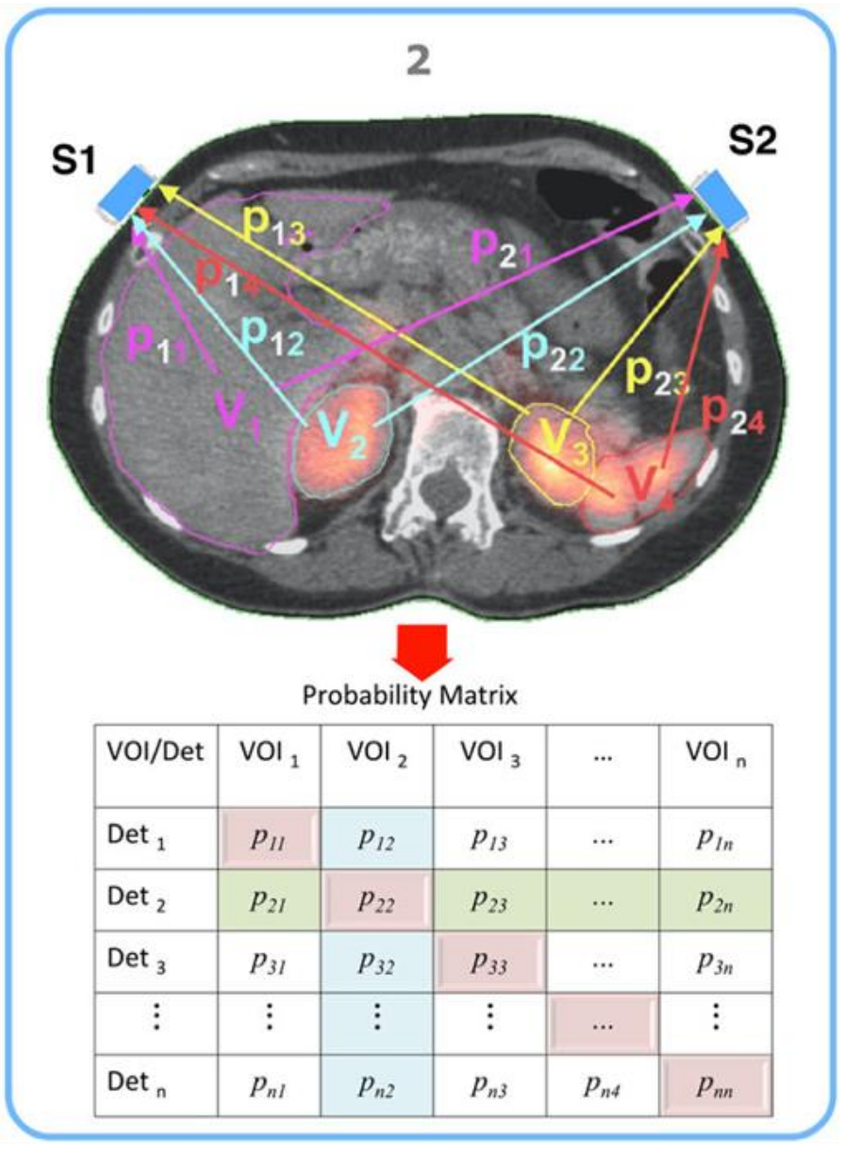


Detector system



VOI/Det	VOI 1	VOI 2	VOI 3	...	VOI n
Det 1	p_{11}	p_{12}	p_{13}	...	p_{1n}
Det 2	p_{21}	p_{22}	p_{23}	...	p_{2n}
Det 3	p_{31}	p_{32}	p_{33}	...	p_{3n}
⋮	⋮	⋮	⋮	...	⋮
Det n	p_{n1}	p_{n2}	p_{n3}	p_{n4}	p_{nn}

MC simulation

The WIDMApp approach

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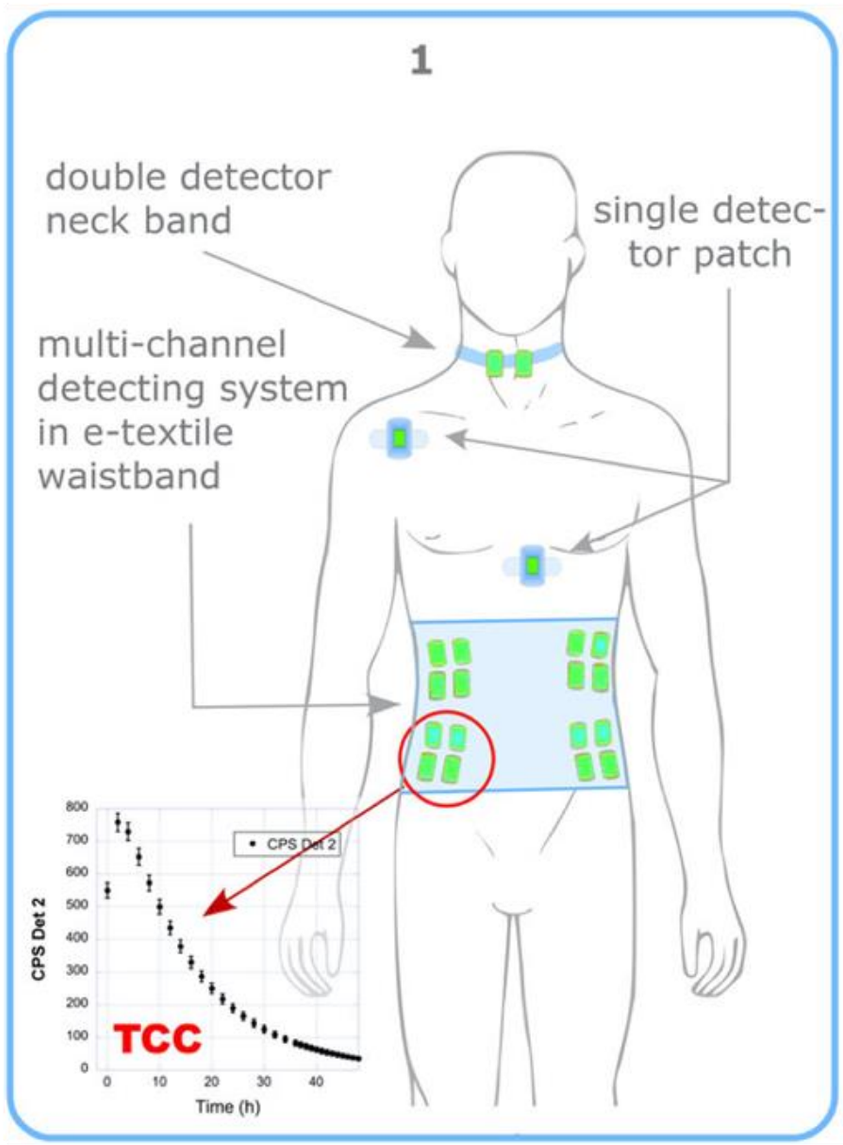
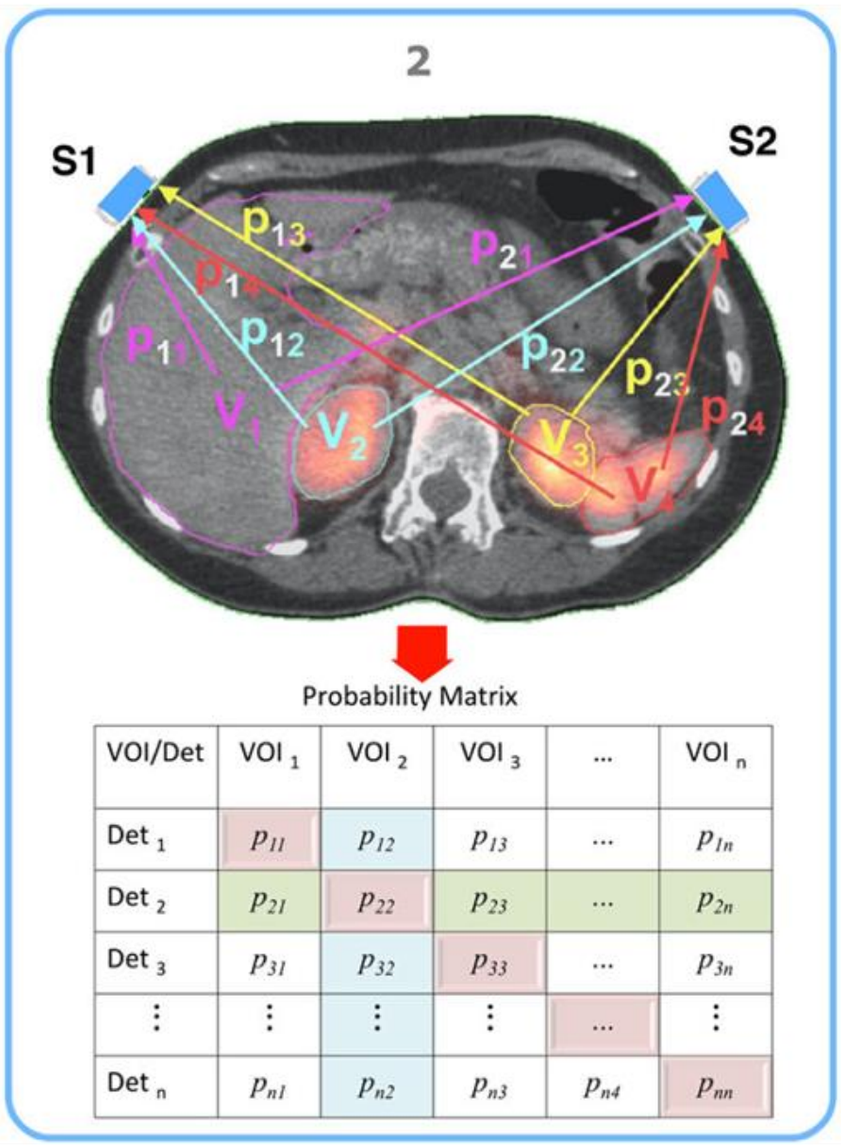
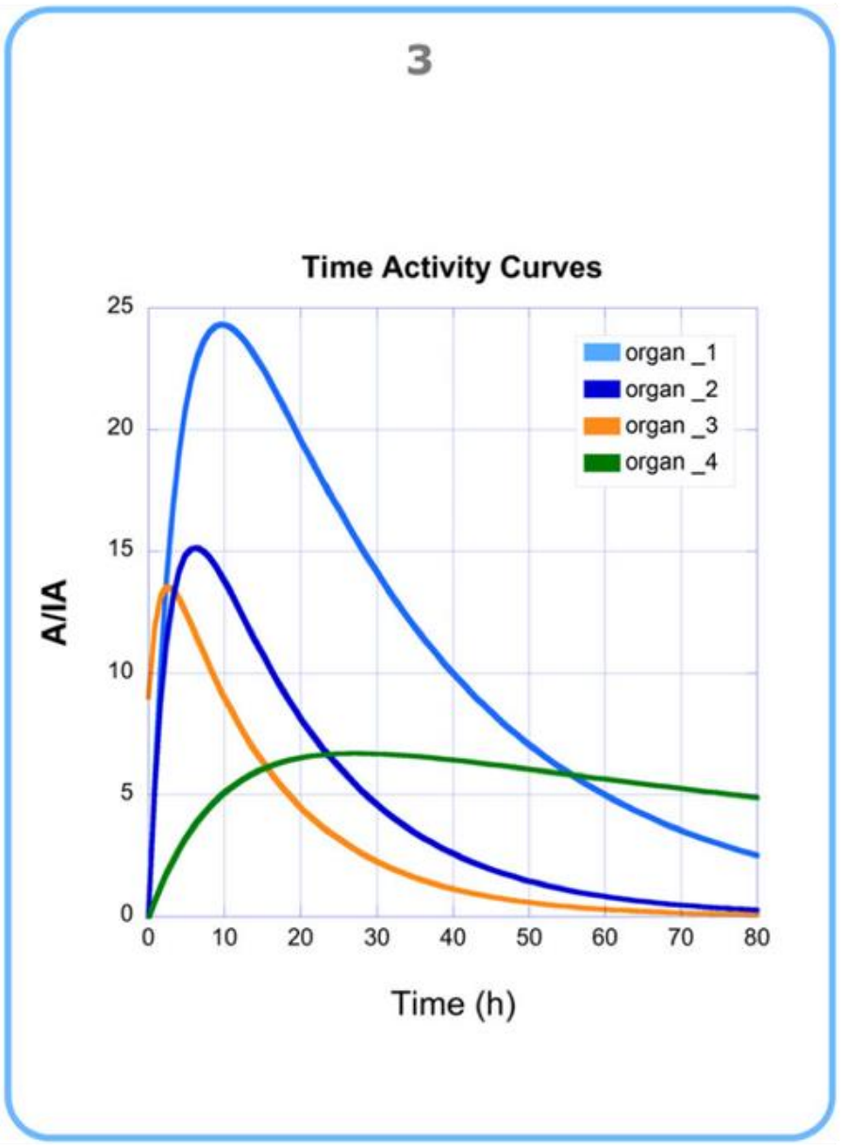






