Multiscale Digital Twins for Personalized Radiopharmaceutical Therapy

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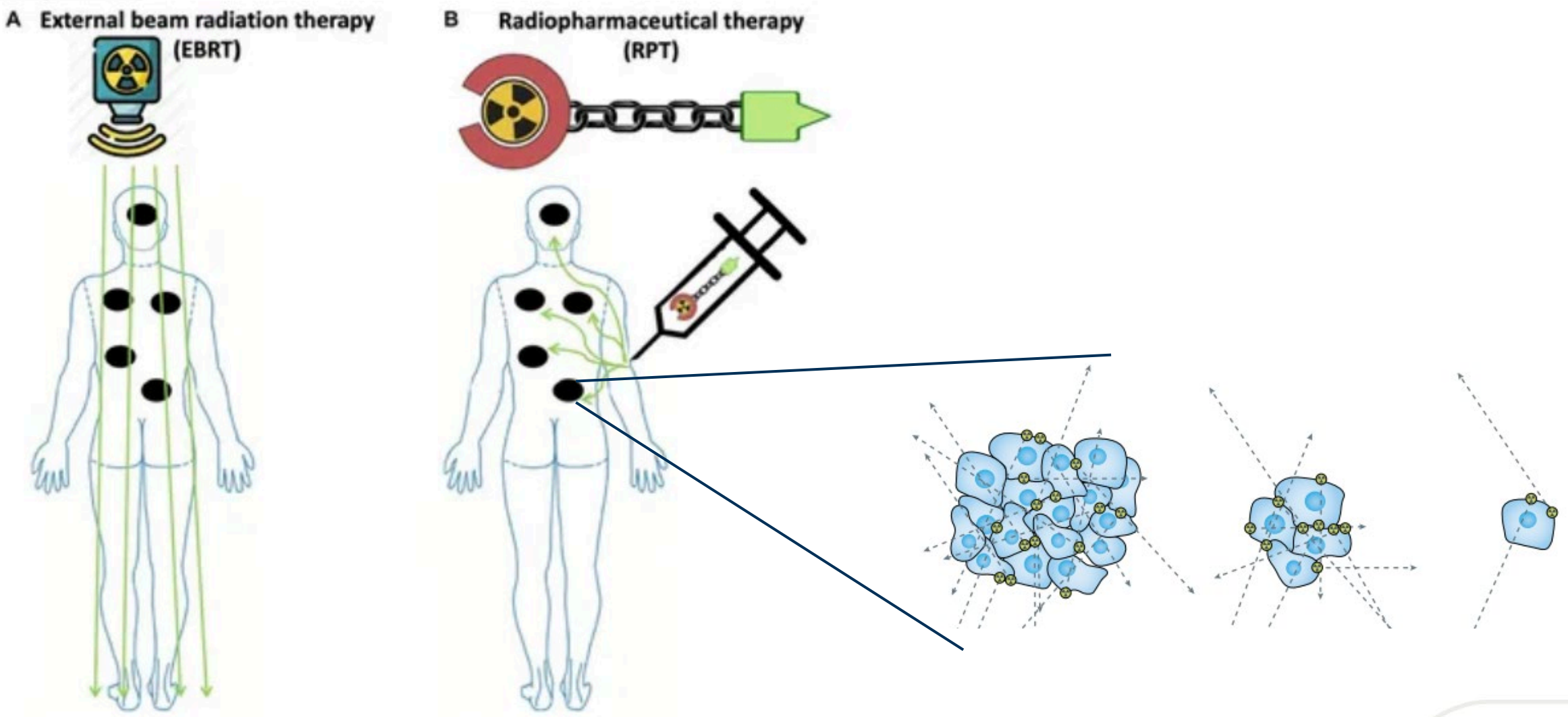
The promise of Radiopharmaceutical Therapy (RPT): selectively target cancer cells while sparing normal tissue



Shea et al. (Frontiers in Nuclear Medicine – 2024)
Sgouros et al. (*Nature Reviews Drug Discovery* – 2020)

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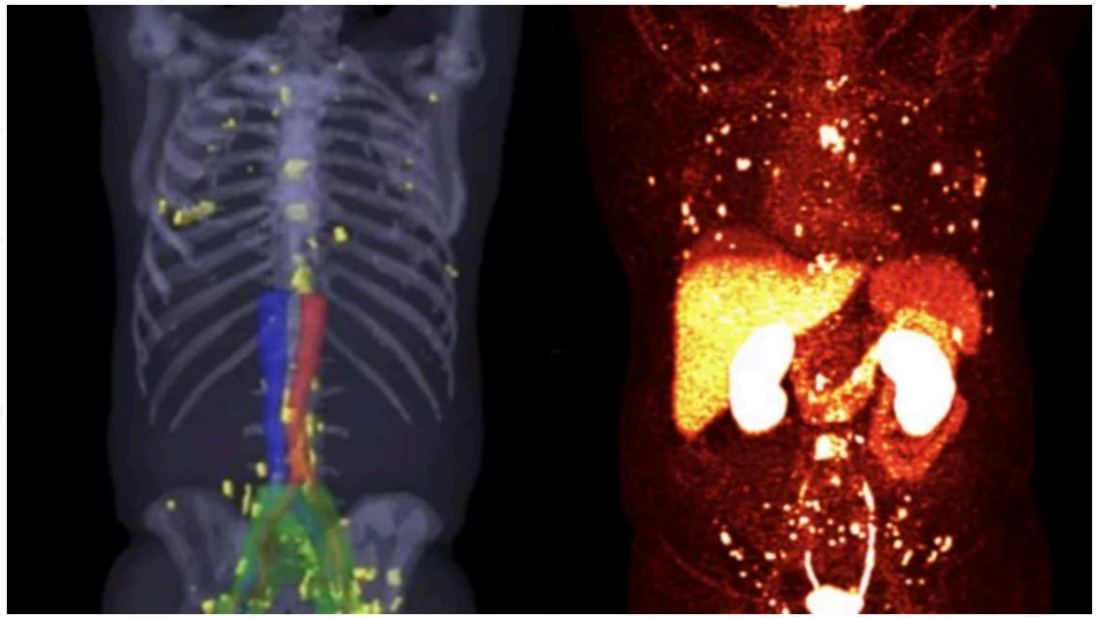
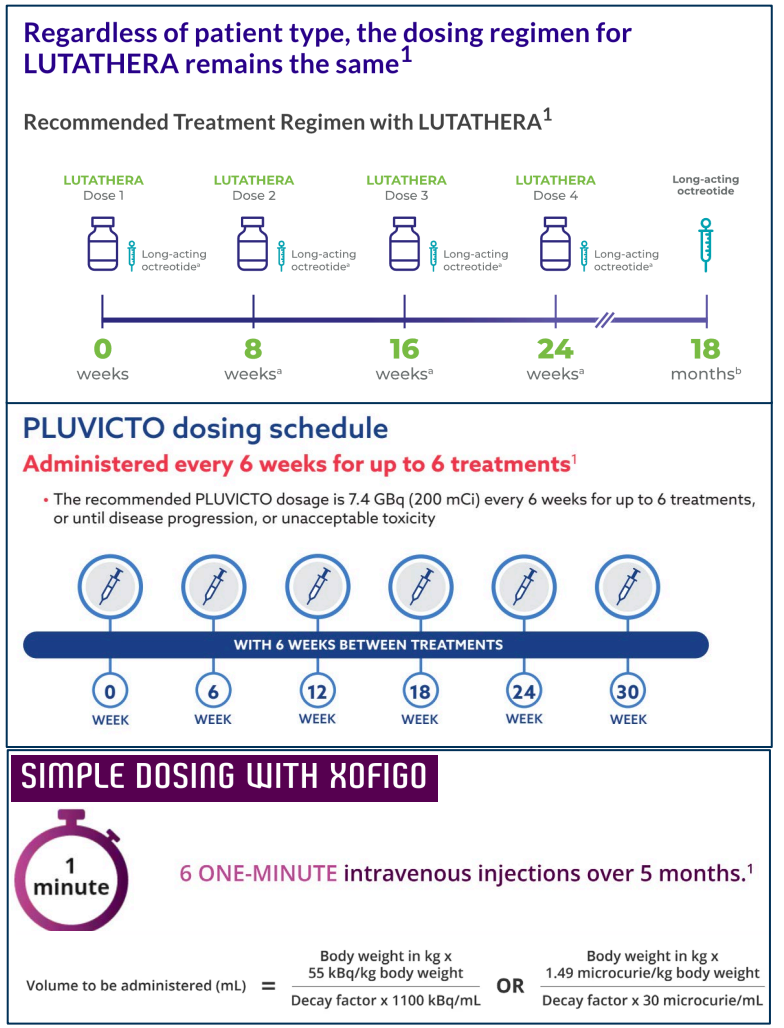
State-of-the-art RPT in the clinic



