107° CONGRESSO NAZIONALE della SOCIETÀ ITALIANA DI FISICA

Advances in Monte Carlo patient-specific internal dosimetry for ^{90}Y-TARE treatments

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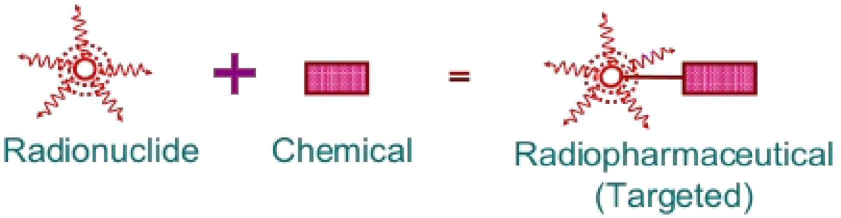
INFN Catania Istituto Nazionale di Fisica Nucleare

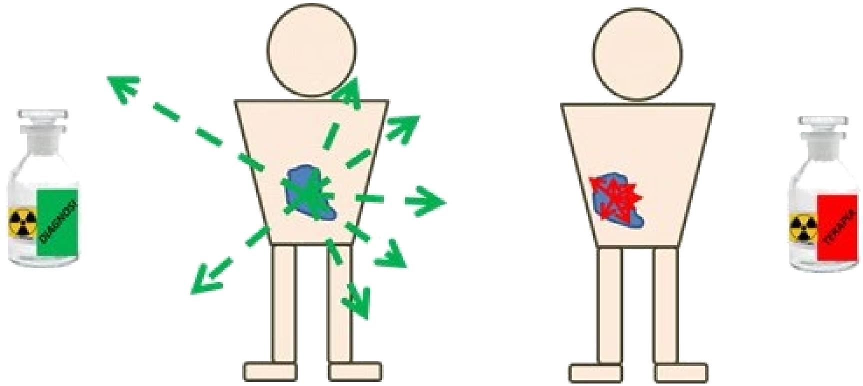
Overview

- Introduction
  - Monte Carlo (MC) internal dosimetry in nuclear medicine
  - ^{90}Y TARE MC dosimetry via ^{99m}Tc-MAA SPECT/CT
- Topic 1
  - Optimization of computation times finding best combinations of simulation parameters
- Topic 2
  - Investigation and possible corrections of dose misevaluations caused by artefacts in input functional scans
- Conclusion and perspectives

Internal dosimetry in nuclear medicine

- Nuclear Medicine: employs radionuclides (radiopharmaceuticals) for diangostic and therapeutic purposes
- Internal dosimetry: quantification of absorbed dose to internally irradiated organs and tissues





Fundamental role:

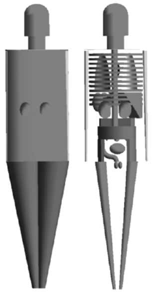
- Damage to pathologic tissues
- Risk for healthy tissues
- Deduce dose-effect correlations →
- → Optimize activity administration

$$D = \frac{dE_{abs}}{dm} \left[Gy = \frac{J}{kg} \right]$$

Monte Carlo dosimetry approach

Models needed for:

- 3D antropomorphic anatomy:
  - Mathematical models
  - Voxel level
    - Standard human models
    - Patient-specific



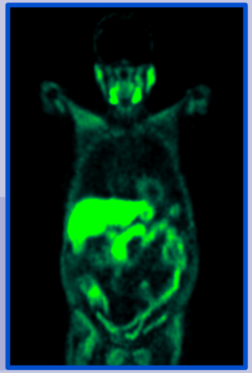
MIRD5 mathematical phantom

ICRP reference voxelized phantoms

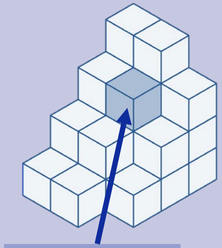
- Mathematical-physical calculation approach
  - Local energy deposition
  - Dose point-kernels convolution
  - S-factors (MIRD)
  - Direct Monte Carlo (MC) simulation

CT scans → model patient's body as voxelized phantom

SPECT or PET scans → model voxelized radionuclide spatial biodistribution



- MC simulation of radionuclide decays and interaction of daughters with matter
- Score absorbed dose in each voxel
- (codes exploting MC algorithms + e.m., weak and hadronic physics)



- MC + morphological and functional imaging
  - Pro: most accurate and patient-specific method
  - Cons: resources and longer computational time →
  - → not routinely used in clinics but excellent for research

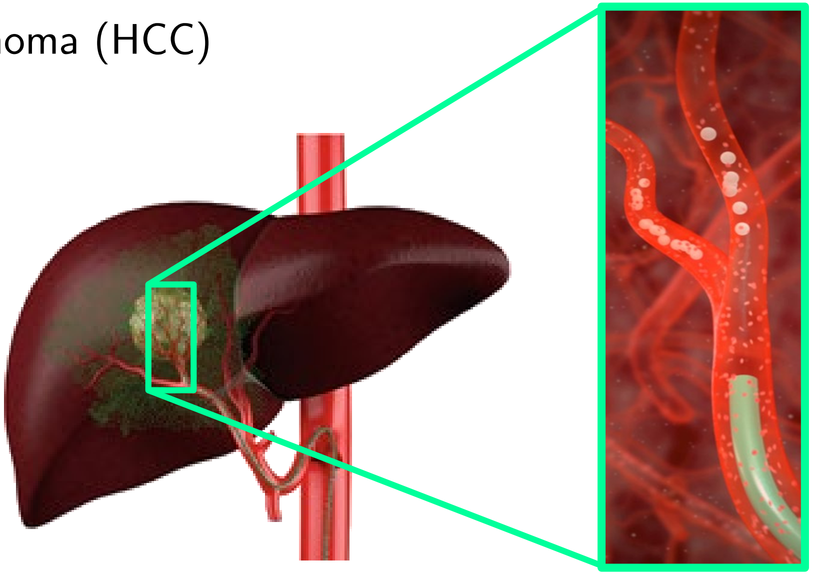
Dewaraja, Y. K. et al. *J. Nucl. Med.* 53(8) (2012)
DOI: 10.2967/jnumed.111.100123.

^{90}Y TARE

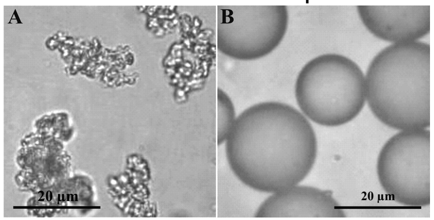
Trans-Arterial Radio-Embolization (TARE) of HepatoCellular Carcinoma (HCC)

- Selective administration of ^{90}Y-labelled microspheres (glass or resin):
  - ^{90}Y: high-energy β^- emitter:
    $\langle E_{\beta-} \rangle = 932.4$ keV, $E_{\beta-\ max} = 2278.5$ keV, $t_{½} = 64.1$ h
  - Microspheres injected via catheter into hepatic hartery
  - → embolization of capillaires supplying lesion, permenent implant
  - → fixed distribution

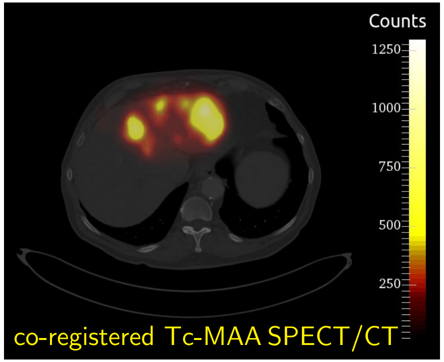
sirtex.com


https://doi.org/10.1007/978-3-319-91977-5_9

- Eligibility → Pre-therapy ^{99m}Tc MacroAggregated Albumin (Tc-MAA) scintigraphy
  - ^{99m}Tc: γ emitter: $E_{\gamma} = 0.1405$ MeV, $t_{½} = 6.0$ h
  - MAA and microspheres: comparable biodistribution → predict TARE
  - Detect eventual shunts/leakages
  - Quantitative Tc-MAA SPECT/CT → dosimetry



ISBN: 978-90-393-5458-1



Topic 1: Optimization of simulation times

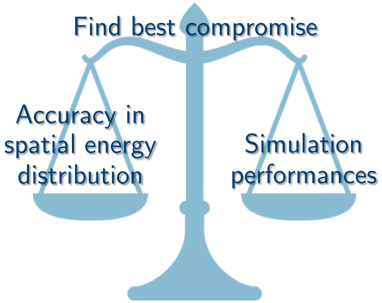
- Optimize simulation times acting on simulation parameters

⇓

- Investigate the behaviour of simulation time as a function of:

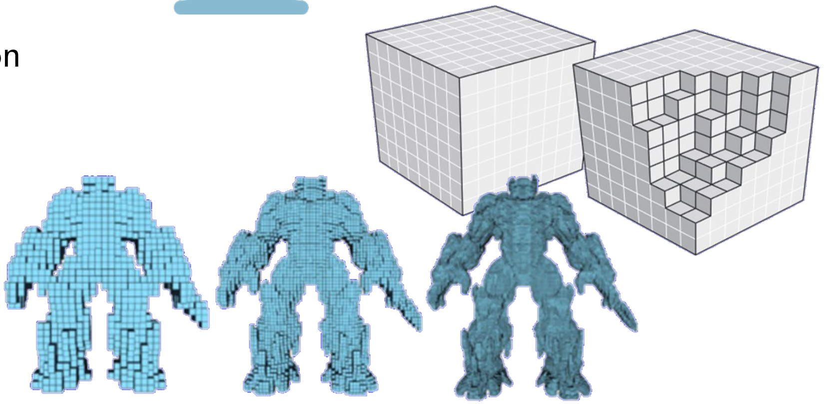
(Geant4 Application for Tomographic Emission)

(GEometry ANd Tracking)



Range cuts on production of secondary particles

- Avoid infrared divergence of low energy secondaries (e.g. delta-rays, bremsstrahlung) → poor CPU perfomance if tracking all until end
- Stop secondaries below a threshold and energy dumped in last point
- Balance to avoid imprecise stopping locations → spatial energy deposition



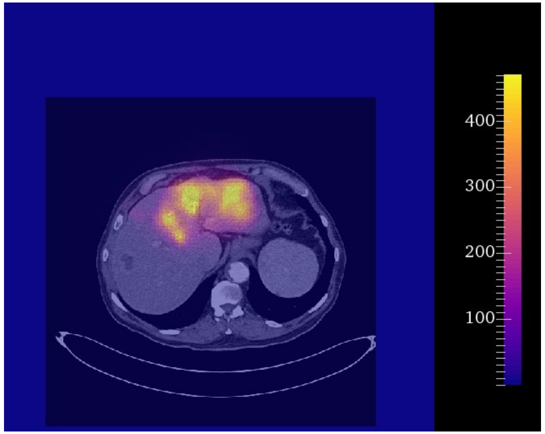
Resolution of the input CT scan

- The higher the resolution, the greater the number of voxels
- → more sub-volumes in which particles are transported, and related quantities scored → larger matrices (→ larger files)

Input data and CT resamplings

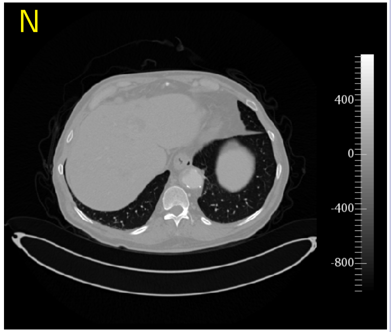
- Starting data: co-registered ^{99m}Tc-MAA SPECT and CT for a patient suffering from HCC enrolled for TARE