Detector system | MC simulation | Unfolding algorithm

Monte Carlo simulation needs for WIDMApp

- Indispensable to estimate the probability that a photon produced in each organ produce a signal in all the detectors

- It will be tailored on each patient
  - Importing the CT
  - ROIs to define the relevant organs
  - ROIs to define detectors (placeholders during the CT)

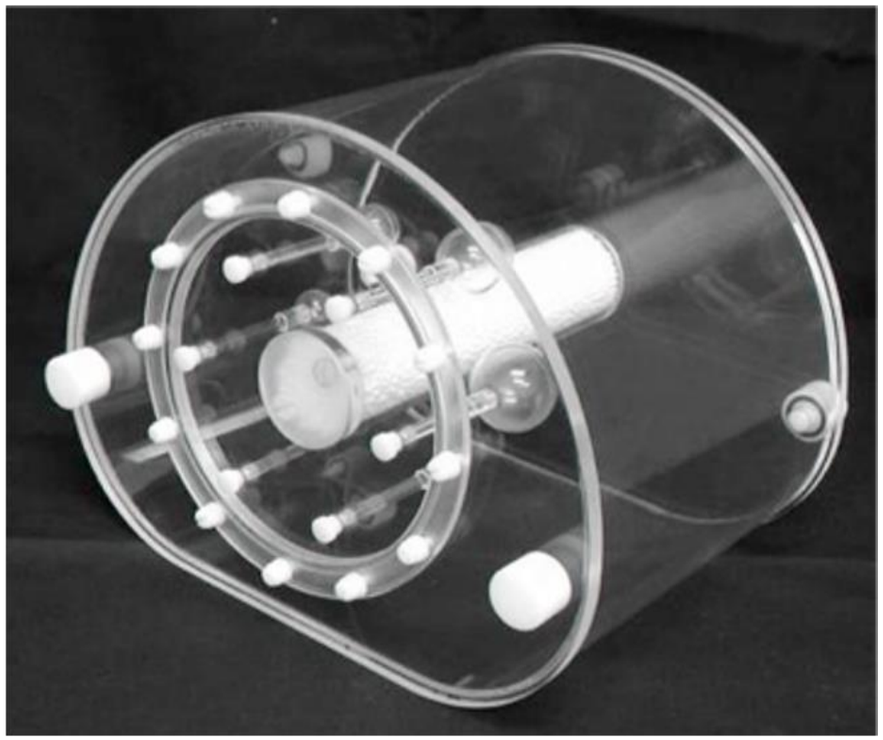
Feasibility study with NEMA phantom

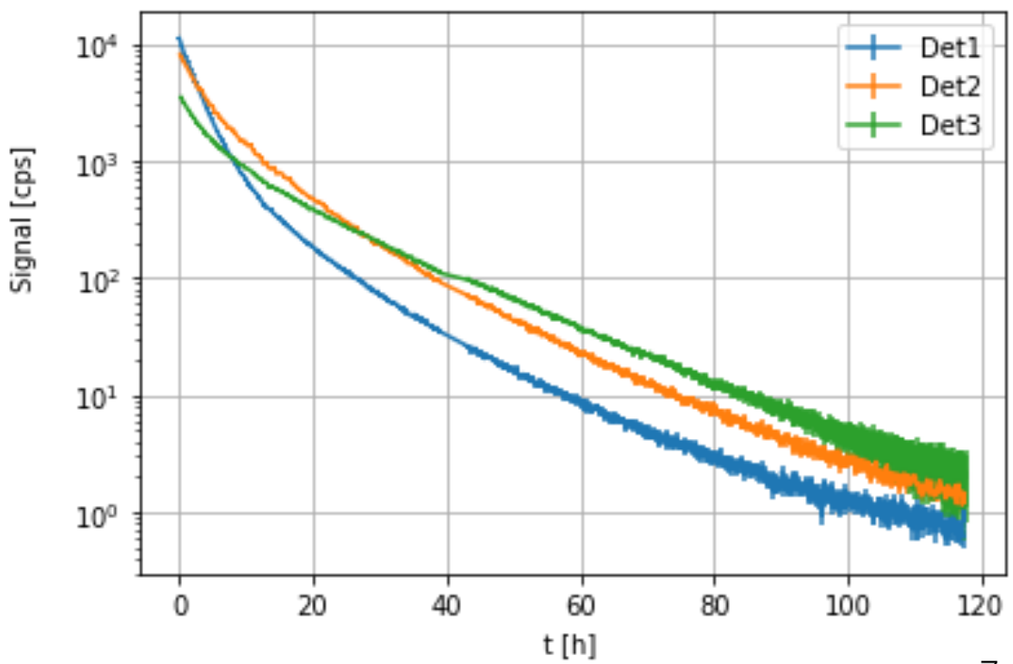
- NEMA a human abdomen phantom (filled with water)
- 3 spheres filled with 3 different isotopes
- to mimic 3 organs with different washout

  ^{18}F (β^+, $t_{1/2}$=1.83 h, A= 54 MBq)

  ^{99m}Tc (140 keV γ, $t_{1/2}$=6.01 h, A= 53 MBq)

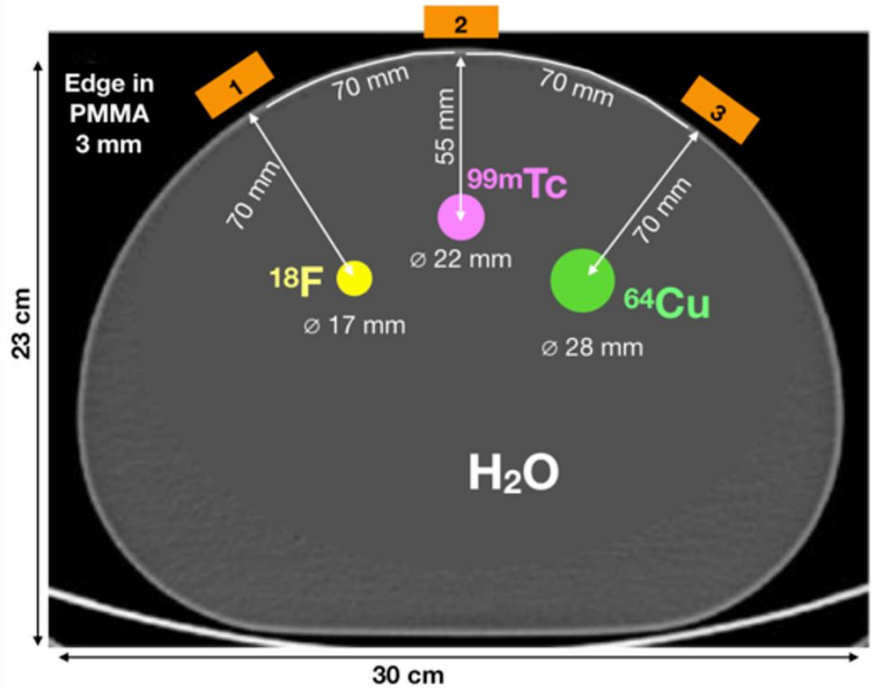
  ^{64}Cu (β^+, $t_{1/2}$=12.7 h, A= 28 MBq)
- 3 detectors placed nearby the 3 spheres