Late-stage cancer treatment

Optimization of RPT:
Maximize cancer cell death,
Minimize other unwanted effects
for each Individual Patient



Mostly, uniform dosing across patients

https://tinyurl.com/fnajy6xx

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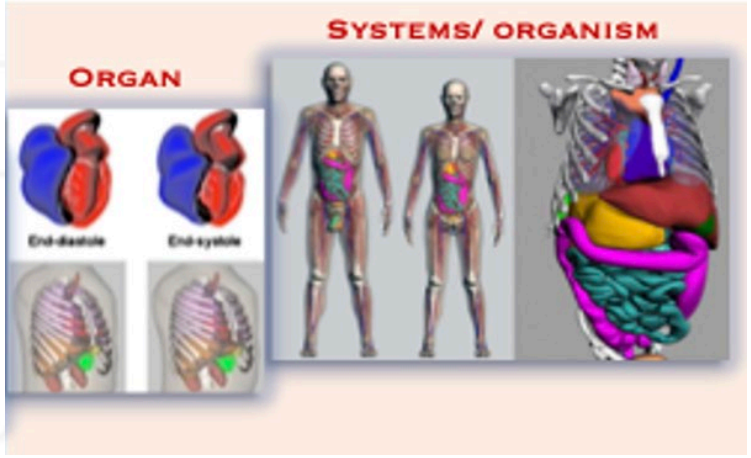
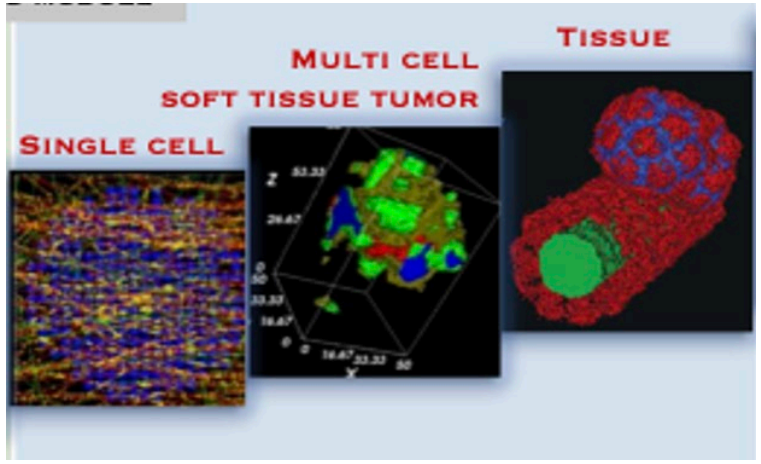
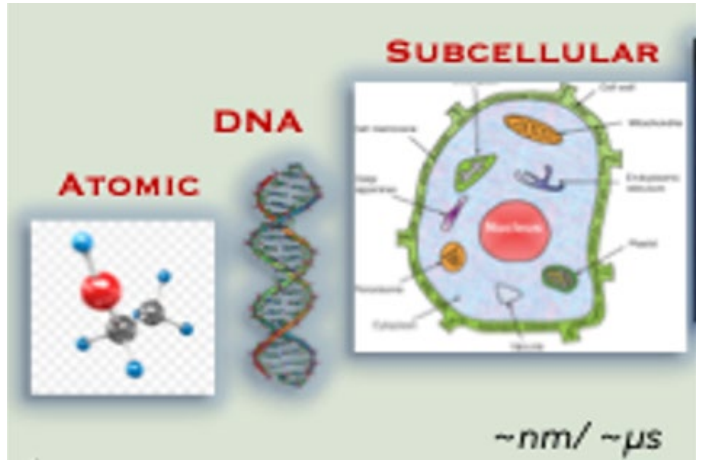
Multiscale Digital Twins for RPT