- CT resamplings performed: 3D Slicer, *Resample Scalar Volume* and *Resample Image (BRAINS)* modules using Laczos interpolation

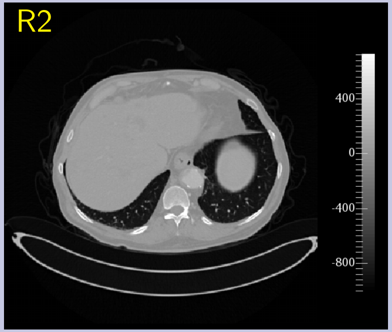


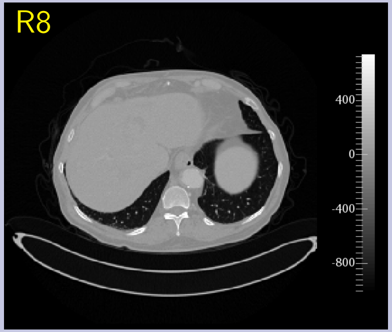
3DSlicer

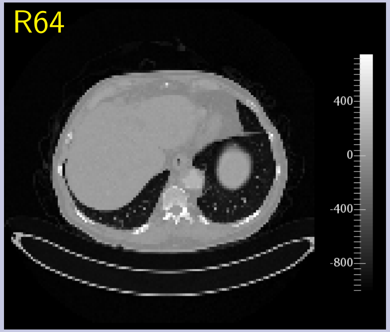
CT name	v_R/v_N	Resolution	Voxel dimensions (mm^3)
N		512×512×146	0.89×0.89×2.00
R2	2.4	384×384×110	1.19×1.19×2.65
R8	8.0	256×256×73	1.79×1.79×4.00
R64	64.9	128×128×36	3.58×3.58×8.11
RS	63.4	128×128×105	4.66×4.66×4.66



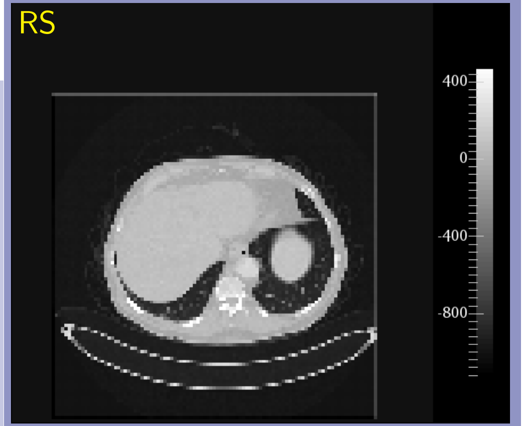
Native CT







Same total volume as N CT



Same tot. vol and resol. as SPECT

Range cuts and other simulations settings

- For each CT resampling, multiple independent simulations with different production cuts on electrons, positrons and photons

CT name	v_R/v_N	Resolution	Voxel dimensions (mm^3)
N		512×512×146	0.89×0.89×2.00
R2	2.4	384×384×110	1.19×1.19×2.65
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R64	64.9	128×128×36	3.58×3.58×8.11
RS	63.4	128×128×105	4.66×4.66×4.66

All the examined combinations

Production cut (mm)	CT				
	N	R2	R8	R64	RS
0.01	✓	✓	✓	✓	✓
0.05	✓	✓	✓	✓	✓
0.1	✓	✓	✓	✓	✓
0.5	✓	✓	✓	✓	✓
1.0	✓				
1.5		✓			
2.0			✓		
4.0				✓	✓

- Each simulation was run with the following settings:
  - GATE v9.0, relying on GEANT4 v10.05p01
  - Phantom definition: density intervals → HU conversion with density tolerance 0.01 g/cm^3, materials → Table below
  - Source definition: Tc-MMA SPECT to simulate ^{90}Y-microspheres distribution
  - Physics: *G4EmStandard_opt3* + *G4RadioactiveDecay*
  - Primaries: ^{90}Y ions at rest ($2 \cdot 10^8$ histories)

Material	HU intervals	ρ (g/cm^3)
G4_AIR	HU $\leq$ -855.75	$\rho \leq 0.10$
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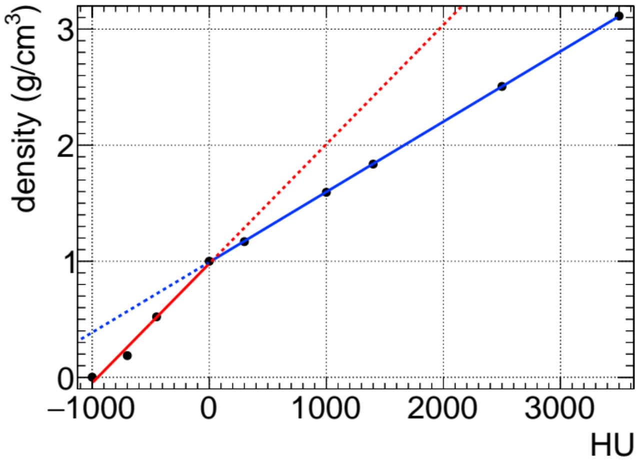
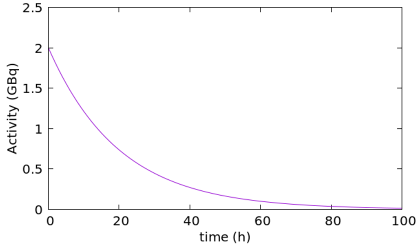
G4_TISSUE_SOFT_ICRP	-38.98 < HU $\leq$ 343.61	$0.94 < \rho \leq 1.2$
G4_BONE_CORTICAL_ICRP	HU > 343.61	$\rho > 1.2$



Dose calculations

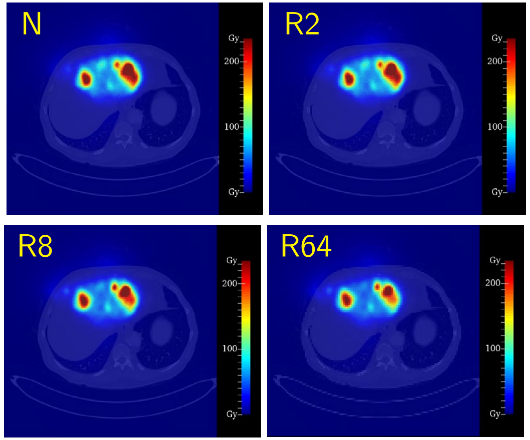
- For each simulations dose maps were scored, with same resolution as corresponding CT used
- Correct values in each voxel deduced as: $D^{ijk} = \frac{D^{ijk}_{\text{out}}}{N_{evts}} \cdot \tilde{A}$

  Assuming (reasonable for TARE):
  - monoexponential behaviour with
  - instantaneous uptake
  - no biological clearance →
  - → effective decay time = physical nuclide decay time

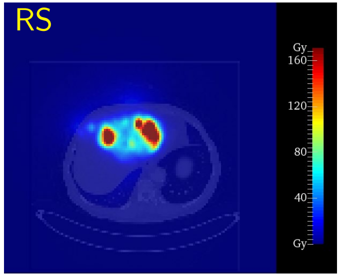


$$\tilde{A} = A(0)\int_0^{\infty} e^{-t/\tau_{^{90}Y}}dt = \boxed{A(0)} \cdot \tau_{^{90}Y}$$

Total injected activity

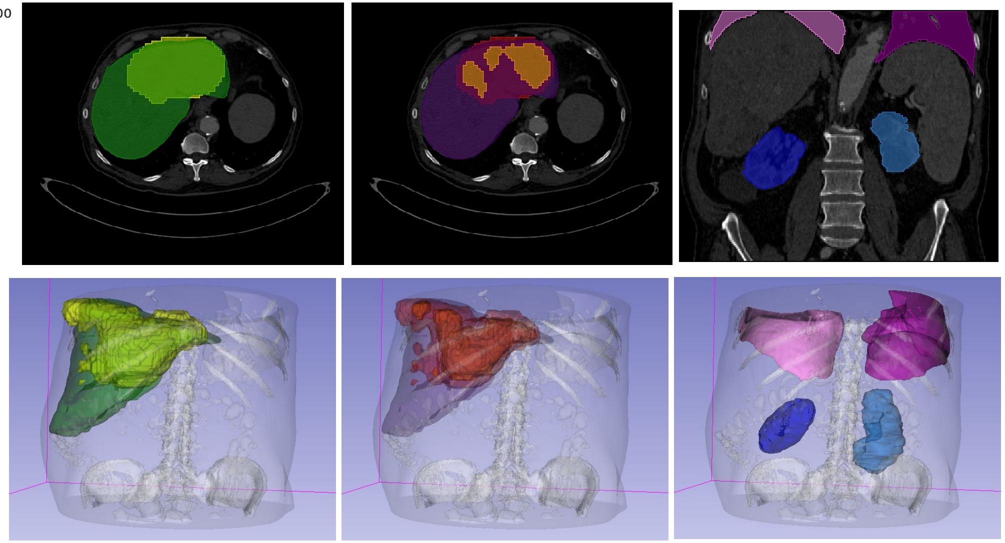


dose maps for range cut = 0.01 mm



- Then, average doses calculated in Volumes Of Interest (VOIs):
  - Liver, lesions, liver perfused, healthy liver, healthy liver perfused, right lung, left lung, right kidney left kidney

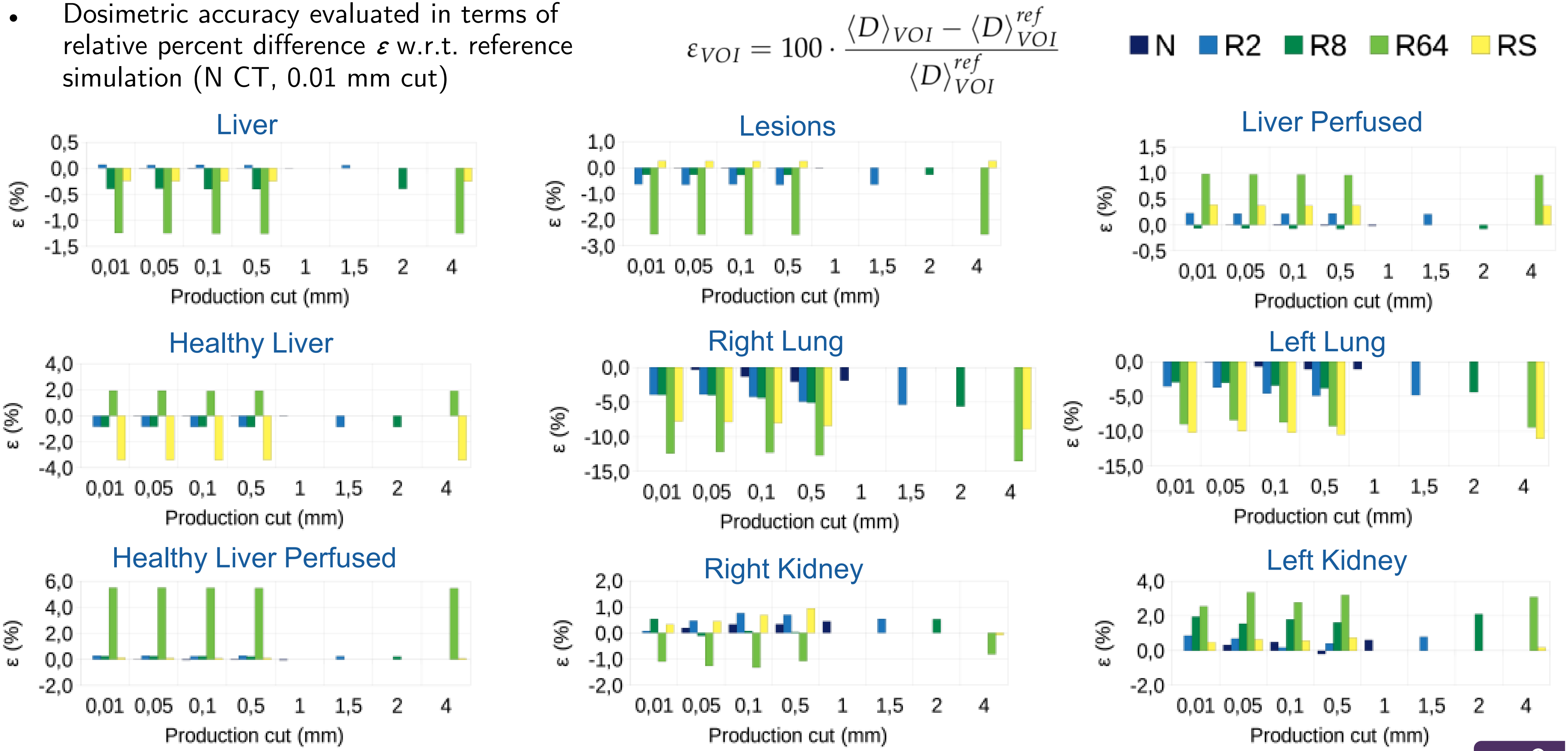
$$\langle D \rangle_{VOI} = \frac{1}{N^{vox}_{VOI}} \sum_{i,j,k \in VOI} D^{ijk}$$