MC simulation

- Developed thinking to the WIDMApp pipeline
- Imports the CT of the NEMA phantom for the geometry
- Sample primaries generation points from “organ” ROIs designed in the DICOM files
  - Hit or miss approach
  - **Winding number** algorithm to check if the point is inside the ROI
- Place the detectors in a G4ParallelWorld

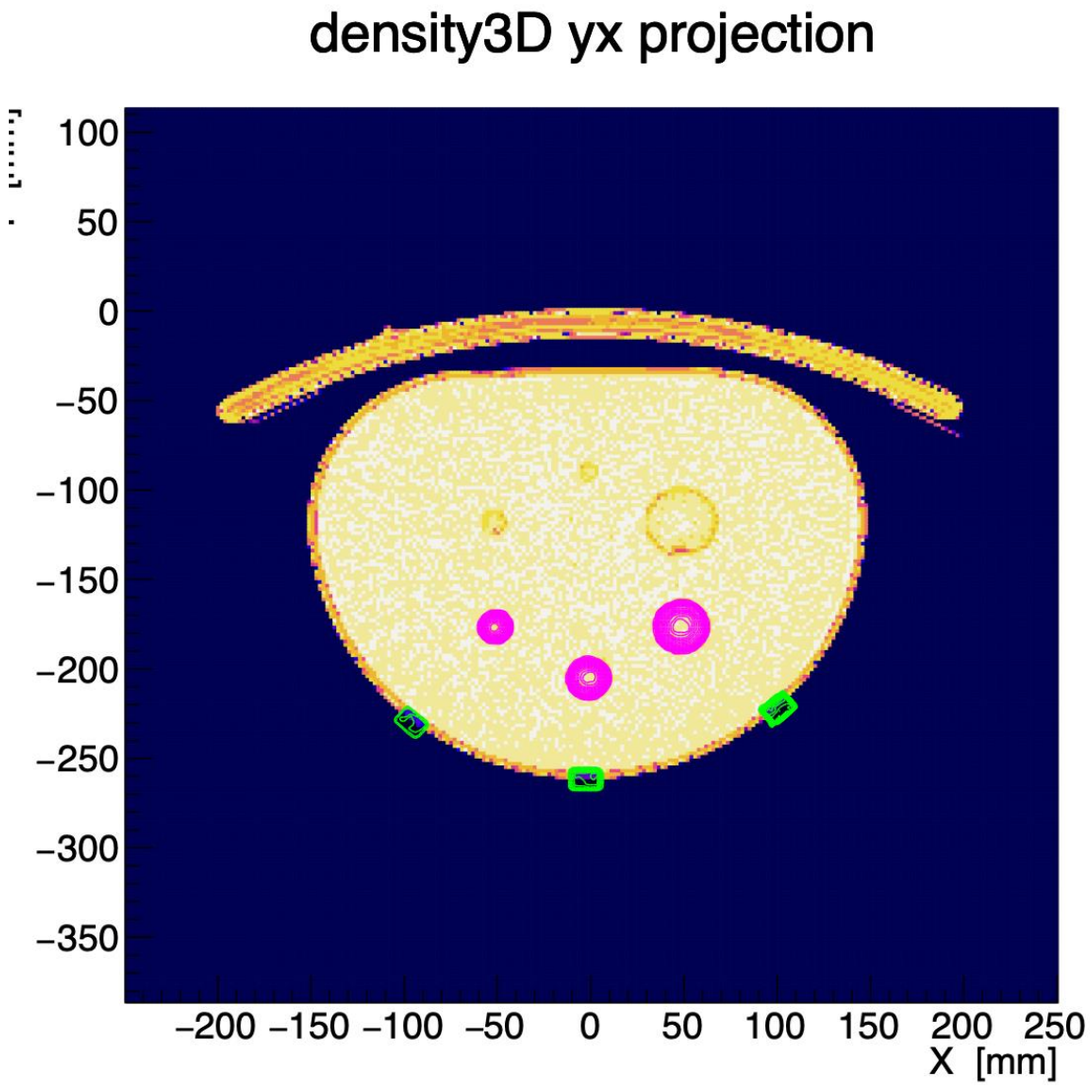


Sensitive detectors

- The detectors are placed in a G4ParallelWorld
- Can be superimposed to the CT geometry
- It’s possible to use all the possible voxel tracking
- It will be possible to define detectors from the ROIs
  - We are working on using CGAL to find a tasselated solid from each DICOM ROI
  - and importing that as a G4TasselatedSolid

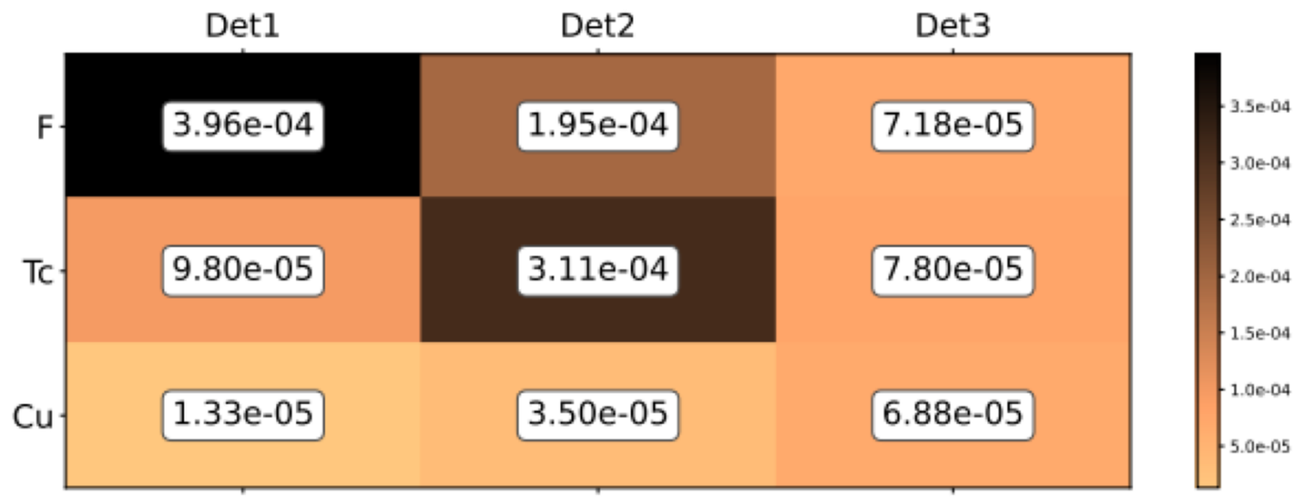
Checking the geometry

- A dedicated run to check the geometry has been developed
- Geantinos are shot from one of the CT planes
  - One per voxel
  - In the direction orthogonal to the plane
- At each step, density and material index are scored



MC output

- The MC output is the probability of each organ to produce a signal in all the detectors



- Such matrix is needed by the unfolding algorithm

Measured signals

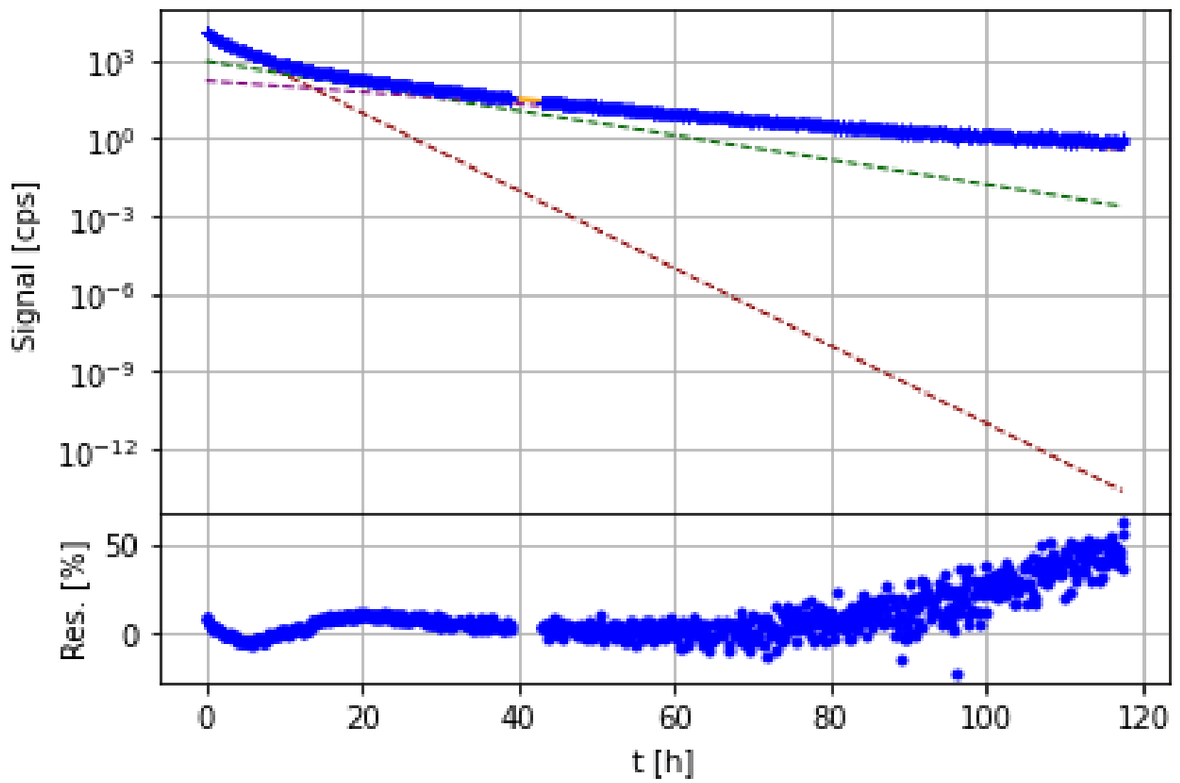
$$\chi^2\left(A'_{0j}, t'^{\,eff}_{1/2_j}\right) = \sum_{i=1}^{N_{det}} \sum_{k} \left(\frac{S_i(t_k) - S_i(t_k; A'_{0j}, t'^{\,eff}_{1/2_j})}{\sigma_i(t_k)} \right)^2$$