Whole body



Multi-cell



Subcellular

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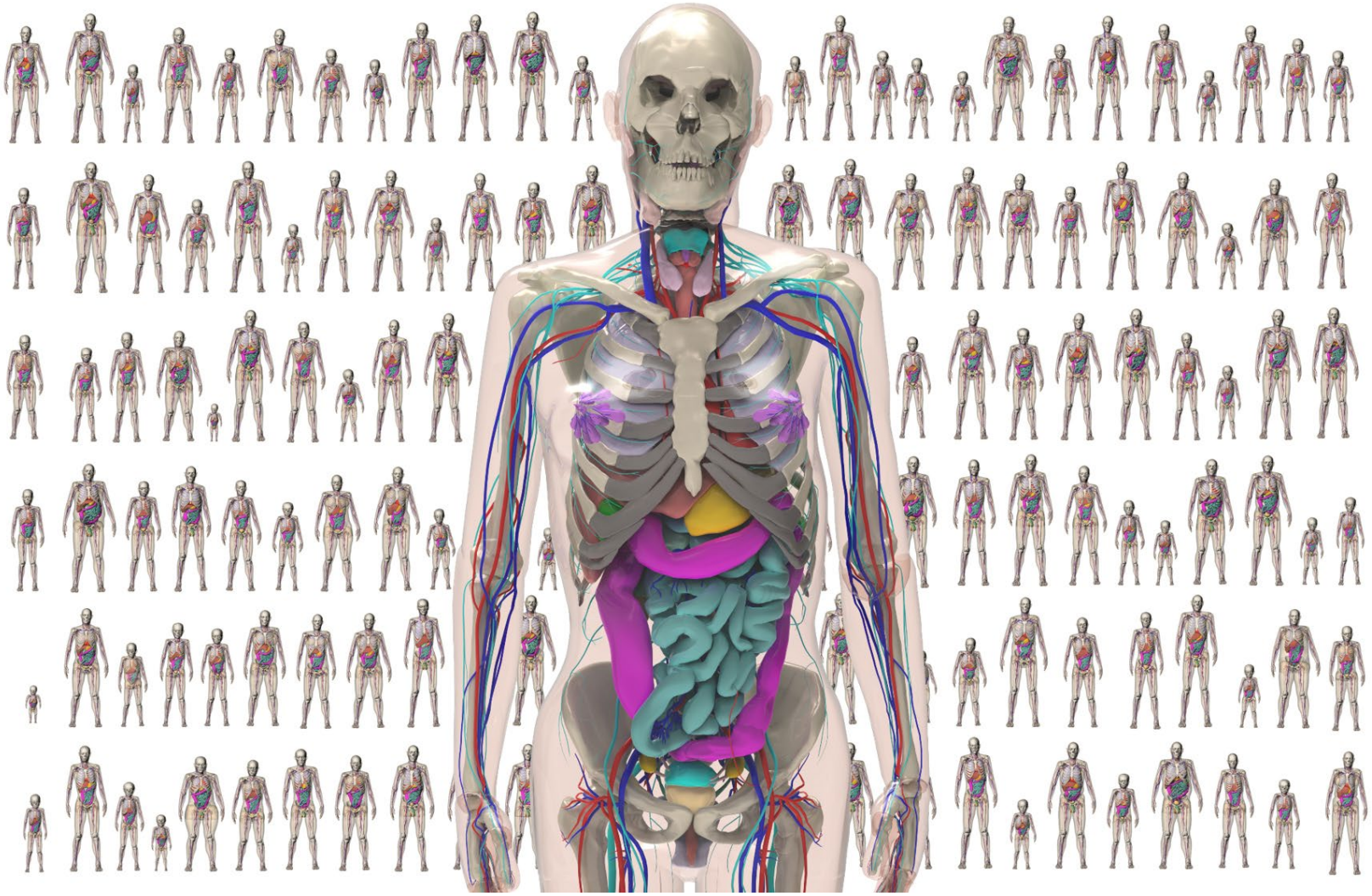
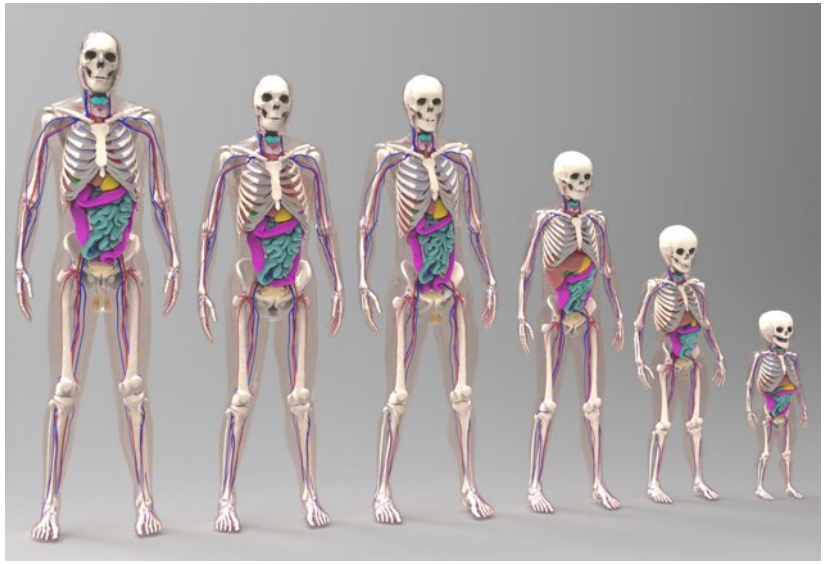
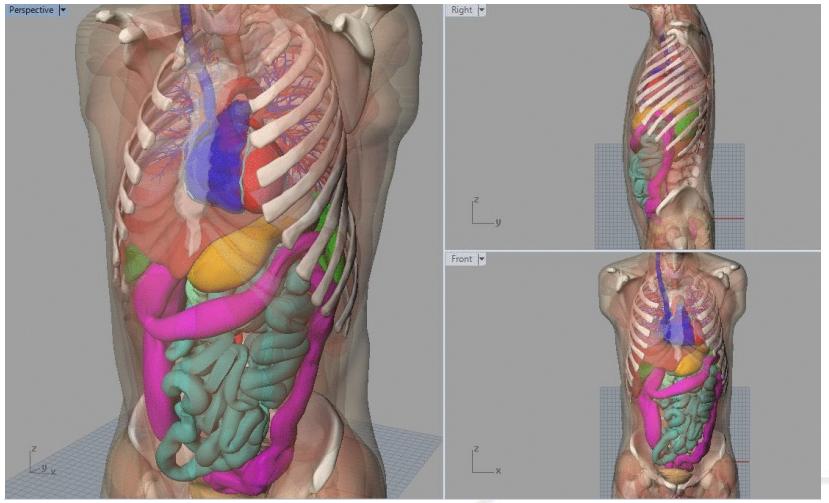
RPT Multiscale Digital twins – Desirable Capabilities

- Tracks radioactivity across scales
- Estimates radiation dose across scales
- Simulates drug uptake
- Predicts therapy outcome
- Patient specific

Virtual human population







eXtended CArdiac Torso (XCAT) phantoms, Duke CVIT, E. Samei and P. Segars, Duke University

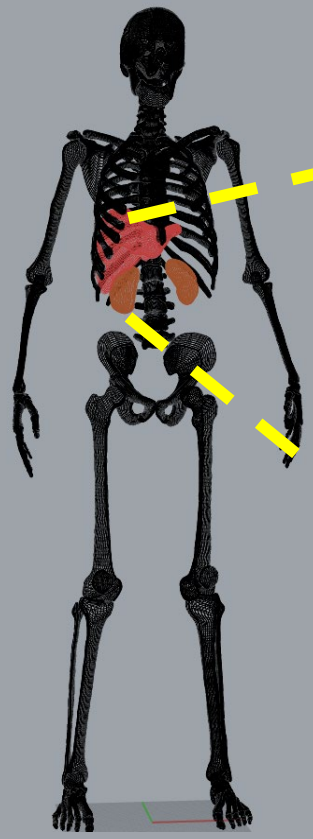
RPT through the scales

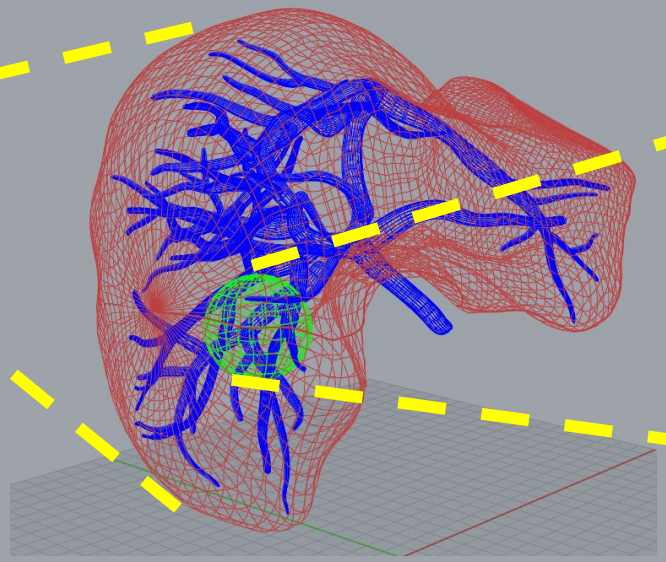
Whole-body XCAT Phantom

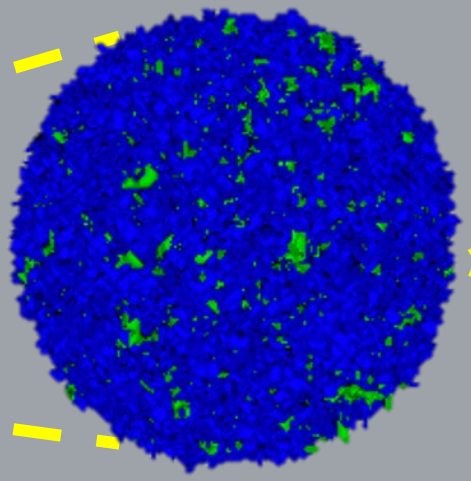
Mesh of a liver with a spherical tumor and major vasculature