Average doses comparison

- Dosimetric accuracy evaluated in terms of relative percent difference ε w.r.t. reference simulation (N CT, 0.01 mm cut)

$$\varepsilon_{VOI} = 100 \cdot \frac{\langle D \rangle_{VOI} - \langle D \rangle_{VOI}^{ref}}{\langle D \rangle_{VOI}^{ref}}$$



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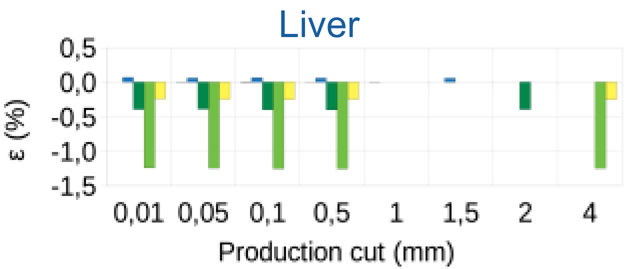
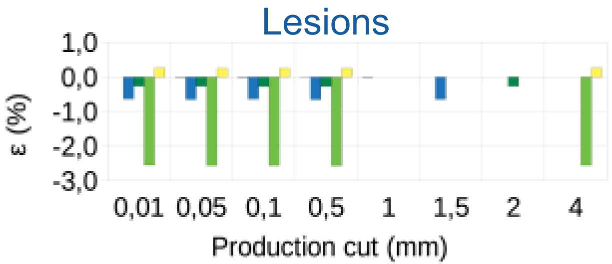
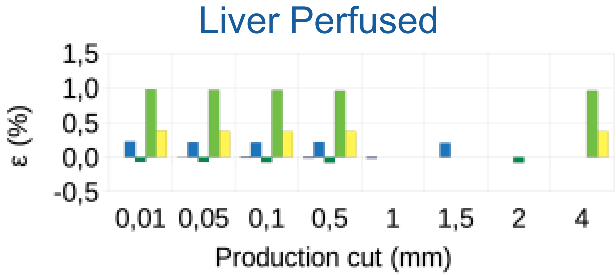
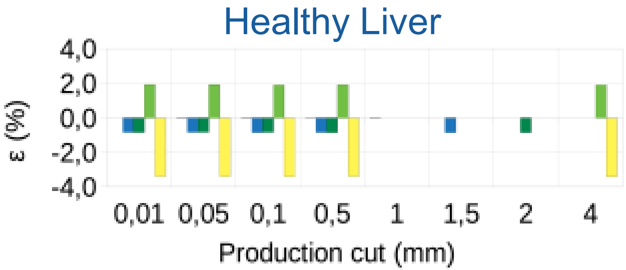
$$\varepsilon_{VOI} = 100 \cdot \frac{\langle D\rangle_{VOI} - \langle D\rangle_{VOI}^{ref}}{\langle D\rangle_{VOI}^{ref}}$$

N R2 R8 R64 RS



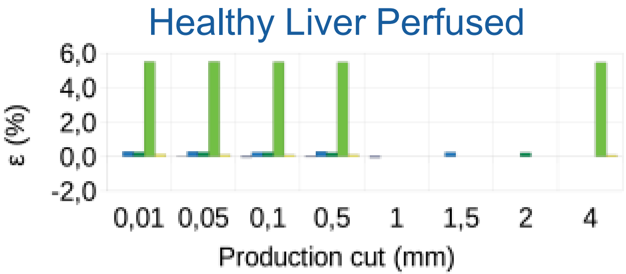


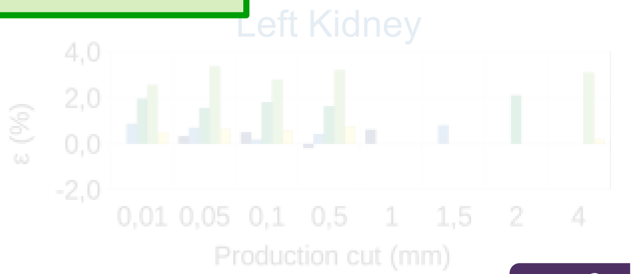




Liver-related VOIs:

- For a fixed resampling no appreciable differences varying cuts
- $|\varepsilon| < 1\%$ for all resamplings except R64 (and RS only for healthy liver)



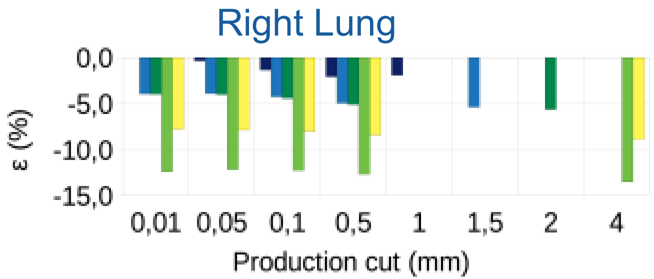


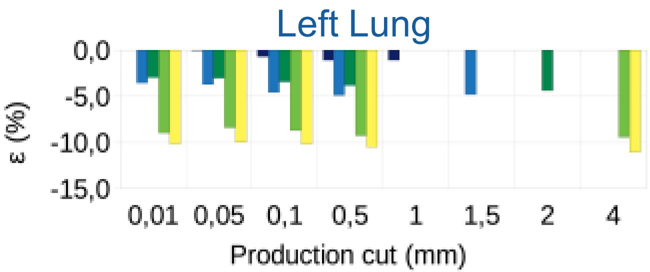
Average doses comparison

- Dosimetric accuracy evaluated in terms of relative percent difference ε w.r.t. reference simulation (N CT, 0.01 mm cut)

$$\varepsilon_{VOI} = 100 \cdot \frac{\langle D \rangle_{VOI} - \langle D \rangle_{VOI}^{ref}}{\langle D \rangle_{VOI}^{ref}}$$

N R2 R8 R64 RS





Lungs VOIs:

- For a fixed resampling only minimal differences varying cuts
- $|\varepsilon| < 5\%$ for R2 and R8 resamplings
- $|\varepsilon| < 10\%$ for RS resampling
- $|\varepsilon| < 13\%$ for R64 resampling

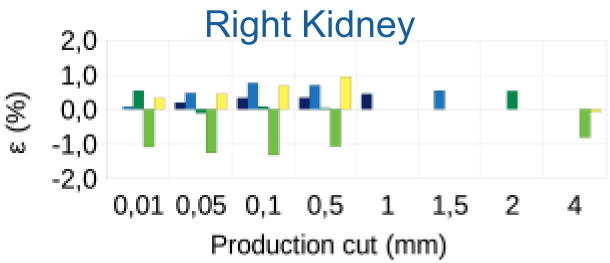
Average doses comparison

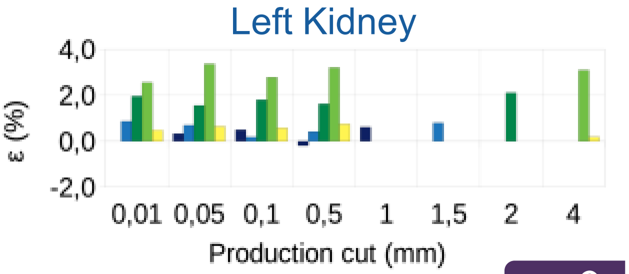
- Dosimetric accuracy evaluated in terms of relative percent difference ε w.r.t. reference simulation (N CT, 0.01 mm cut)

$$\varepsilon_{VOI} = 100 \cdot \frac{\langle D \rangle_{VOI} - \langle D \rangle_{VOI}^{ref}}{\langle D \rangle_{VOI}^{ref}}$$

N R2 R8 R64 RS

Kidneys VOIs:
- For a fixed resampling only minimal differences varying cuts
- $|\varepsilon| < 4\%$ for R64 resamplings
- $|\varepsilon| < 2\%$ for all the other resamplings



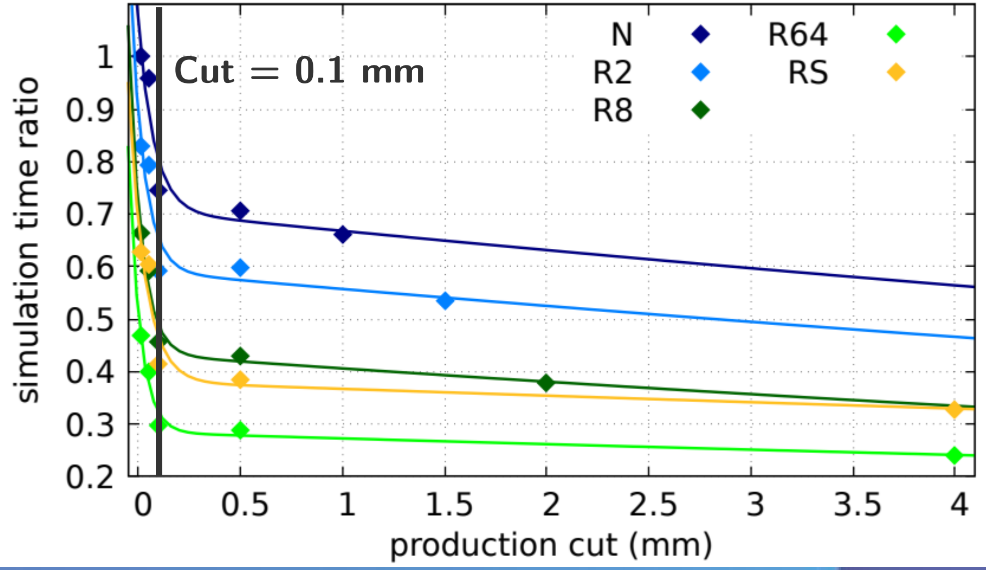


Simulation times vs parameters values

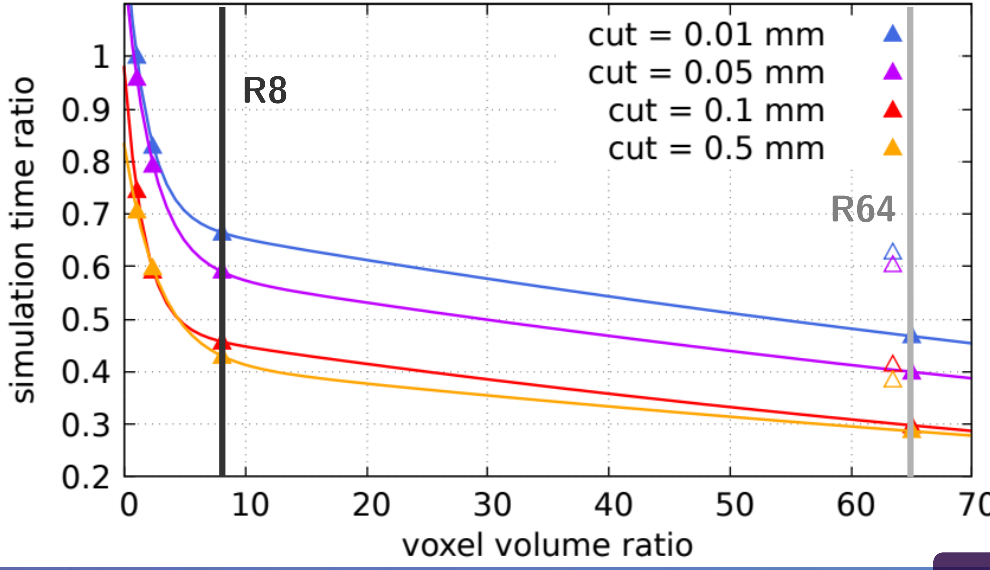
- All simulations run in single cores of a Intel(R) Xeon(R) CPU E5-2620 v4 @ 2.10GHz processor
- Simulation times registered as GATE variable *ElapsedTimeWoInit*
- and compared in terms of ratio with reference simulation