$$S_i(t_k; A'_{0j}, t'_{1/2j}) = \sum_{j=1}^{Norg} p_{ij} A_{0j} e^{-t_k/(t_{1/2j}/ln(2))}$$

Results

- Estimation of the total absorbed dose with an error of 3-7% on $t_{1/2}$
- Larger error on ^{99m}Tc A0
- WIDMApp is not designed to estimate A_0s
- ^{99m}Tc emits a ɣ with lower energy

	$t_{1/2}$ [h]	err	A_0 [MBq]	err
^{18}F	1.97 ± 0.06	7%	54.8 ± 3.3	1%
^{99m}Tc	6.20 ± 0.35	3%	43.7 ± 3.8	-18%
^{64}Cu	13.34 ± 0.08	5%	28.3 ± 1.9	<1%



Container

- The WIDMApp MC simulation has several external dependencies
    - Geant4
    - DCMTK (for each patient a simulation is needed -> reading DICOM is mandatory)
    - CGAL (in future)
- A Docker container has been developed with all the dependencies installed

Conclusions

- WIDMApp is a project aimed at monitoring MRT
- MC simulation is a key point to infer the organs dose from the detector measures
- It will have to be tailored for each patient
- We developed a Geant4 application designed to use ROIs to identify organs and detectors
- A paper will be submitted soon

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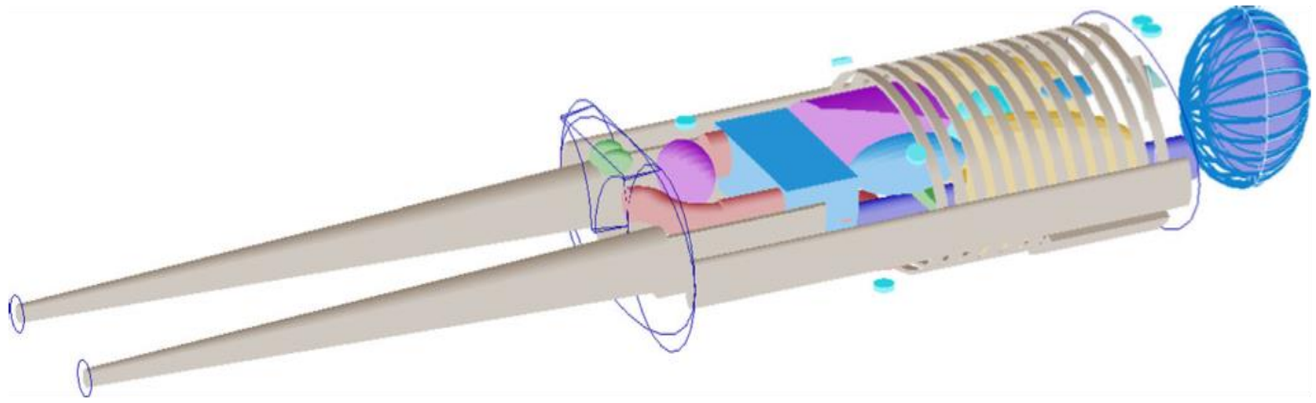
thank you for your attention!

BACKUP SLIDES

First feasibility study

- MIRD Phantom
  - 6 activated organs

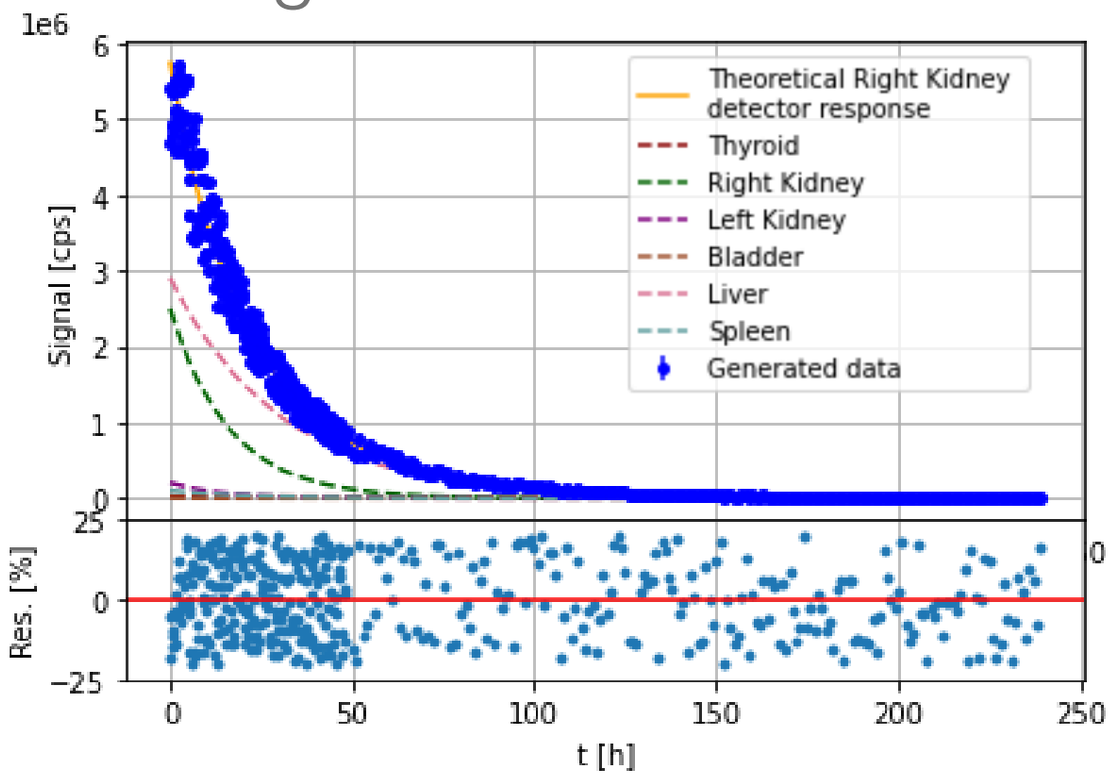


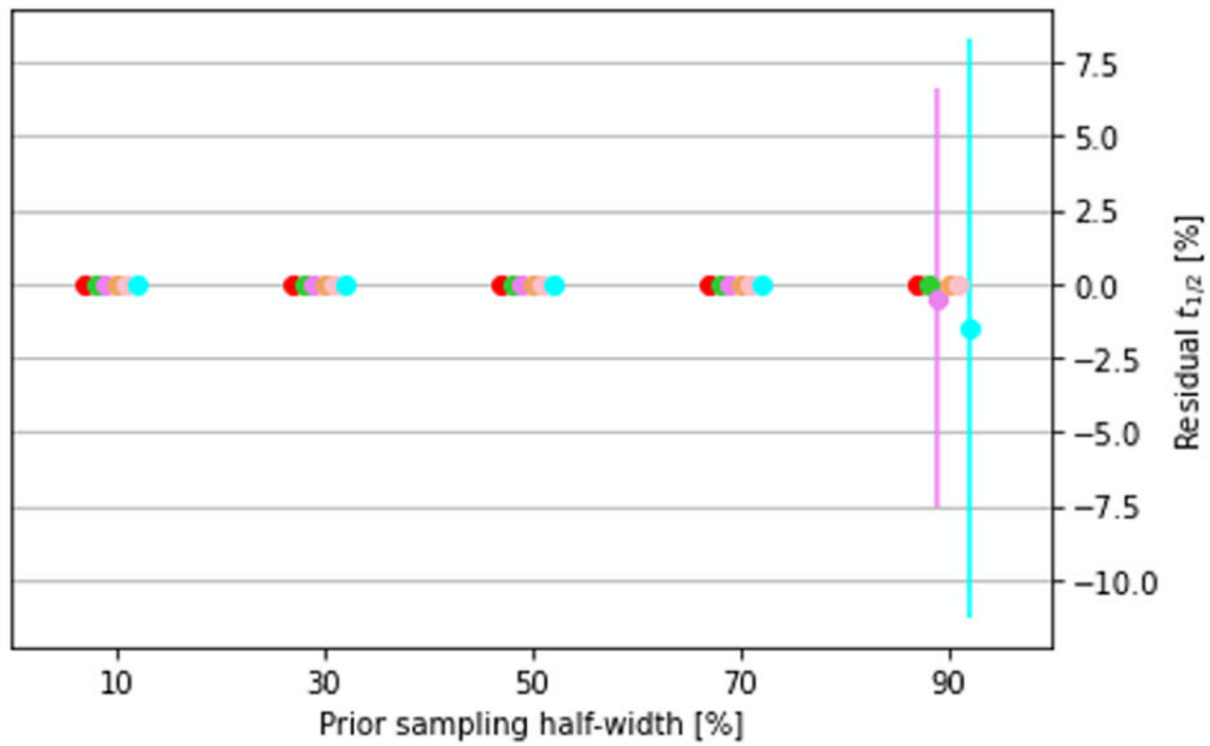
- Source:
  - I131 uniform emission;
  - 2.5 GBq treatment
    (30% in thyroid, 60% on other organs: Liver, Kidneys, Spleen, Bladder)