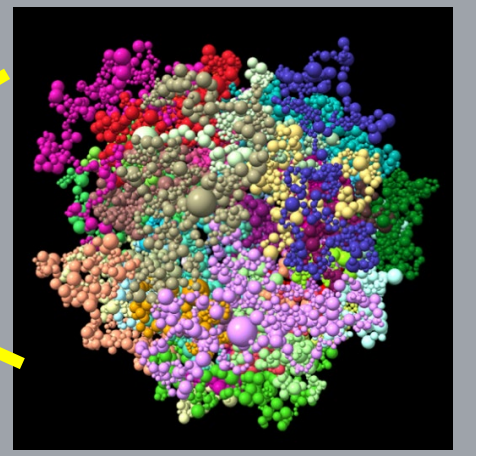
A slice of the generalized cellular model of the spherical tumor

3-D chromosome conformation of a cell's DNA









A Multiscale Computational Radiation Dosimetry Framework for Radiopharmaceutical Therapy: A Proof-of-Concept Demonstration, GA Agasthya, et al - AAPM 66th Annual Meeting & Exhibition, 2024

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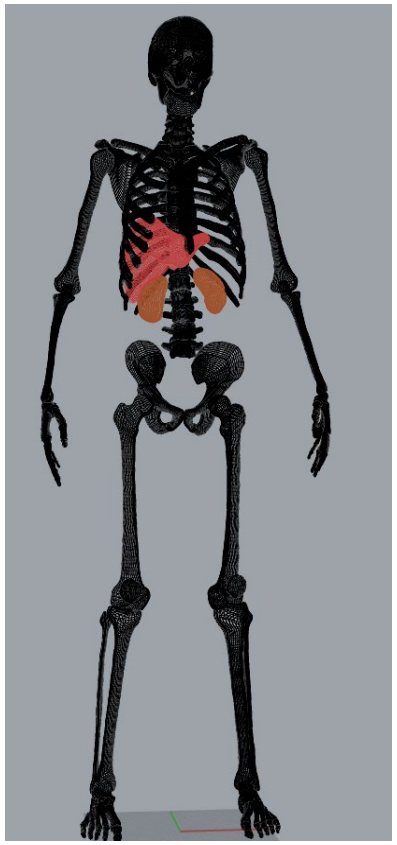
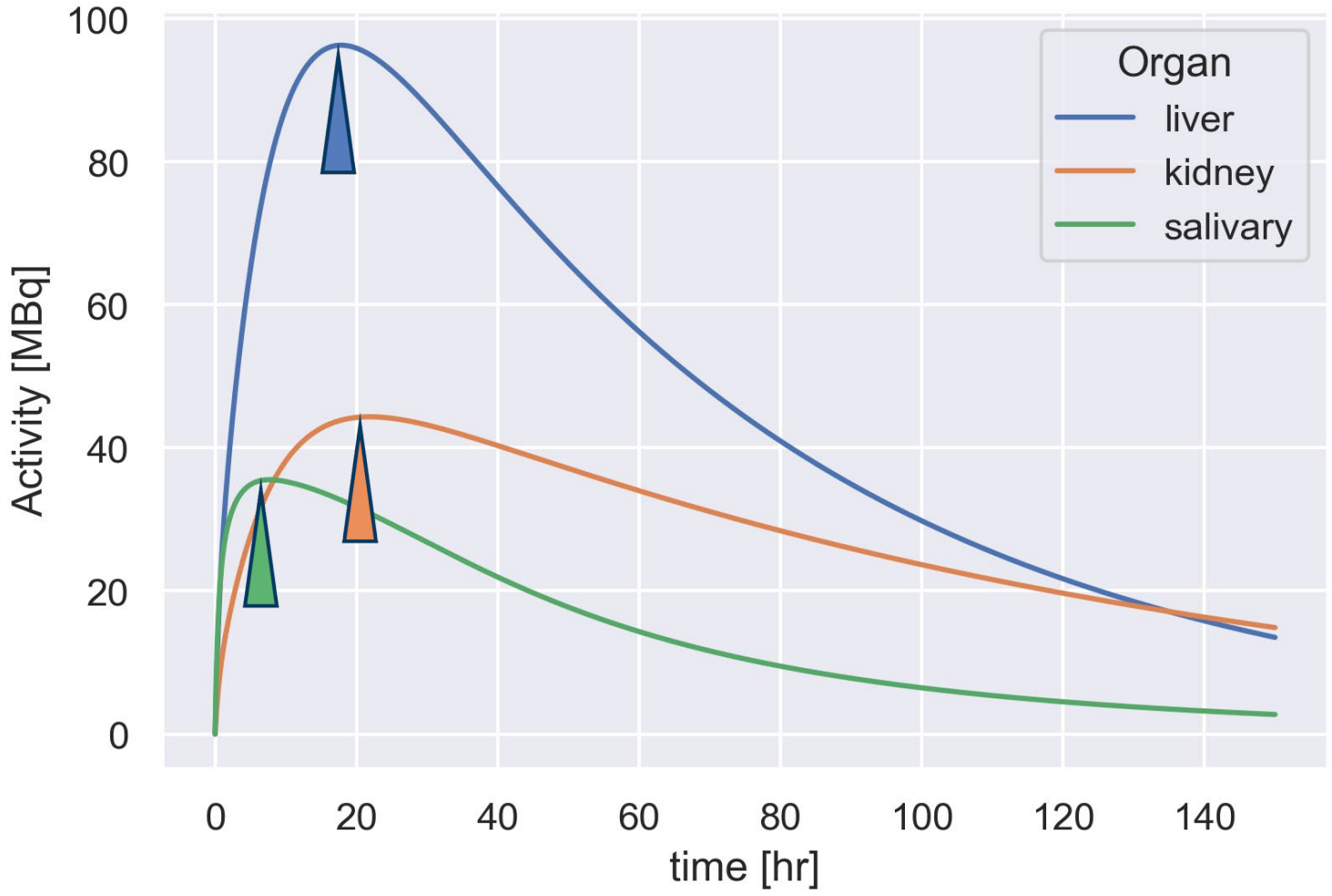
Whole body scale with pharmacokinetic models

XCAT Phantom



Male patient
BMI: 24.4
RPT agent: ^{177}Lu-PSMA-617
Dose: 3 GBq



Jayasai et al, SEAAPM 2025

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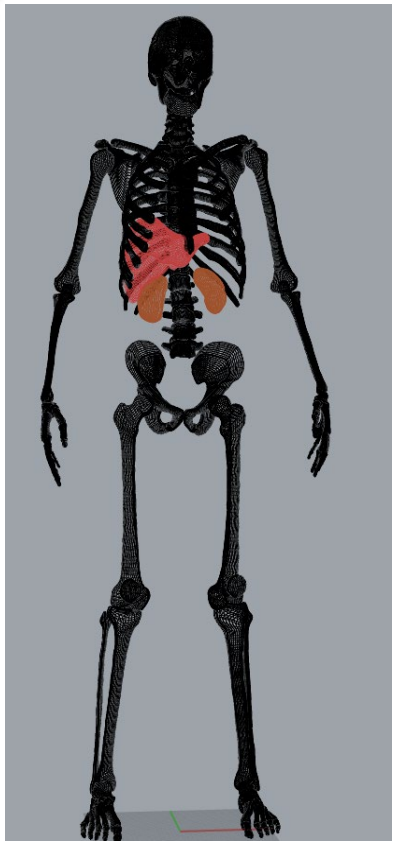
Radiation dose to critical organs