- Increasing cut lenght and reducing CT resolution (voxel volume ratio w.r.t. reference, in plots): $f(x) = ae^{-bx} + ce^{-dx}$
  - Early rapid decrease + late slow decrease, well described by biexponential
  - But excluding RS results in right plot (open trianlges) → do not conserve N CT's total volume

- Given a CT resol., cuts > 0.1 mm reduce only slightly time



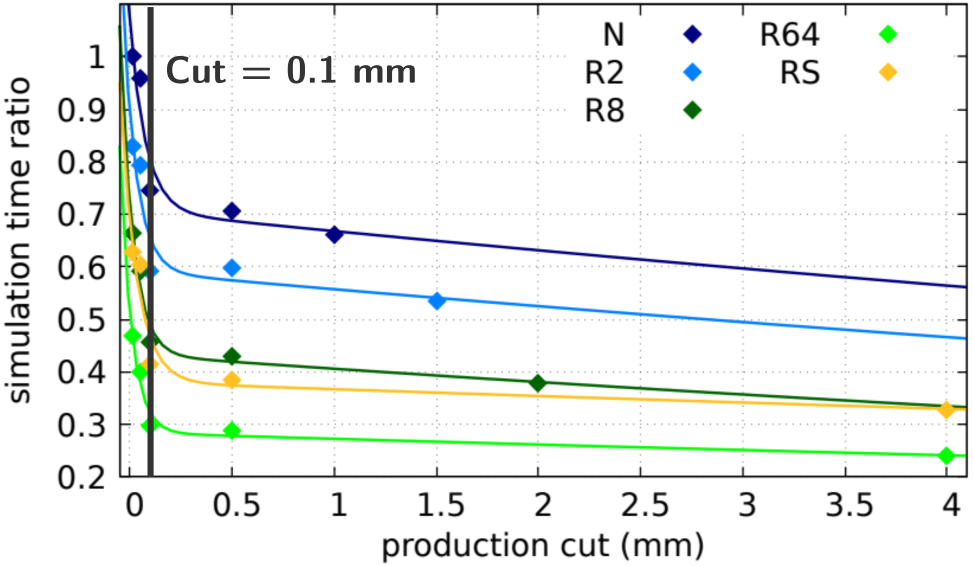
- Given a cut, R64 does not reduce much time w.r.t. R8

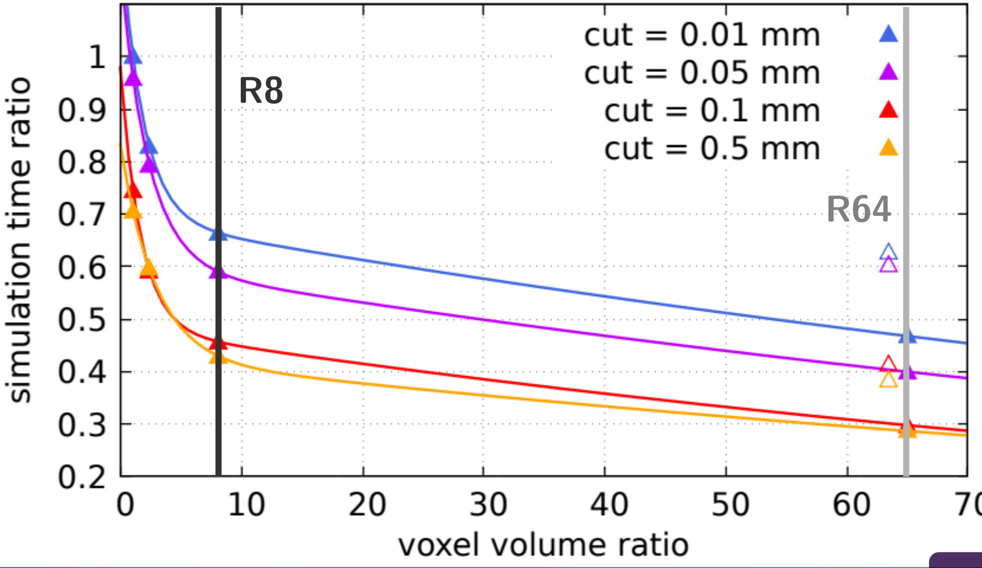


Simulation times vs parameters values

Taking into account both dosimetric accuracy and time saving

- Best combination of parameters:
  - R8 resampling (doubling voxel dimensions) + 0.1 mm cut →
  - Simulation time reduced to 45-50% of reference
  - Ensures agreemenet ($|\varepsilon|$) of 1% in liver-related VOIs, 4% in lungs, 2% in kidneys
- Fastest simulations:
  - R64 resampling, cuts 0.1-0.5 mm
  - Agreement of 6% in healthy liver perf., 3% in other liver sections, while reducing simulation time to 30% of reference
  - Acceptable for liver-related VOIs alone





Topic 2: Dose misevaluations due to artefacts in input scans

As already said

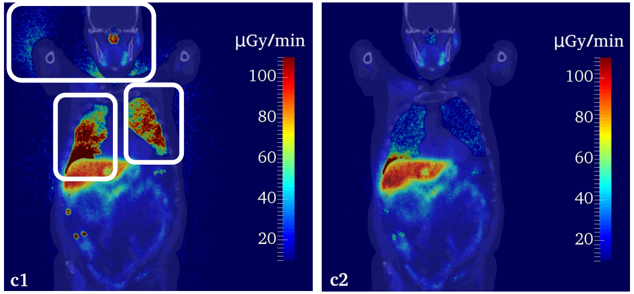
- Direct Monte Carlo + patient-specific input data = gold standard for internal dosimetry

but

- **Provided that** simulated system reproduces precisely the real system

The map is not the territory

- Possible **dose misevaluations** in **low-density regions** (e.g. **lungs**) due to functional imaging artefacts (background noise, reconstruction noise, motion blurring)
  - ➢ Observed in our recent sudies on diagnostic dosimetry for ^{18}F-choline PET



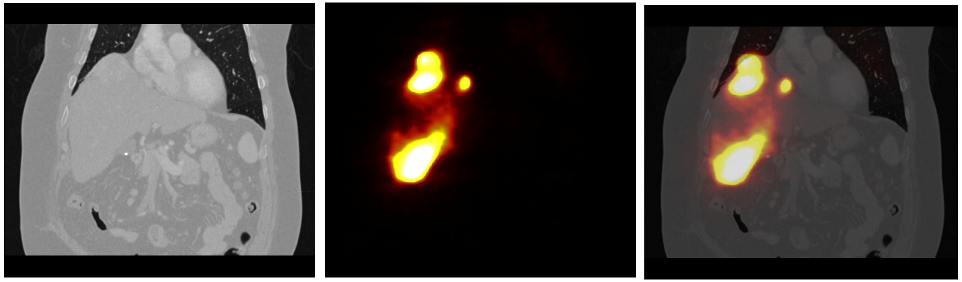
Pistone D. et al. 2020 AAPP
https://doi.org/10.1478/AAPP.981A5

Aim

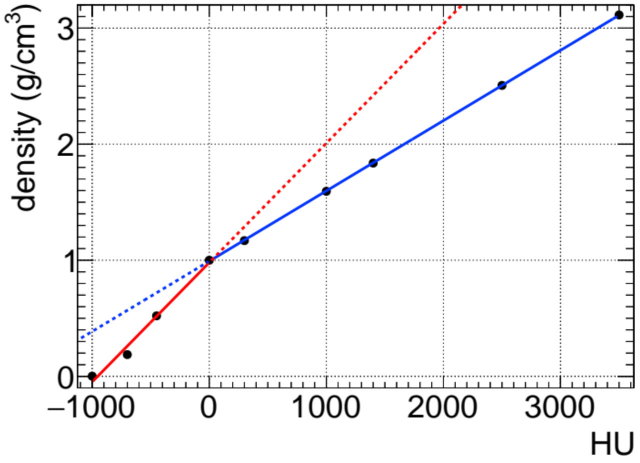
- Investigate such misevaluations and find corrections for ^{90}Y TARE dosimetry via SPECT filtering techniques

Data and simulations settings

- Simulations run with the following settings:
  - Software: GATE v9.0 and independently GAMOS v6.0.0
  - Input data: co-registered ^{99m}Tc-MAA SPECT and CT
  - Phantom definition: density intervals → HU bilinear conversion, materials → Table below
  - Source definition: Tc-MMA SPECT to simulate ^{90}Y-microspheres distribution
  - Physics: *G4EmStandard_opt3* + *G4RadioactiveDecay*
  - Primaries: ^{90}Y ions at rest ($2{\cdot}10^{8}$ histories)



CT | ^{99m}Tc-MAA SPECT | co-registered



Material	HU intervals	ρ (g/cm³)
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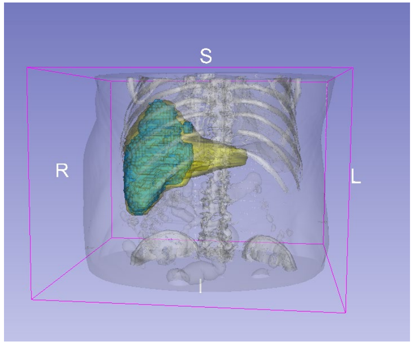
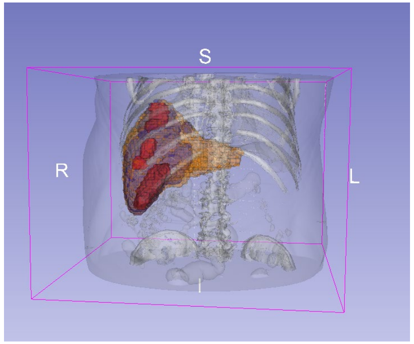
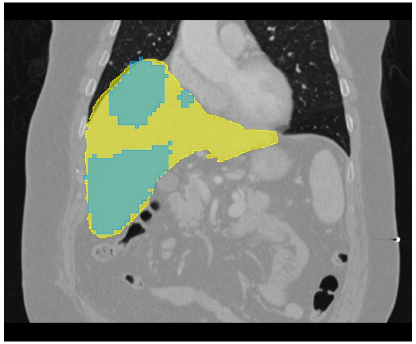
G4_LUNG_ICRP	-855.75 < HU ≤ -126.50	$0.10 < \rho \leq 0.85$
G4_ADIPOSE_TISSUE_ICRP	-126.50 < HU ≤ -38.98	$0.85 < \rho \leq 0.94$
G4_TISSUE_SOFT_ICRP	-38.98 < HU ≤ 343.61	$0.94 < \rho \leq 1.2$
G4_BONE_CORTICAL_ICRP	HU > 343.61	$\rho > 1.2$