- Detectors:
  - Radius 1.3 cm, thickness 0.3 cm;
  - Efficency = 100%;
  - One per organ (two on thiroid);

First feasibility study

- The algorithm manages to converge to the true values
- We tested also its stability with respect to priors and background





- S. Morganti et al., A wearable radiation measurement system for collection of patient-specific time-activity data in radiopharmaceutical therapy: system design and Monte Carlo simulation results. Med Phys. 2021;1-10. https://doi.org/10.1002/mp.15311

The algorithm converges up to fluctuations on the measured points of 15%

Primaries generation

- The generation of primaries is done sampling (with a hit-or-miss approach) points within the “organs” ROIs

- Firstly selecting a slice of the ROI and so its Z

- Then sampling a points within
  (Xmin : Xmax, Ymin : Ymax, Z-dZ : Z+dZ)

  - where X/Ymin and X/Ymax are the ROI extremes

  - Z is the ROI slice one and dZ its thickness

Checking if the point is inside the ROI

- To accept the sampled point we have to check if it lies inside the selected ROI slice

- The fastest and precisest method is the *winding number* algorithm:

  - Find all the edges of the polygon that cut through the line passing through the query point and is parallel to one axis.

  - For these edges, check if the query point is on the left or right side of the edge when looking at all the edges in anticlockwise direction

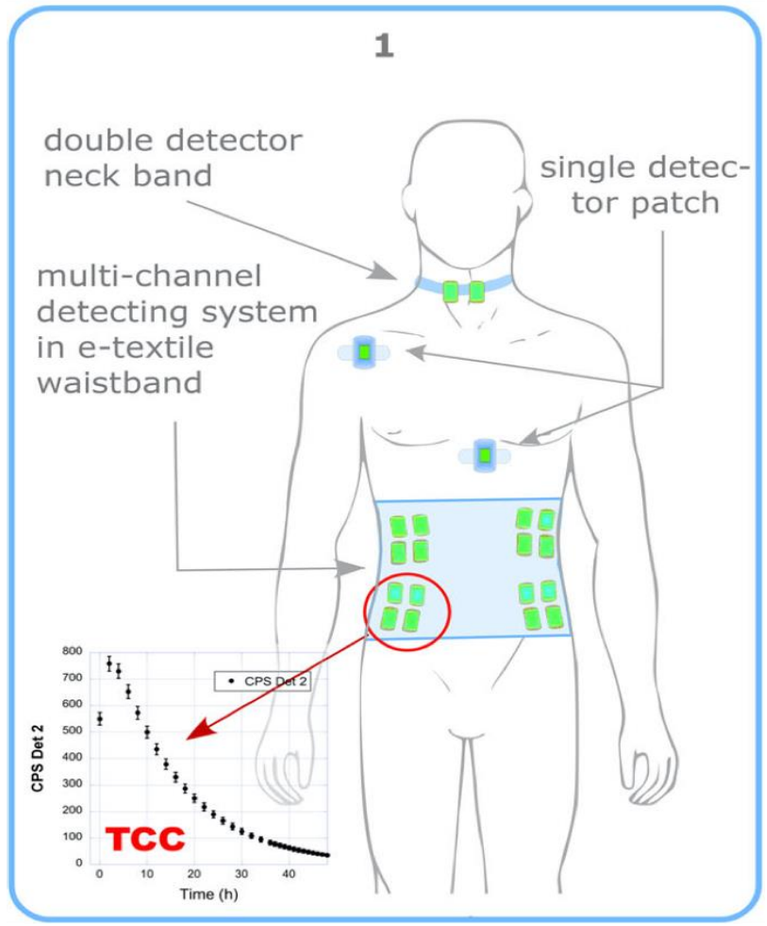
  - Increase the value of winding number by one if query point is on the left side and decrease by one if query point is on the right side

  - If the final winding number is non zero, the point lies inside the polygon

The WIDMApp detector

Requirement for the **wearable γ detecting sensor:**

- • thin, lightweight, comfortable, mechanical robust, simple, compatible device;
- • linear response over a **wide counting rate range** (from few CPS to ~ 10kCPS);
- • low power consuming and battery operated



The first prototype

First Sensor Prototype:

Para-tephernyl 15x15 mm^2, h= 3mm;

2x2 6mm C-Series SiPM array.

- Shape of the sensor and read-out are not yet optimized
  - A simulation will be perfomed for this
- It has a known non linearity for high rate values
  - The saturation in data has been corrected
- The efficiency have been calculated with a dedicated test

Detector efficency

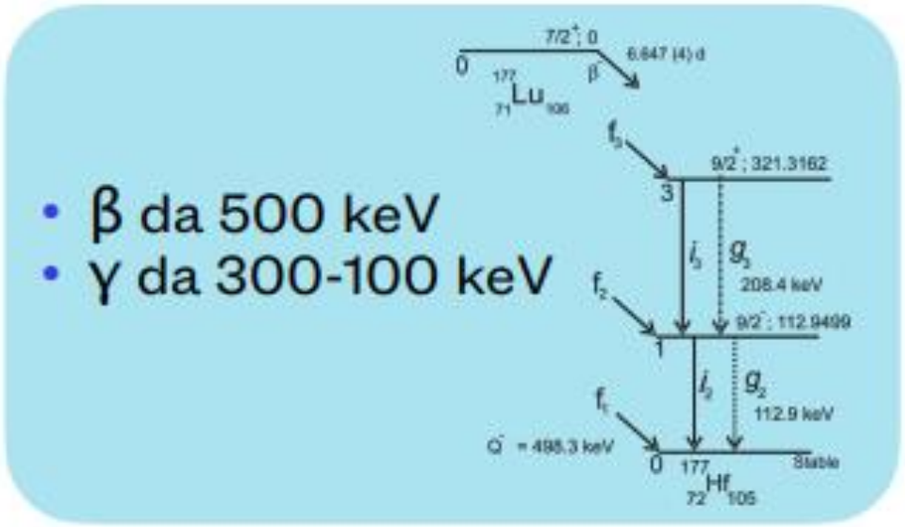
$$CPS(t) = A(t) \times \epsilon_{Geom} \times \epsilon_{Int} \times \epsilon_{Det} = A(t) \times \epsilon_{MC} \times \epsilon_{Det},$$

- Measurements with only one active sphere per time inside the phantom have been acquired
- Single isotope measurements have been used to evaluate the efficiency of each detector, according to:

$$\epsilon_{Det}^{ij} = \frac{CPS(0)^j}{A(0)^i \times \epsilon_{MC}^{ij}},$$

- T=0, i.e. the test start time.

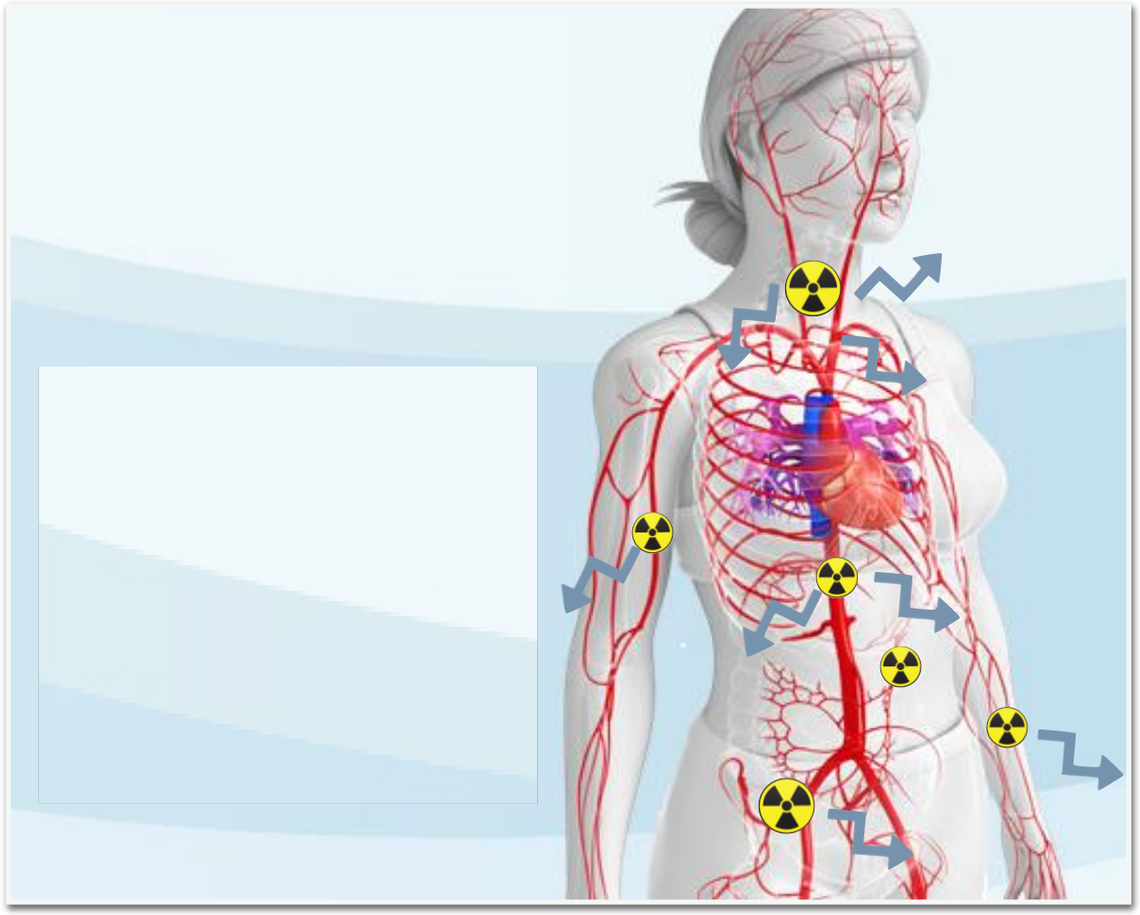
Clinical case of interest



- Neuroendocrins tumor with Lu177
- PROS:
  - Great interest on this isotope only lately used in the clinical practice;
  - Many questions on the dose absorbed by kidneys;
- CONS
  - The literature about is poor
  - These kind of tumors are mostly in the abdomen region