XCAT Phantom



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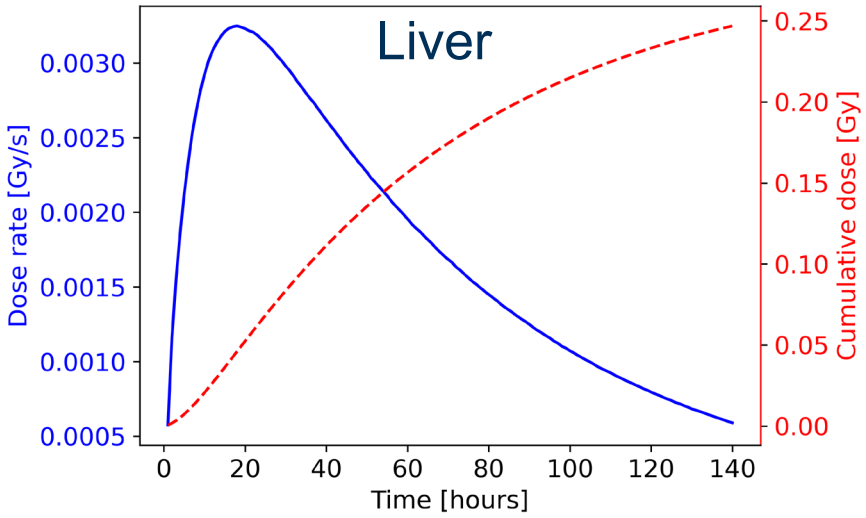
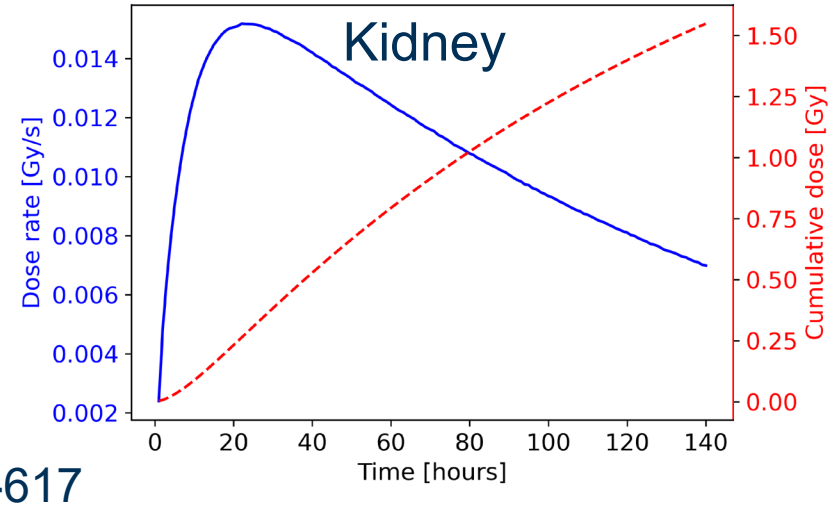
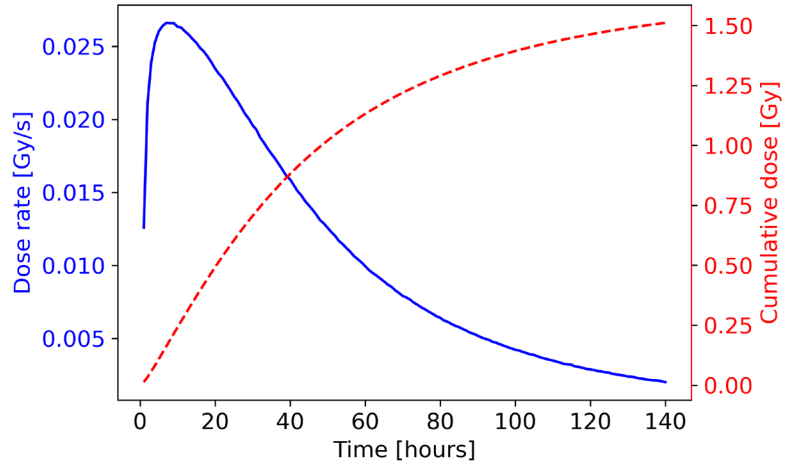




Salivary Glands



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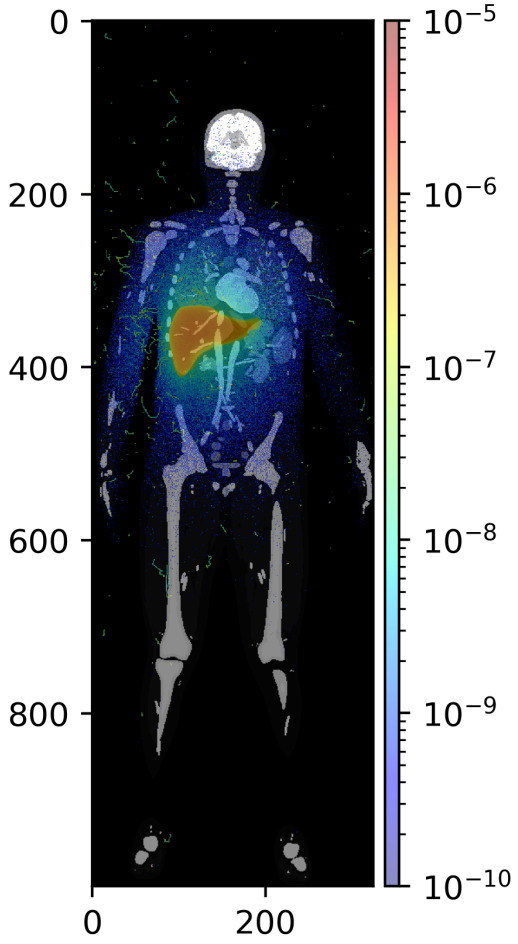
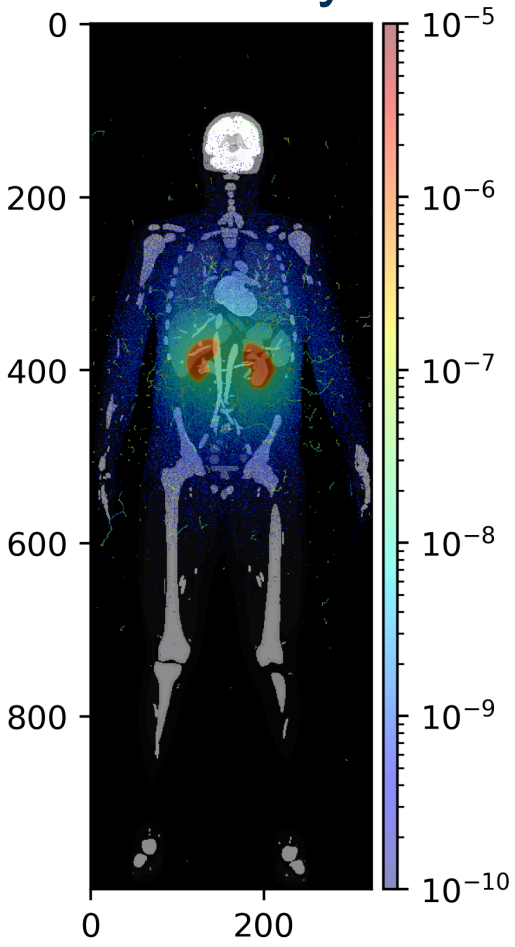
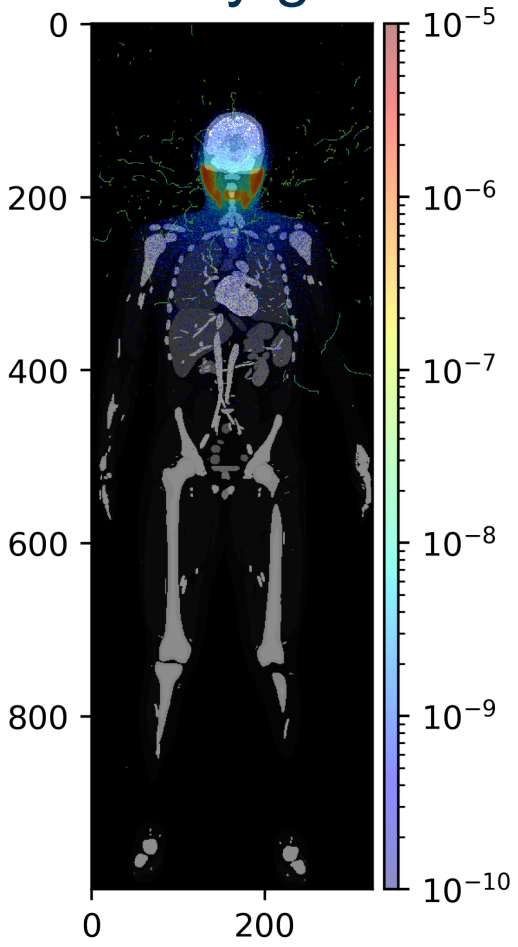
Liver