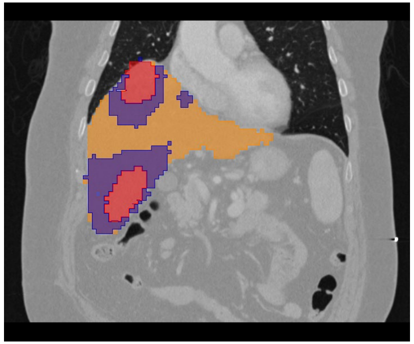
Volumes of interest (VOIs)

Liver, Lesion (segmented on CT, manual)
Liver Perfused (segmented on SPECT, threshold based)
Healthy Liver (= Liver – Lesion)
Healthy Liver Perfused (= Liver Perfused – Lesion)

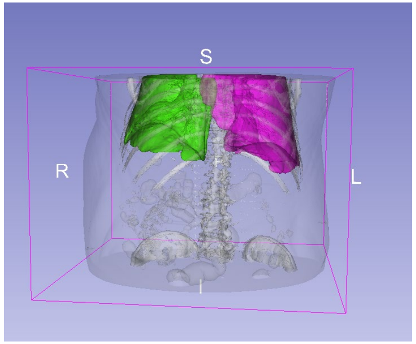


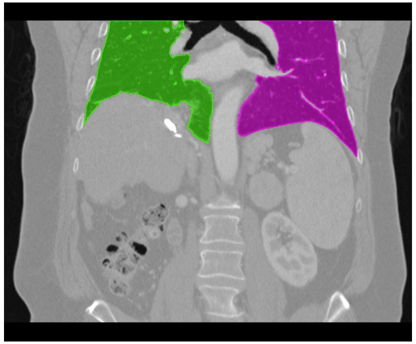






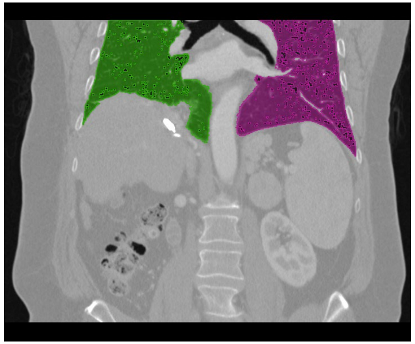
Visible sections of Right Lung and Left Lung in the FOV of the CT
(segmented on CT, threshold based: HU < -150)



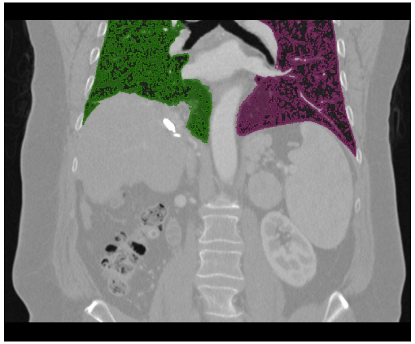


Alternative lungs segmentations: air removal

1) R. L., L. L. -air (HU < -900)



2) R. L., L. L. -air (HU < -855)

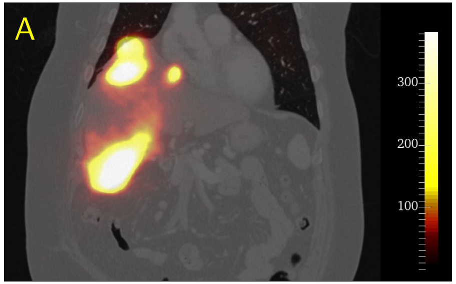


Material	HU intervals	ρ (g/cm^3)
G4_AIR	HU $\leq$ -855.75	$\rho \leq 0.10$
G4_LUNG_ICRP	-855.75 < HU $\leq$ -126.50	$0.10 < \rho \leq 0.85$

SPECT filtering techniques

- To investigate the effect of SPECT artefacts

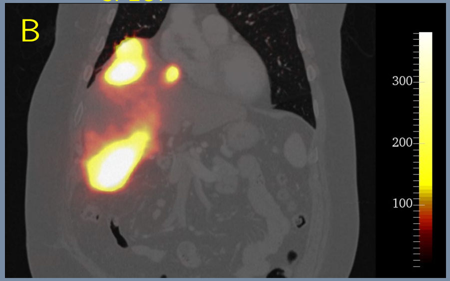
Starting from Native Tc-MAA SPECT



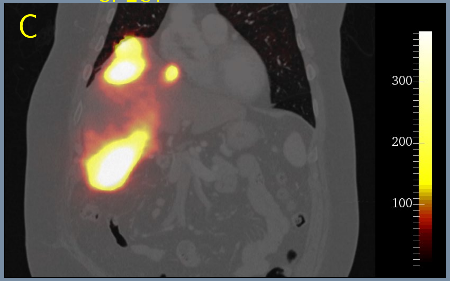
Filtered SPECTs

Setting decay probability = 0 in air

1) $c_{A\ SPECT} = 0$ if $HU_{CT} < -855$

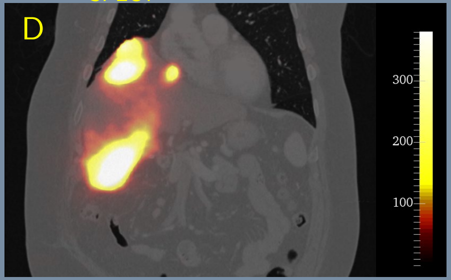


2) $c_{A\ SPECT} = 0$ if $HU_{CT} < -900$



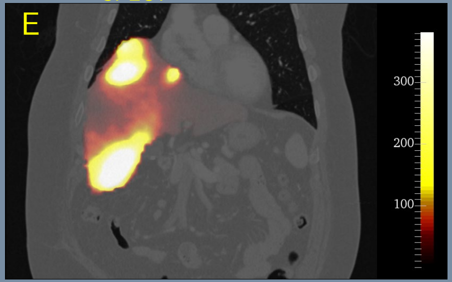
Setting decay prob. = 0 in lungs

3) $c_{A\ SPECT} = 0$ within lungs VOIs

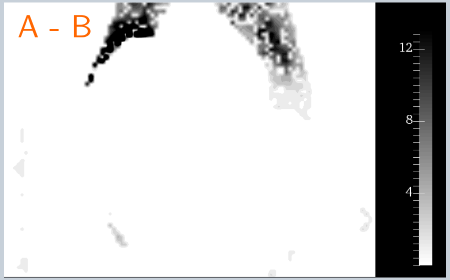


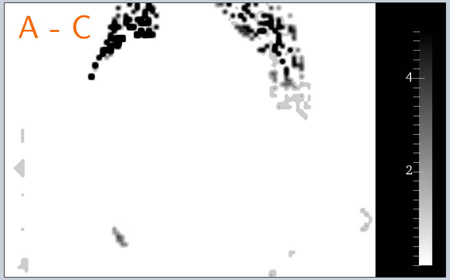
Setting decay prob. = 0 outside liver

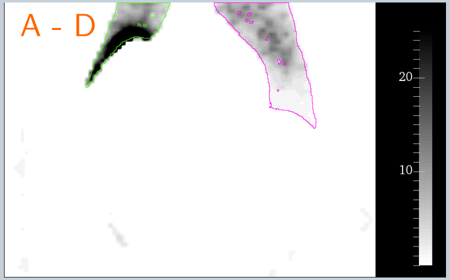
4) $c_{A\ SPECT} = 0$ outside liver VOI

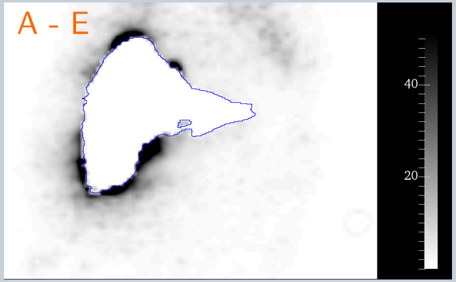


Difference with respect to native (native SPECT – filtered SPECT)









Dose calculations

- Indepentent simulations run for native SPECT and each filtered SPECT described, both with GATE and GAMOS

- For each simulation Dose in each voxel: $$D^{ijk} = \frac{D^{ijk}_{MC\ output}}{N_{evts}} \tilde{A}$$

- Assuming:
- instantaneous uptake
- no biological clearance → effective decay time = physical nuclide decay time

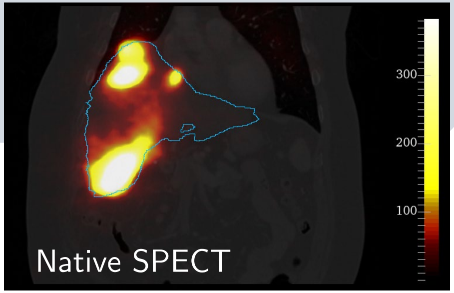
Total injected activity

$$\tilde{A} = \int_0^\infty A(t)dt = A(0)\int_0^\infty e^{-\lambda_{90Y} t} dt = \boxed{A(0)} \cdot \tau_{90_Y}$$

- Additional caclulation:
Native SPECT with post-simul. background correction factor

$$D^{ijk}_{bkg\ corr} = D^{ijk}_{native} \cdot b$$

$$b = \frac{A_{whole\ SPECT}}{A_{liver\ VOI}}$$



- Average dose in a VOI:

$$\bar{D}_{VOI} = \frac{1}{N_{voxels \in VOI}} \sum_{ijk \in VOI} D^{ijk}$$

- Single voxel dose stat. uncert.: standard deviation of the mean

$$\sigma^{ijk} = \sqrt{\frac{1}{N_{evts}-1}\left(\frac{\sum_{n=1}^{N_{evts}}\left(d_n^{ijk}\right)^2}{N_{evts}} - \left(\frac{\sum_{n=1}^{N_{evts}} d_n^{ijk}}{N_{evts}}\right)^2\right)}$$

d_n^{ijk} = deposited dose in a single primary event n

- Quantity used for stat. unc. on average doses in VOIs: average value of σ^{ijk} within VOI

$$\bar{\sigma}_{VOI} = \frac{1}{N_{voxels \in VOI}} \sum_{ijk \in VOI} \sigma^{ijk}$$

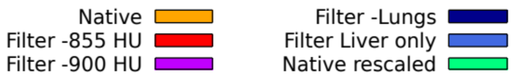
- Native-filtered SPECT simul. comparison: relative percent difference of dose average values

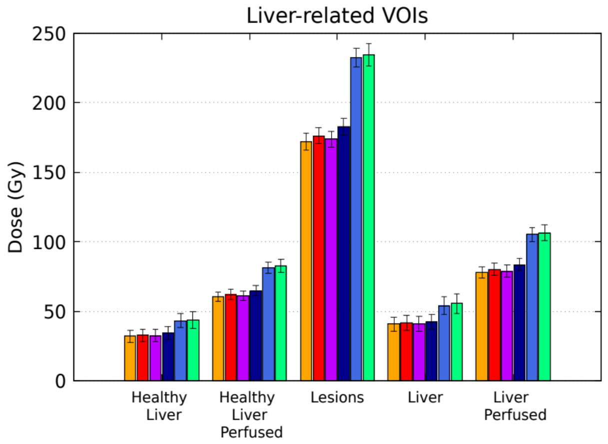
$$\delta_{VOI} = 100 \cdot \frac{\bar{D}^{filtered}_{VOI} - \bar{D}^{native}_{VOI}}{\bar{D}^{native}_{VOI}}$$