Targeted Radionuclide Therapy

- **Targeted Radionuclide Therapy - How does it work?**
  - A **radiopharmaceutical** is injected in the patient
  - Due to its **specificity** for the tumor, the drugs binds to the tumor
  - **Radiation** emitted by the radionuclide damages the tumor

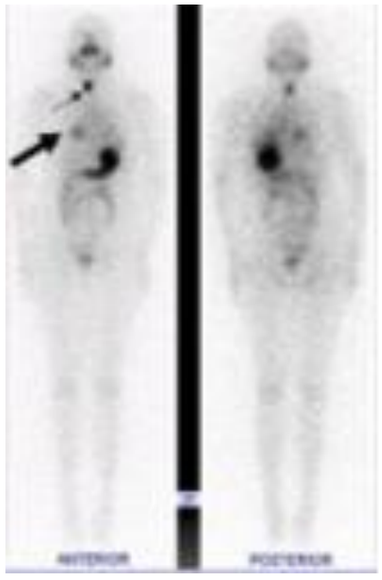


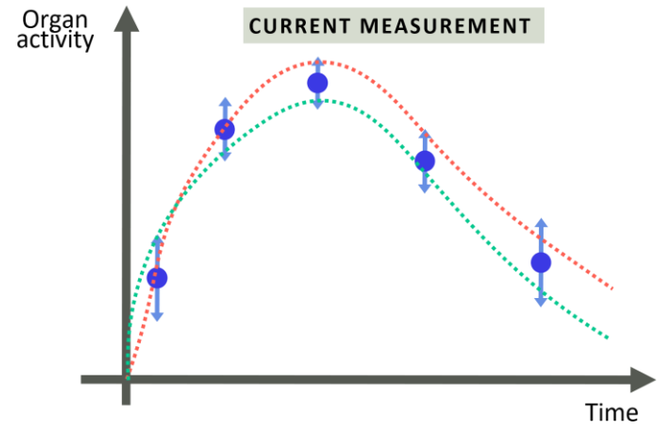
Dose Monitoring in TRT

- A **systematic measurement of the internal activity distribution** in all the patient undergoing TRT would enable improvements in treatment control and an **individualization of the activity** to be administered;

- This personalization would increase the **local tumor control** while **sparing healthy tissue** and **lowering toxicity**.

When the hospital resources are available, the state-of-the-art method utilizes SPECT scan imaging:





- The activity of each organ is measured with a SPECT scan at regular time intervals (1, 4, 24 and 72 hour from the injection)

The integral of the Time Activity Curve (TAC) is the total absorbed dose by the organ

The final error on the dose absorbed by each organ is >30%

Dose Monitoring in TRT

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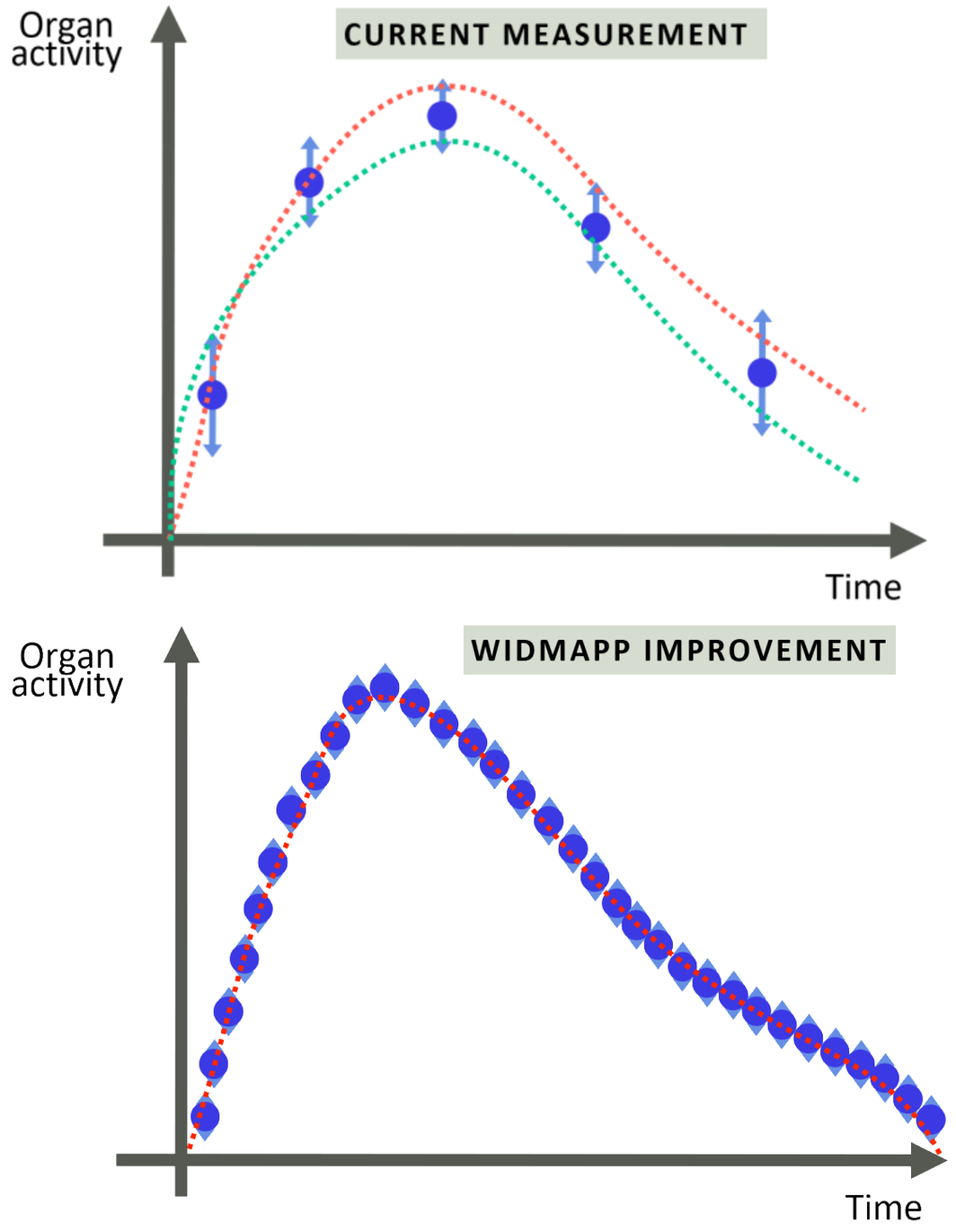
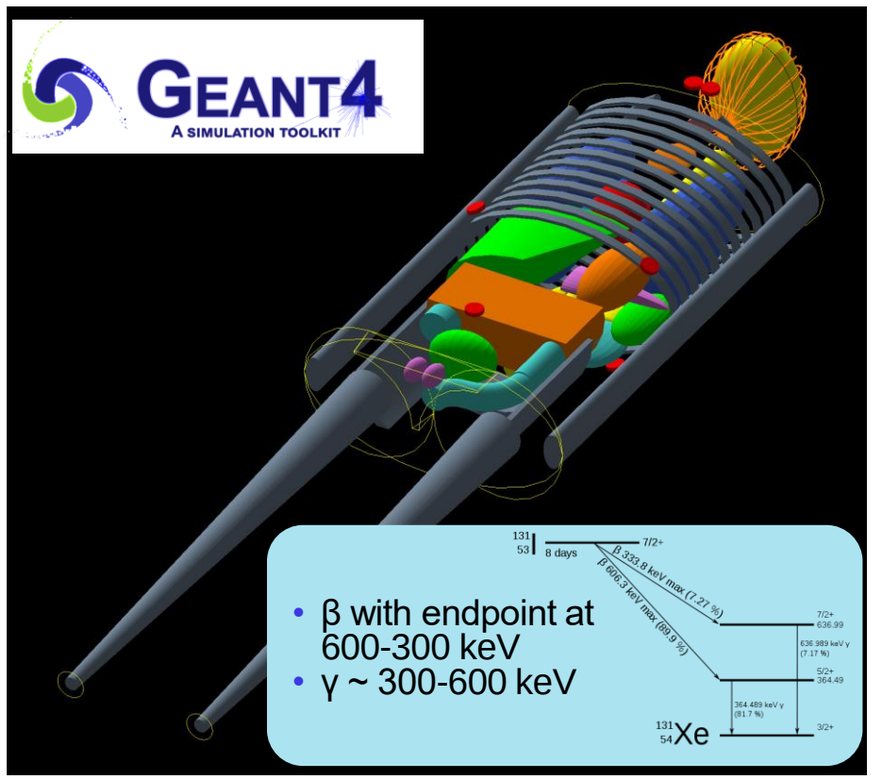
Need for a system for dosimetry measurements capable of a continuous mapping of the organs TAC