Kidney



Salivary gland



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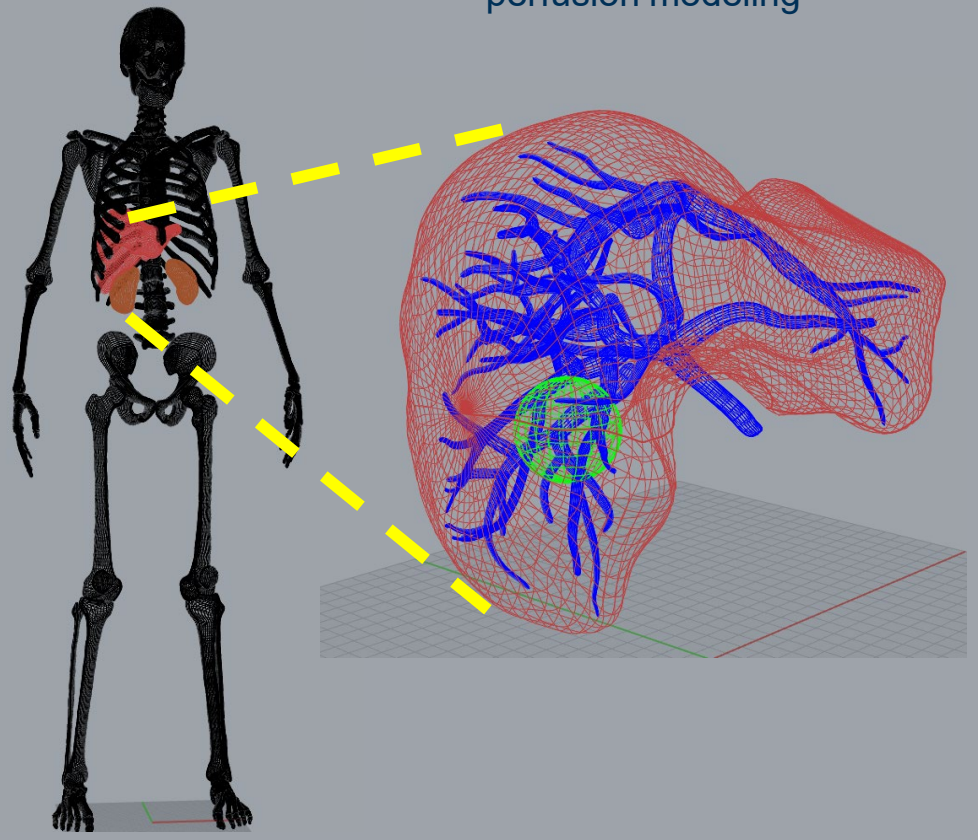
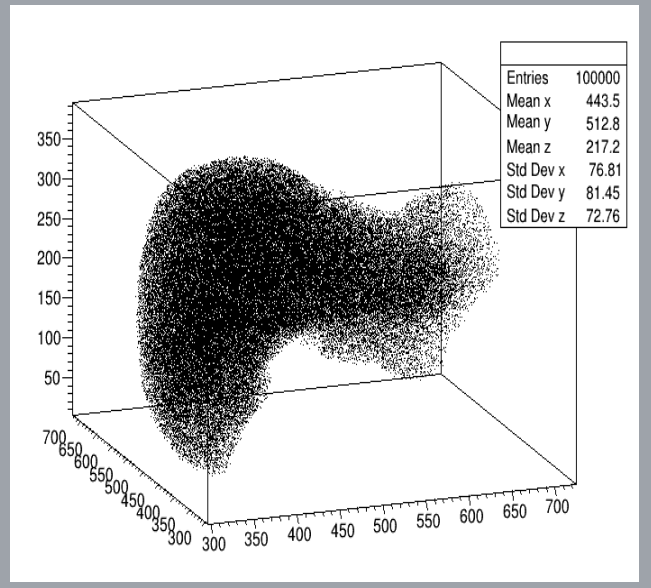
Organ Model -> CFD (OpenFOAM)

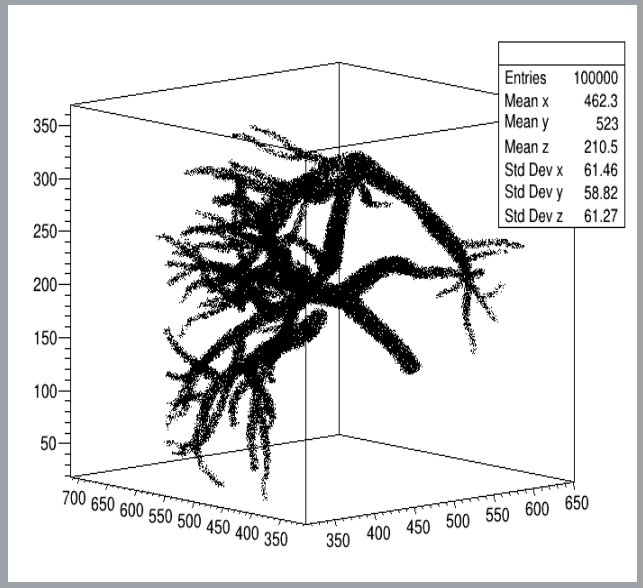
XCAT Phantom

Hepatic vasculature for perfusion modeling



2. Radioisotope activity distribution





Radiopharmaceutical spatial distribution reconstruction in the liver volume (left) and liver vasculature (right)