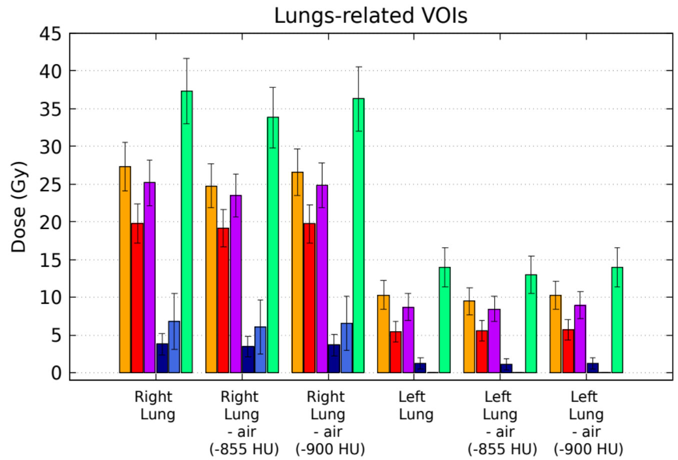
- GATE-GAMOS simul. comparison: relative percent difference of dose average values

$$\varepsilon_{VOI} = 100 \cdot \frac{\bar{D}^{GAMOS}_{VOI} - \bar{D}^{GATE}_{VOI}}{\bar{D}^{GATE}_{VOI}}$$

GATE simulations

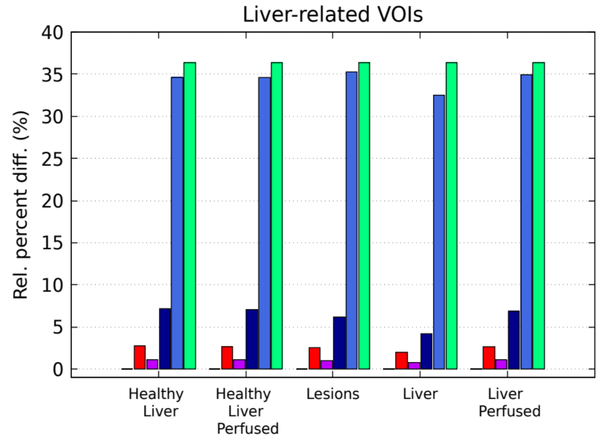


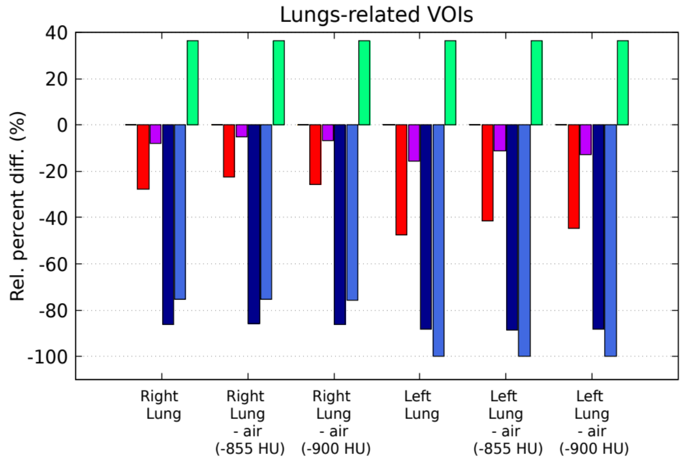




Relative percent difference of dose average values

$$\delta_{VOI} = 100 \cdot \frac{\overline{D}_{VOI}^{filtered} - \overline{D}_{VOI}^{native}}{\overline{D}_{VOI}^{native}}$$



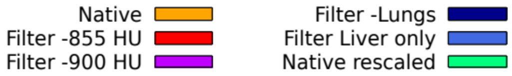


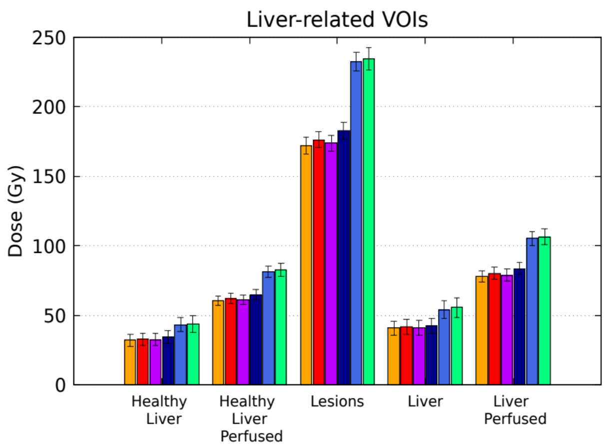
Average doses comparison

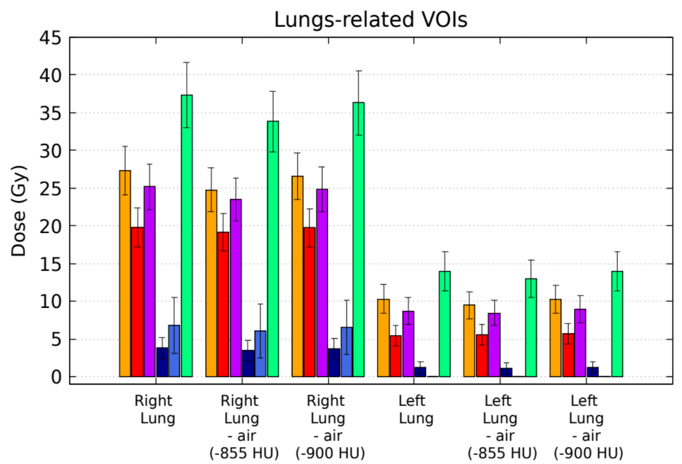
GATE simulations

Liver-related VOIs

- Dose increase with filters
- $|\delta| < 7\%$ for air and lungs filters
- $|\delta| < 35\%$ for liver filter and native rescaled

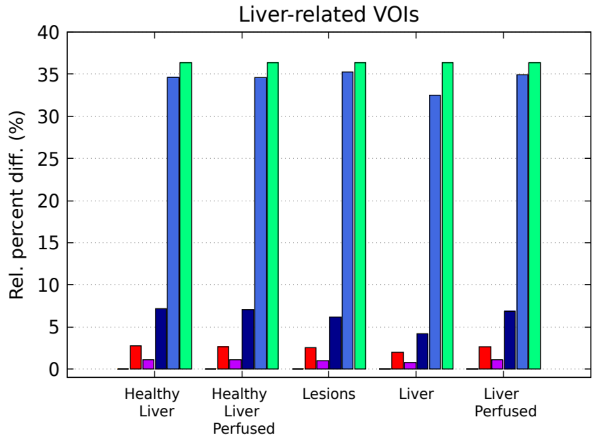


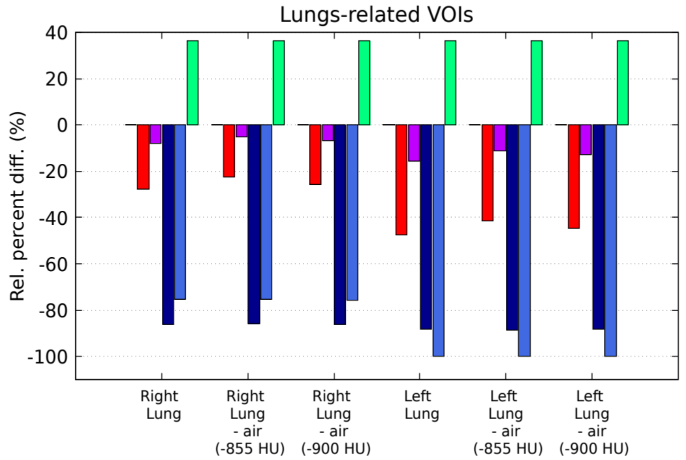




Relative percent difference of dose average values

$$\delta_{VOI} = 100 \cdot \frac{\overline{D}_{VOI}^{filtered} - \overline{D}_{VOI}^{native}}{\overline{D}_{VOI}^{native}}$$



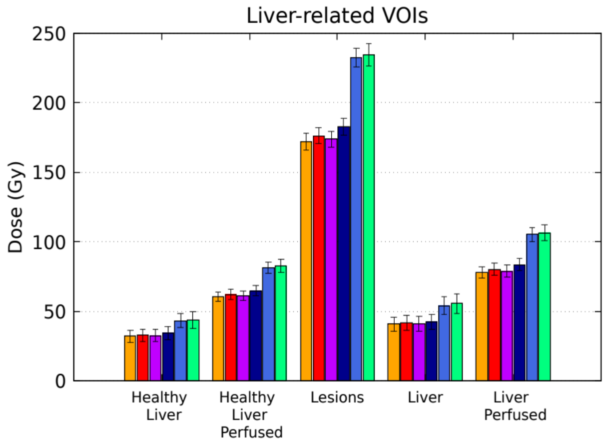


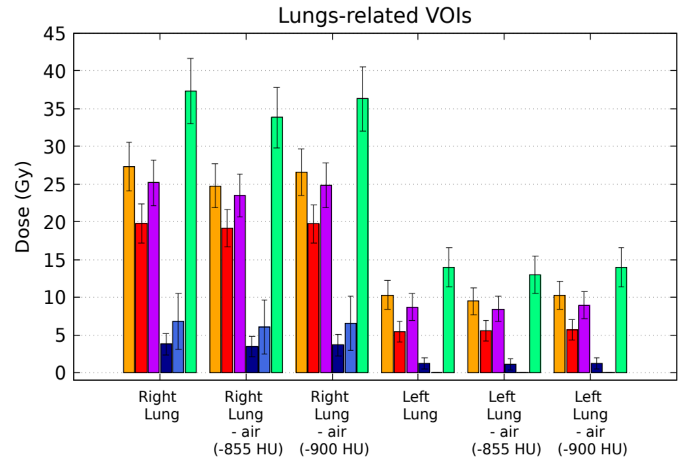
Average doses comparison

GATE simulations

Lungs-related VOIs

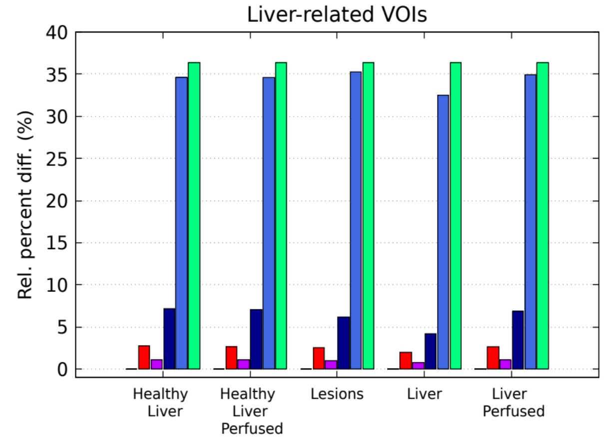
- Dose reduction, strongly depenent on filter
- $|\delta| < 85\%$ for lungs filter
- $|\delta| < 99\%$ for liver filter in left lung