Feasability Study - Simulation

MC Simulation → *contribution from each organs emission for all the placed detectors*



- **MIRD Phantom**:
  - Simplified, reference in radio protection studies
- **Detectors**:
  - Radius 1.3 cm, thickness 0.3 cm;
  - Efficency = 100%;
  - Placed in correspondance with the organs of interest
- **Source**:
  - Organ source: I^{131} uniform emission

Organs
Thyroid
Liver
Kidney DX
Kidney SX
Spleen
Bladder

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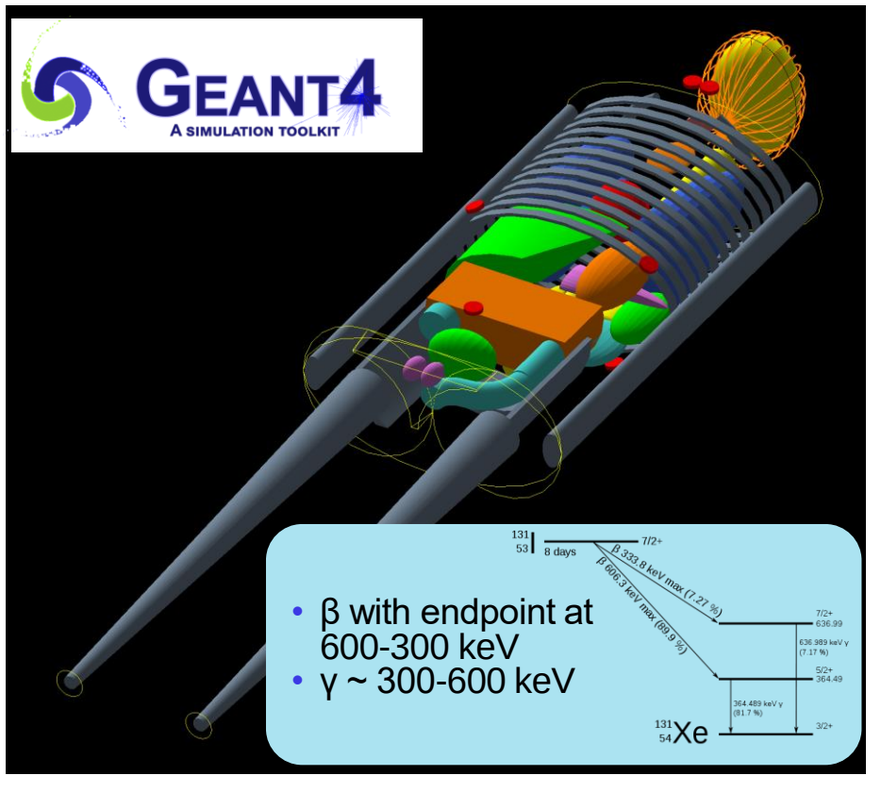
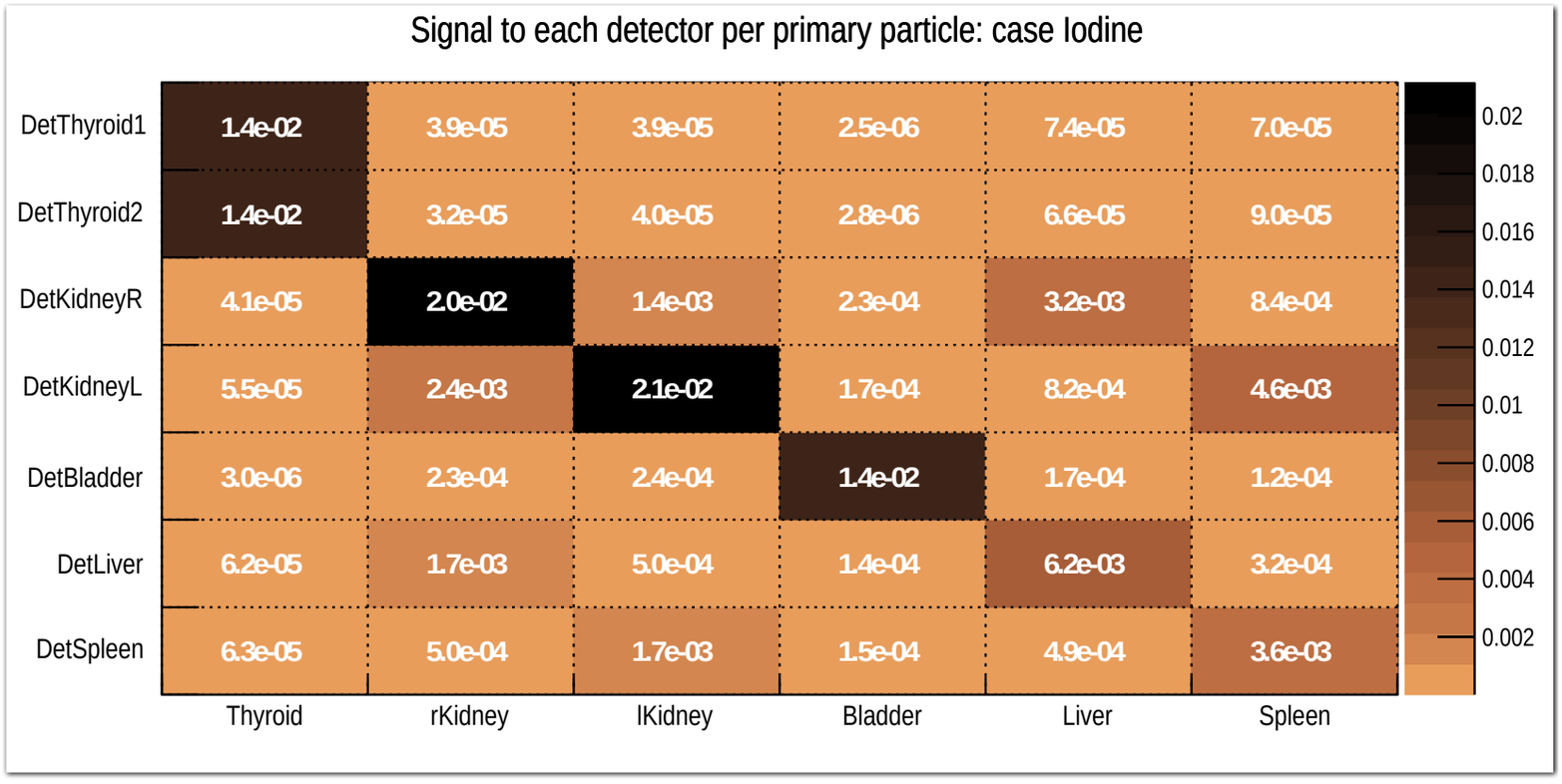
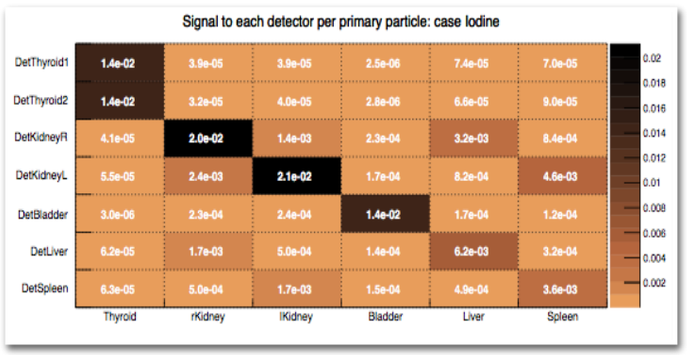




we obtain the values of the weight ϵ_{ij} for each detector-organ combination

Feasability Study - Dataset creation



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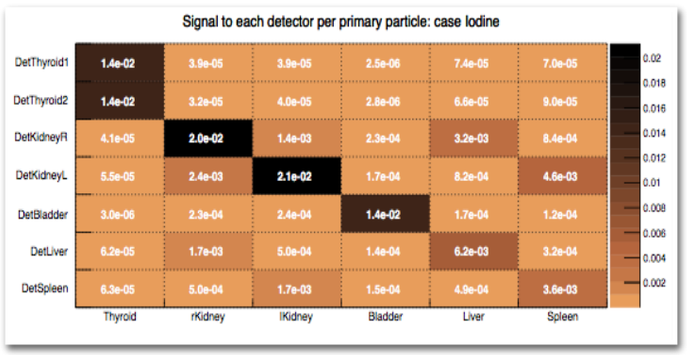
Assumptions on ^{131}I Biokinetic (A_0 and τ_{organ})

→

Input for the definition of a realistic data set

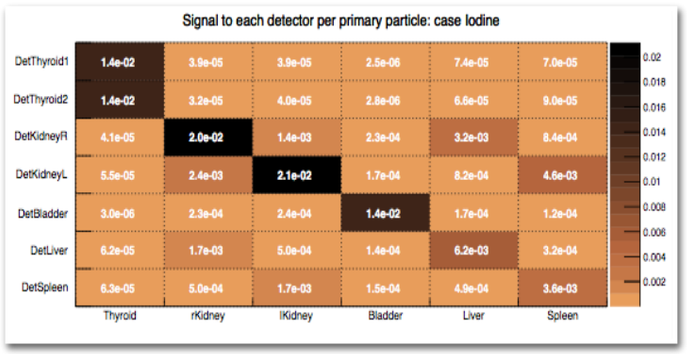
Feasability Study - Dataset creation



+ *Assumptions on ^{131}I Biokinetic (A_0 and τ_{organ})* → **Input for the definition of a realistic data set**

- A **2.5 GBq** administration is assumed;
- We roughly assigned **30% of the activity to the thyroid**, given its high specificity for Iodine, and 70% equally divided;
- We further divided this second part among the 5 other active organs assuming for them the same specific activity of radiopharmaceutical.