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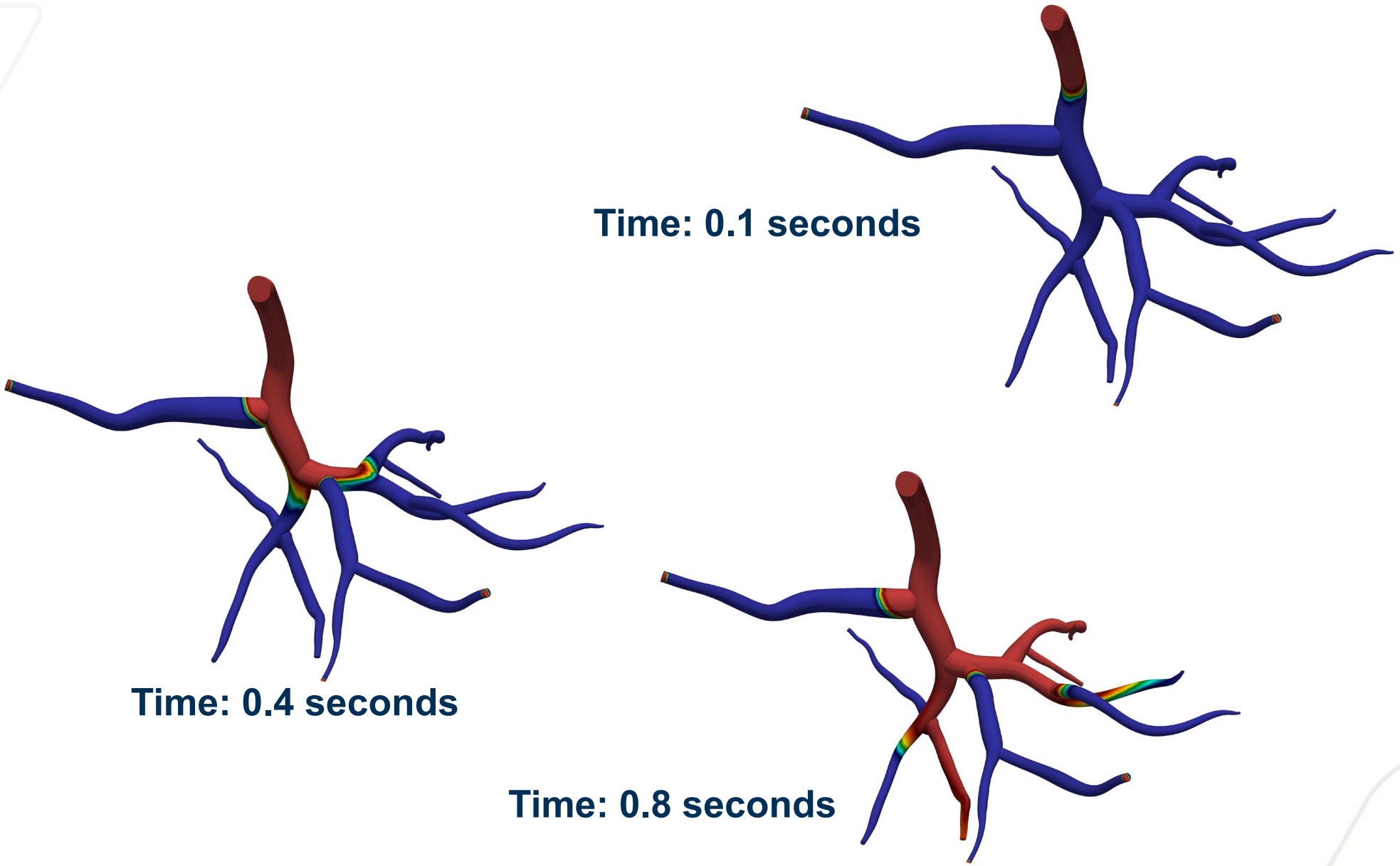
Spatio-temporal distribution of radiopharmaceutical



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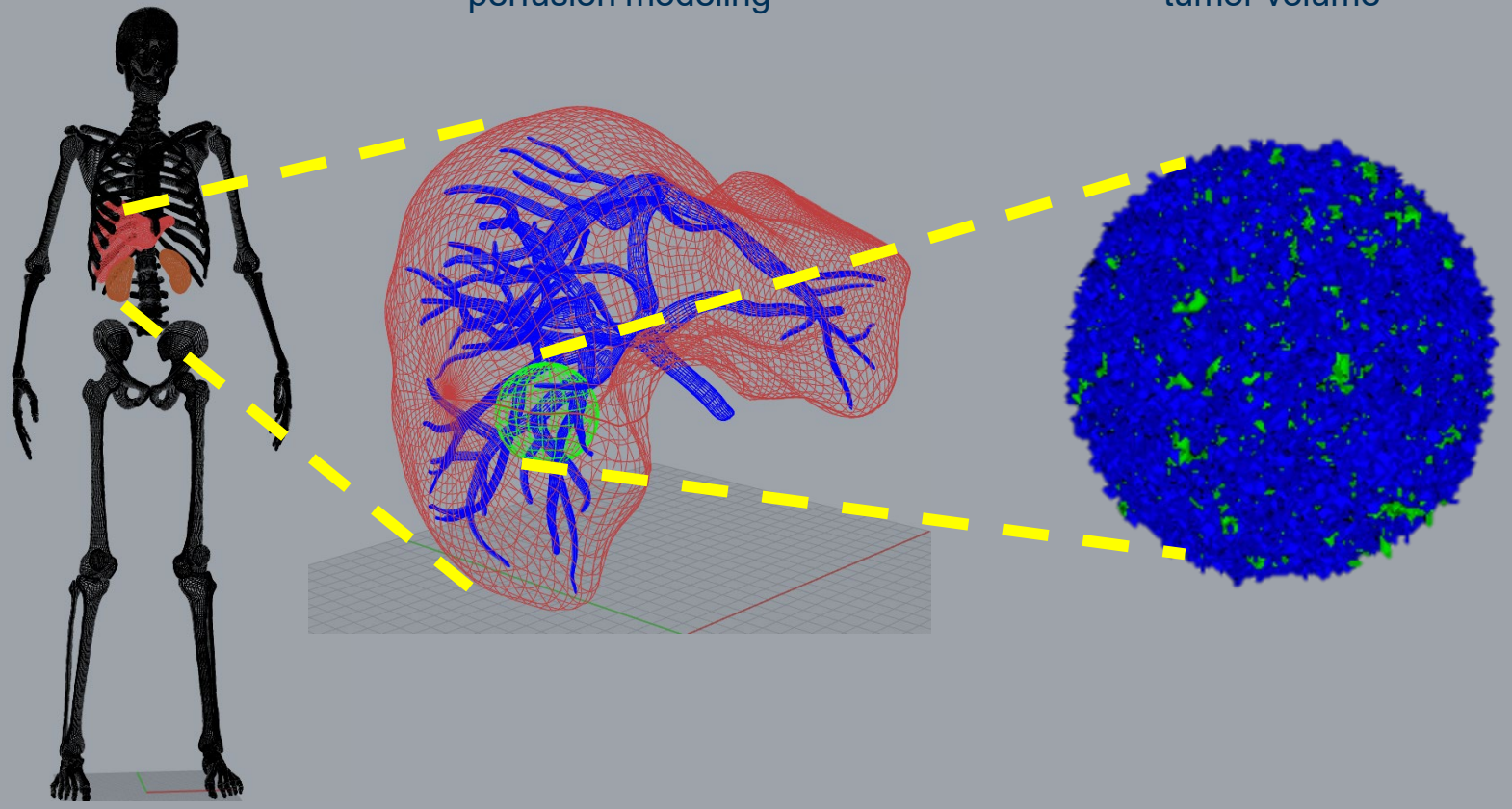
3D Tumor modeling