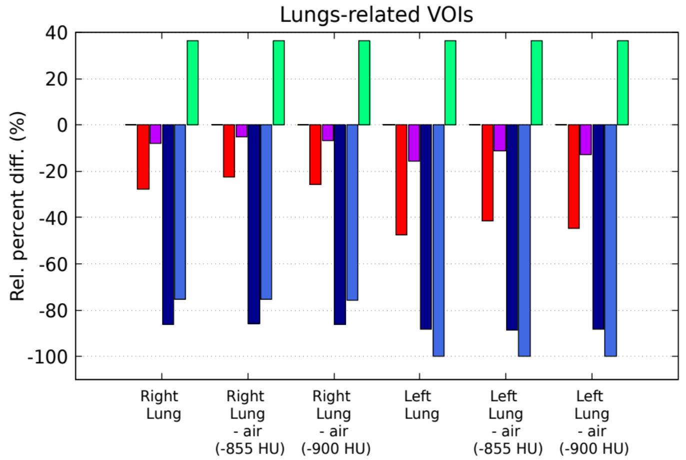




Relative percent difference of dose average values

$$\delta_{VOI} = 100 \cdot \frac{\overline{D}_{VOI}^{filtered} - \overline{D}_{VOI}^{native}}{\overline{D}_{VOI}^{native}}$$



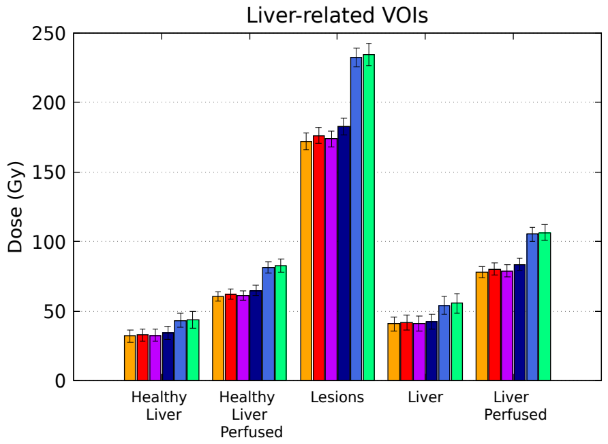


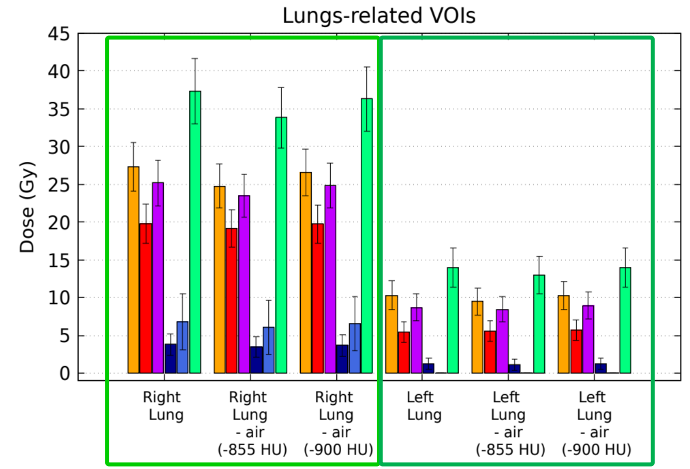
Average doses comparison

GATE simulations

Lungs-related VOIs
- No significant difference between standard lung VOIs and VOIs with air voxels removed

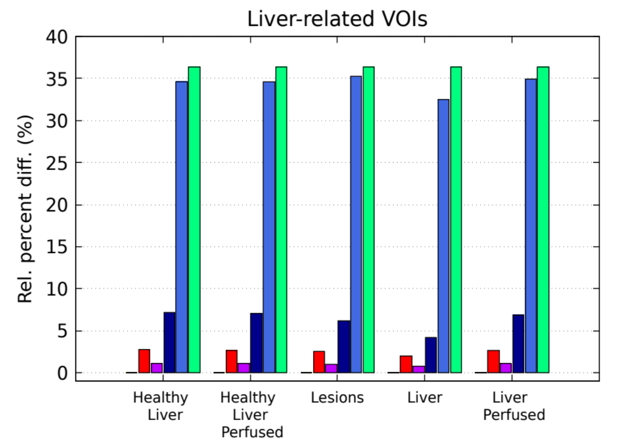
Native | Filter -855 HU | Filter -900 HU | Filter -Lungs | Filter Liver only | Native rescaled

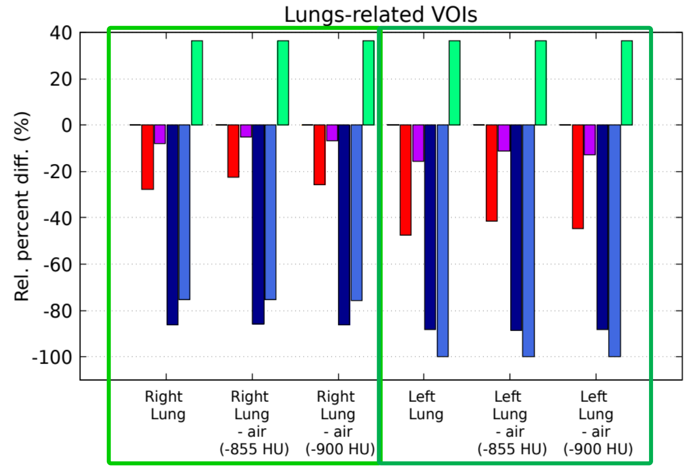




Relative percent difference of dose average values

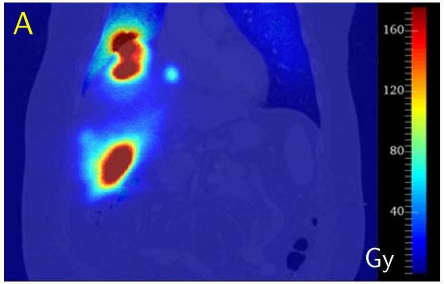
$$\delta_{VOI} = 100 \cdot \frac{\overline{D}_{VOI}^{filtered} - \overline{D}_{VOI}^{native}}{\overline{D}_{VOI}^{native}}$$





Dose maps comparison

GATE simulations

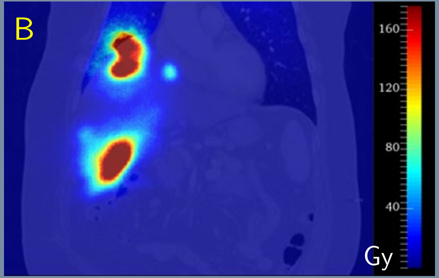


Native SPECT simulation dose map (fused with CT)

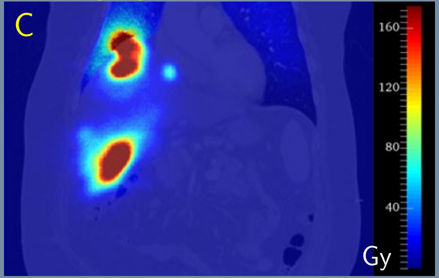
Filtered SPECT simulations dose maps (fused with CT)

Setting decay probability = 0 in air

1) $c_{A\ SPECT} = 0$ if $HU_{CT} < -855$

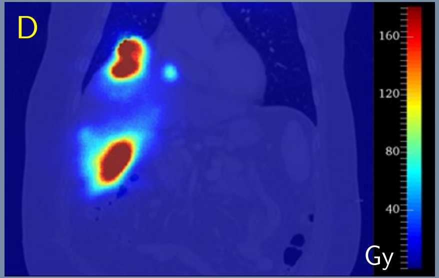


2) $c_{A\ SPECT} = 0$ if $HU_{CT} < -900$



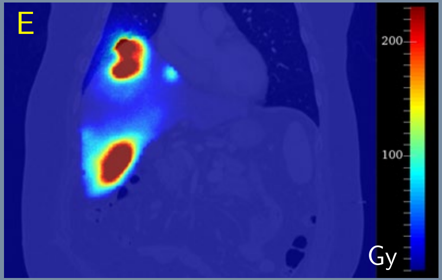
Setting decay prob. = 0 in lungs

3) $c_{A\ SPECT} = 0$ within lungs VOIs

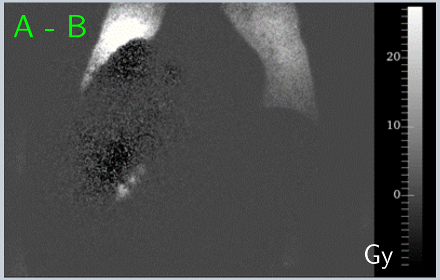


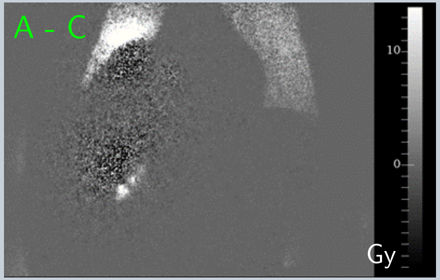
Setting decay prob. = 0 outside liver

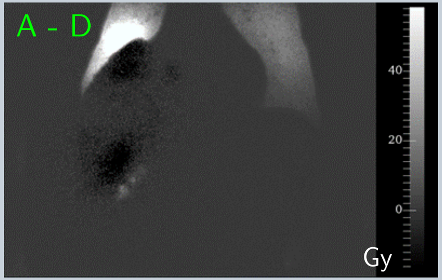
4) $c_{A\ SPECT} = 0$ outside liver VOI

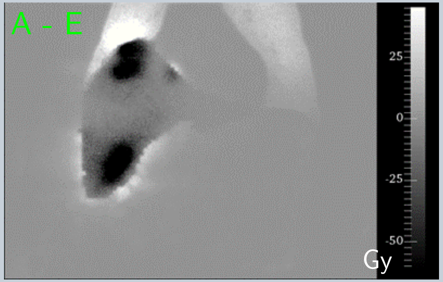


Difference with respect to native (native SPECT sim. dose map – filtered SPECT sim. dose map)

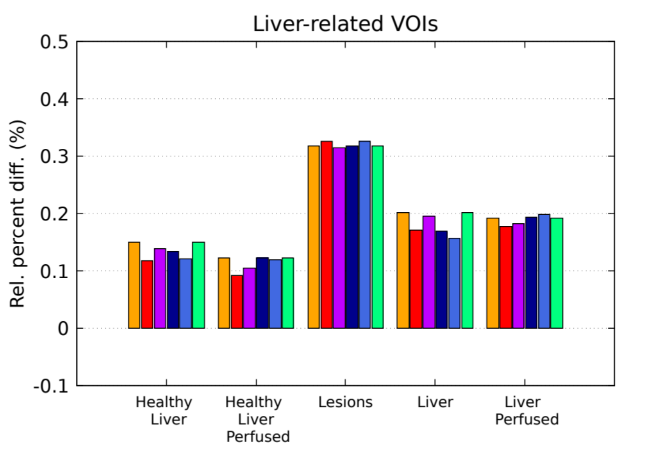


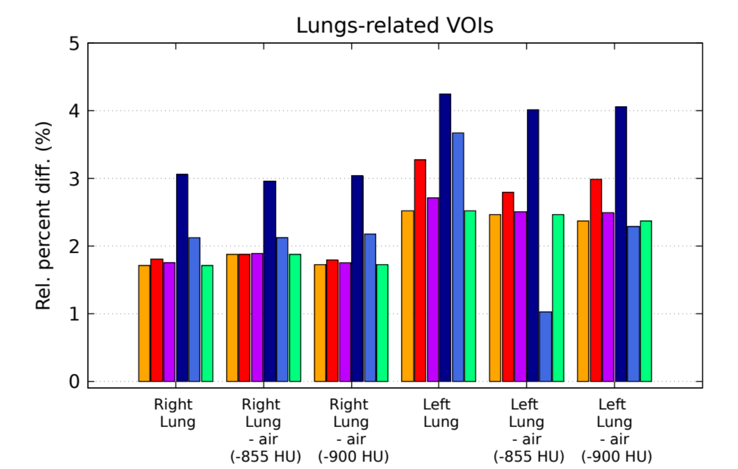






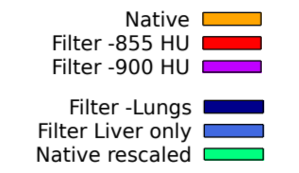
GATE-GAMOS comparison





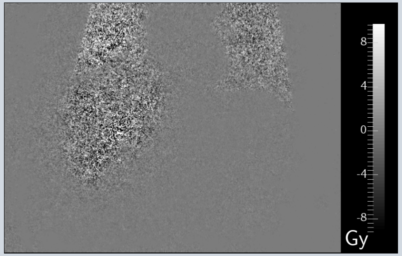
Relative percent difference of dose average values