Feasability Study - Dataset creation



+

Assumptions on ^{131}I Biokinetic (A_0 and τ_{organ})

→

Input for the definition of a realistic data set

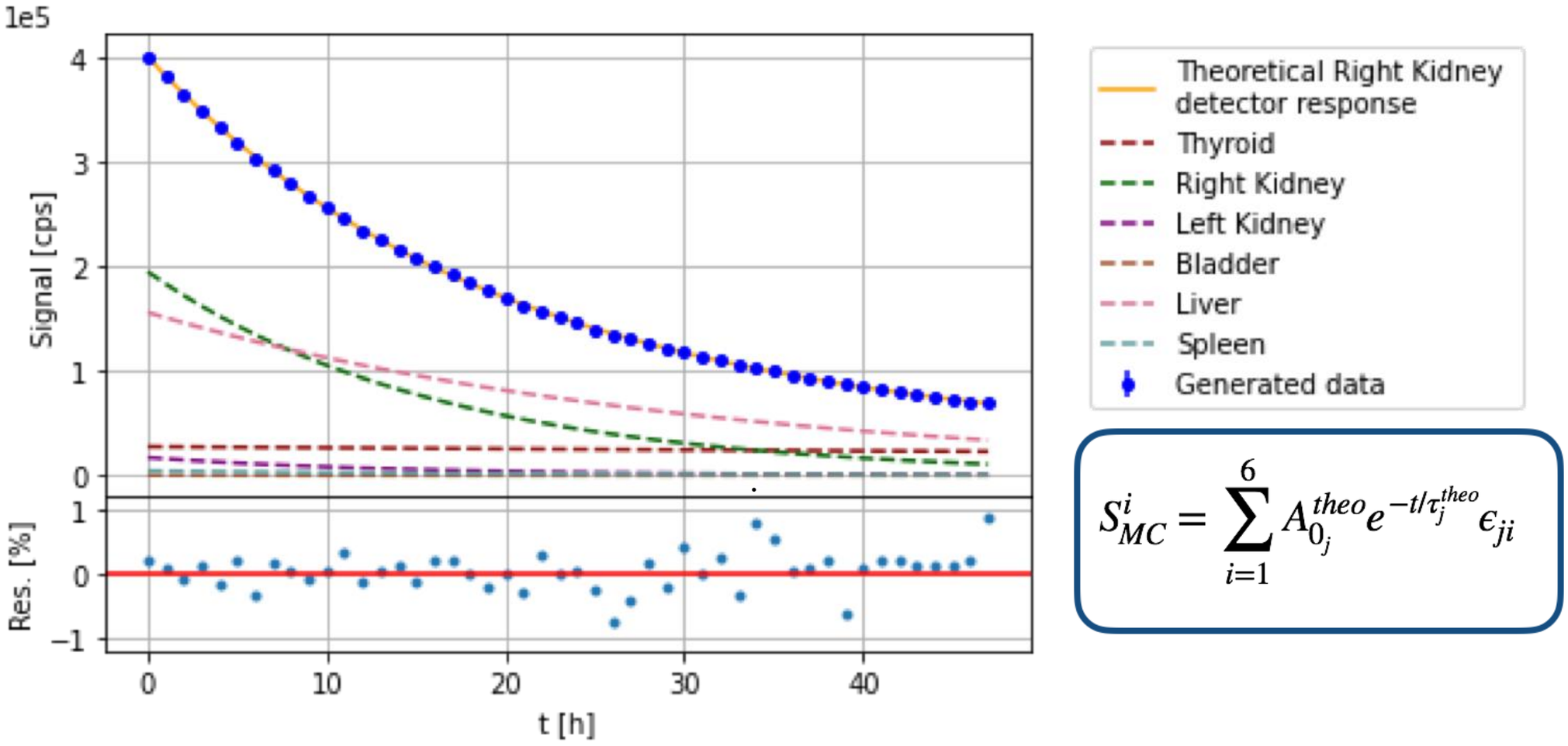
- The number of total counts (i.e. from all the organs) is obtained as a function of the time at the given detector:

$$S^i_{MC} = \sum_{i=1}^{6} A^{theo}_{0_j} e^{-t/\tau^{theo}_j} \epsilon_{ji}$$

- As described in **the equation**, considering the contribution of each organs (j) we obtain a **Time Counts Curves (TCC)** for each detector (i);

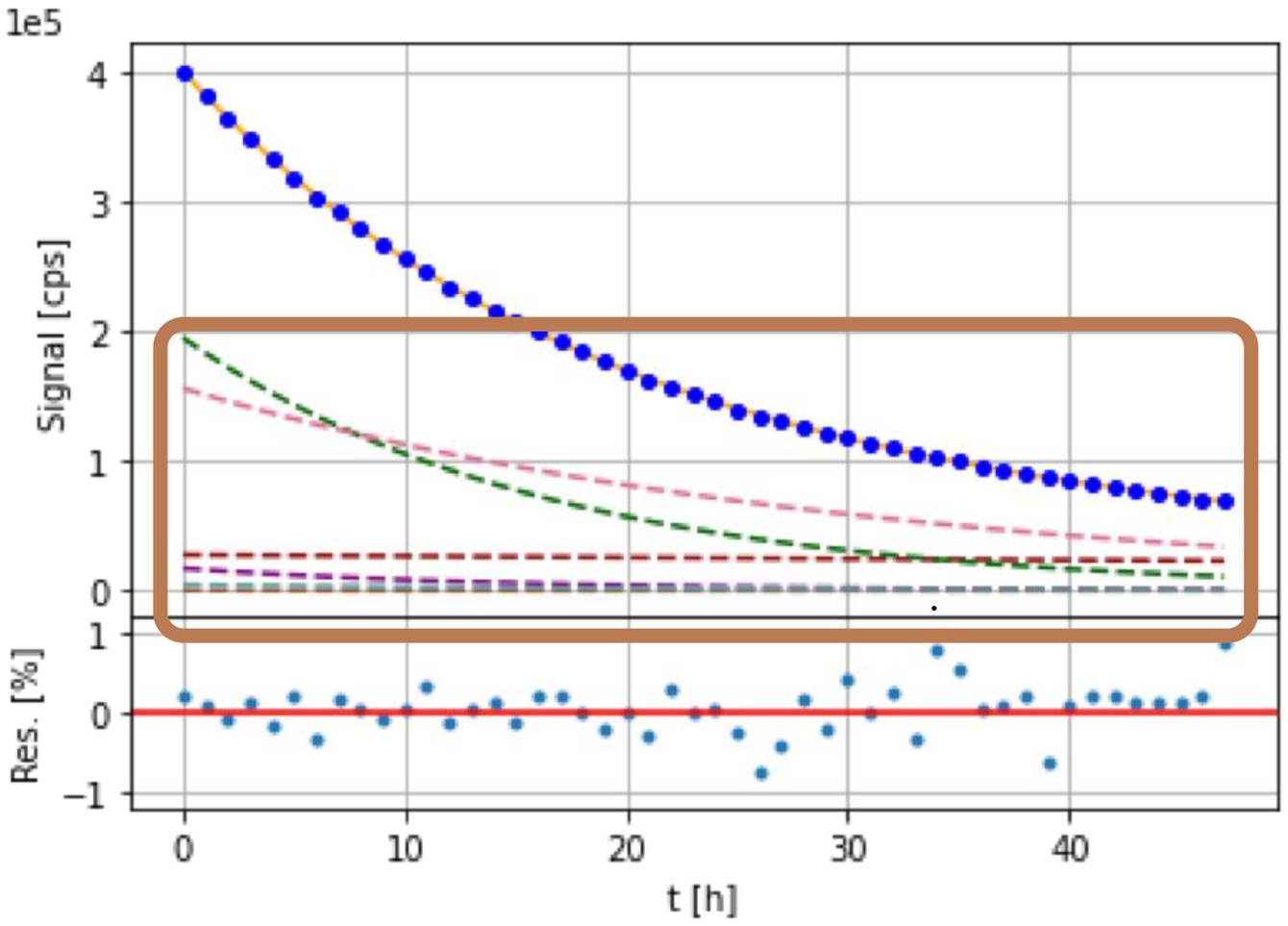
- In order to simulate the detector response, we sampled the detector responses assuming a Poissonian distribution;

Feasability Study - Deconvolution Algorithm



$$S^i_{MC} = \sum_{i=1}^{6} A^{theo}_{0_j} e^{-t/\tau^{theo}_j} \epsilon_{ji}$$

Feasability Study - Deconvolution Algorithm



$$S^i_{MC} = \sum_{i=1}^{6} A^{theo}_{0_j} e^{-t/\tau^{theo}_j} \; \epsilon_{ji}$$

The role of the WIDMApp algorithm is to infer from these 7 TCCs the 6 TACs, one per organ, that originated them.

Feasability Study - Deconvolution Algorithm

The role of the WIDMApp algorithm is to infer from these 7 TCCs the 6 TACs, one per organ, that originated them.

$$S^i_{MC} = \sum_{i=1}^{6} A_{0_j}^{theo} e^{-t/\tau_j^{theo}} \epsilon_{ji}$$

- The algorithm has thus to identify the combination of 6 pairs of parameters A_{0j} and τ_j that best reproduces all the 7 TCCs data points at the same time;

- This is achieved by defining a merit function $\chi^2(A_{0j}, \tau_j)$ that considers all the points from all the 7 TCCs:

$$\chi^2(A_{0j}, \tau_j) = \sum_i^{N_{det}} \sum_k \left(\frac{S_i^{sim}(t_k) - S_i(t_k; A_{0j}, \tau_j)}{\sigma_i(t_k)} \right)^2$$

- Given the **strong correlation** between the unknown parameters, different minimization algorithms were compared in terms of robustness, varying:
  - Initial parameters of the fit;
  - Uncertainties applied to the data;