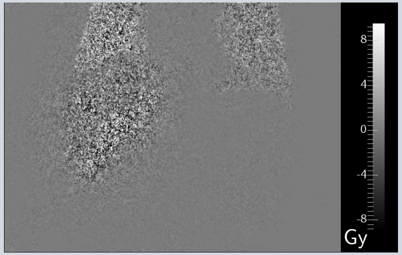
$$\varepsilon_{VOI} = 100 \cdot \frac{\overline{D}_{VOI}^{GAMOS} - \overline{D}_{VOI}^{GATE}}{\overline{D}_{VOI}^{GATE}}$$

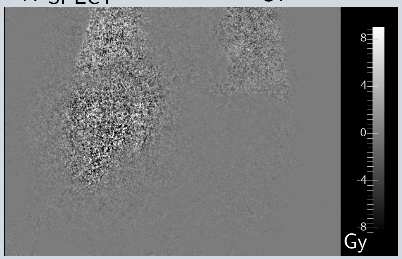


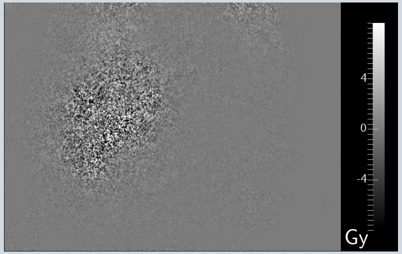
GAMOS-GATE differences (GAMOS sim. dose map – GATE sim. dose map)

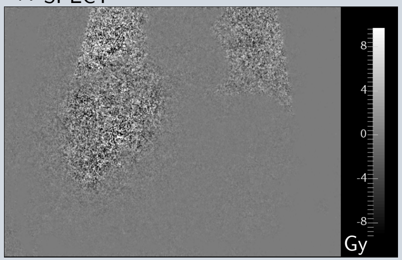
native	$c_{A\ SPECT} = 0$ if $HU_{CT} < -855$	$c_{A\ SPECT} = 0$ if $HU_{CT} < -900$	$c_{A\ SPECT} = 0$ within lungs	$c_{A\ SPECT} = 0$ outside liver VOI



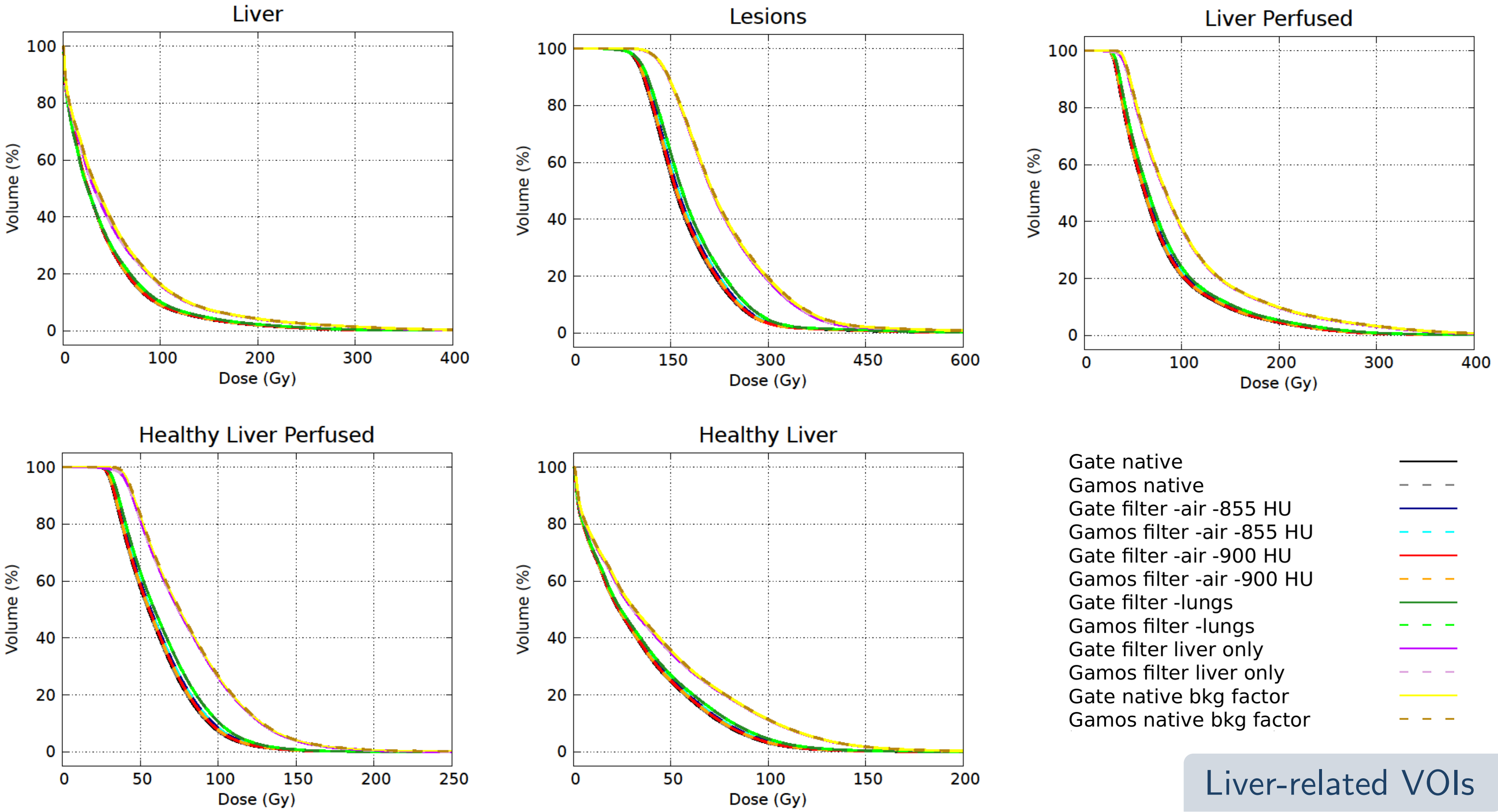






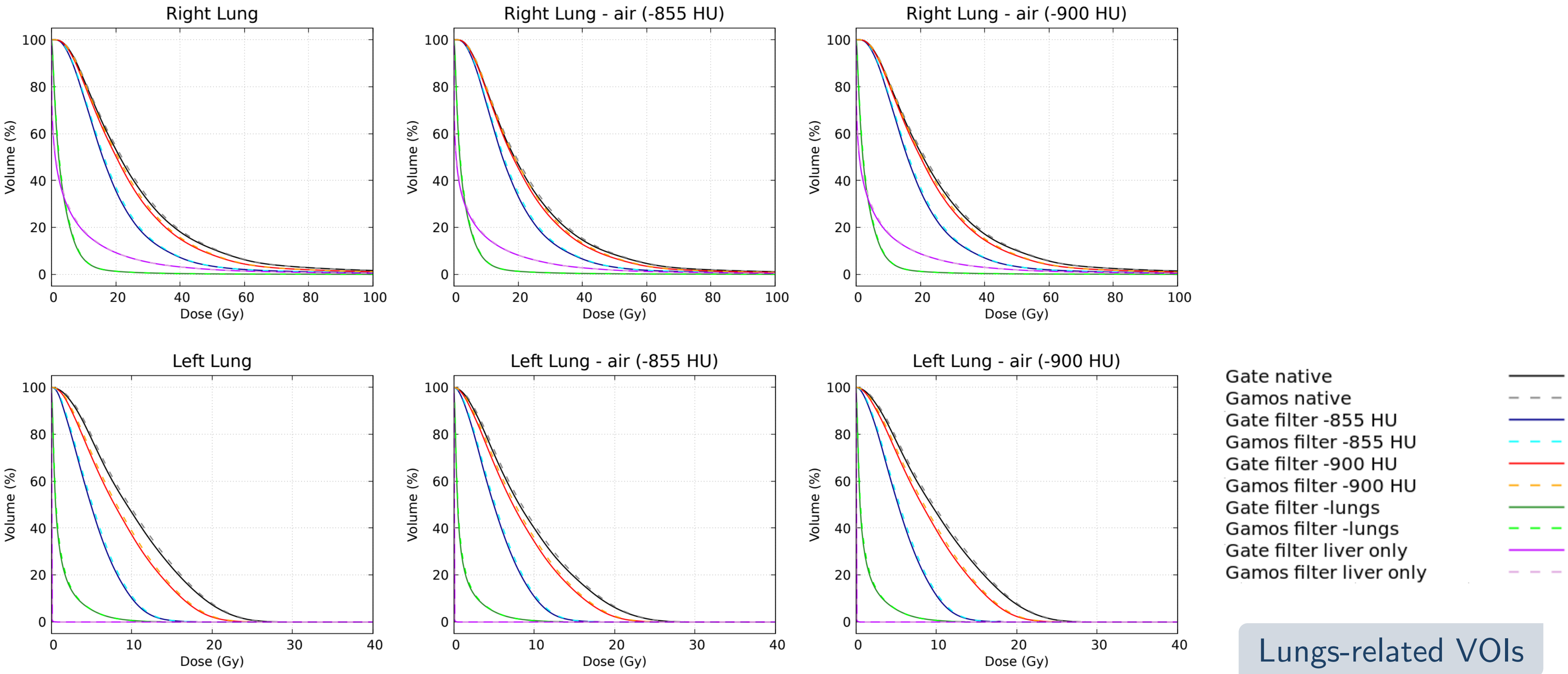


Dose-Volume Histograms (DVHs)



Liver-related VOIs

Dose-Volume Histograms (DVHs)



Lungs-related VOIs

Conclusion

- Two main studies reported, aimed at optimizing voxel-level patient-specific MC internal dosimetry for ^{90}Y TARE treatments
- 1) Behaviour of simulation time vs CT resolution and production range cuts
  - Best parameters combination: resampling giving CT voxels of the order of 2.0x2.0x4.0 mm^3 (dimensions ≈ 2x conventional CT voxels) + 0.1-0.5 mm cuts
- 2) Investigation and correction of dose misestimations due to artefacts in input functional scans (background noise, reconstruction noise, motion blurring)
  - Even if MC is gold standard for internal dosimetry, must be used with criterion!
  - Using merely native SPECTs as input can produce:
    - Overestimation of lungs doses
    - Underestimation of liver doses
  - Appropriate filtering procedures (thresholds + logical operations) of functional scans could lead to more realistic simulations → more reliable results
- Perspectives:
  - Extend the studies to further cases (ongoing)
  - Possible experimental + MC studies on phantoms

SOCIETÀ ITALIANA DI FISICA

107° CONGRESSO NAZIONALE

13-17 settembre 2021

Thank you for your attention!

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