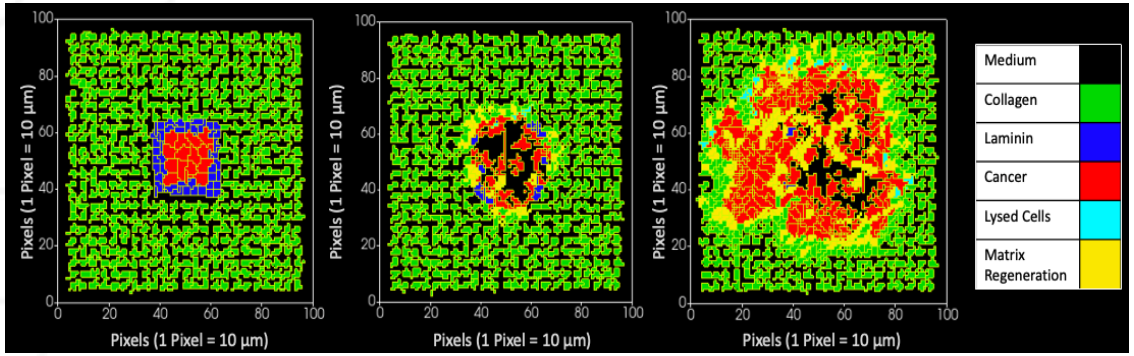
XCAT Phantom

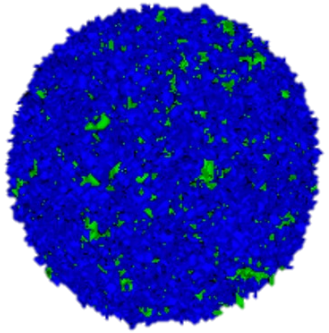
Hepatic vasculature for perfusion modeling

Embedded 3D tumor volume



Tumor modeling and outcomes prediction

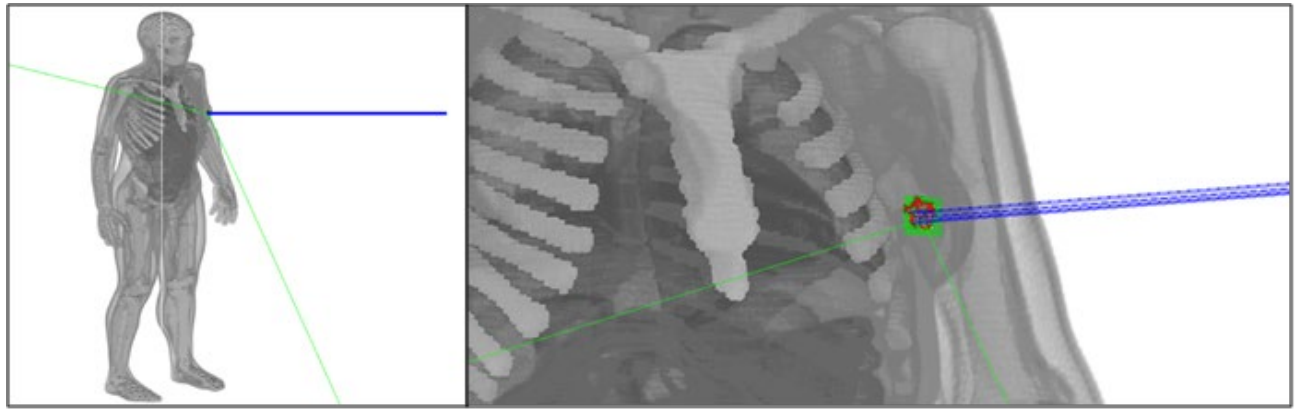


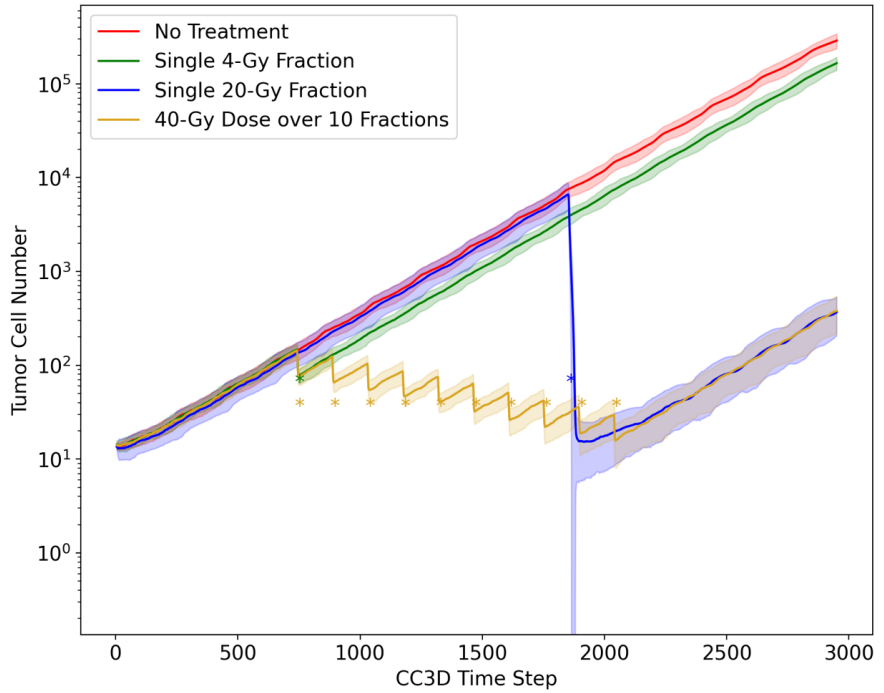


$$V(t) = V_0 e^{rt}$$

$V(t)$ → volume as a function of time
t → simulation time
V_0 → volume as a function of time
r → growth rate

Multicell breast cancer model: initialization (left), early tumor growth (middle), and post-treatment development (right)





Inman et al, AAPM 2022

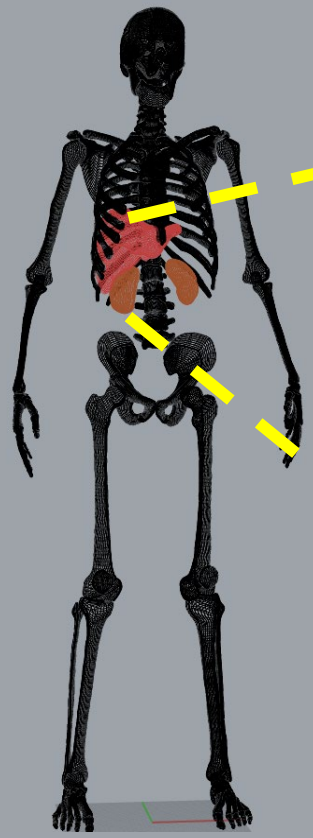
3D Chromosome conformation → DNA damage

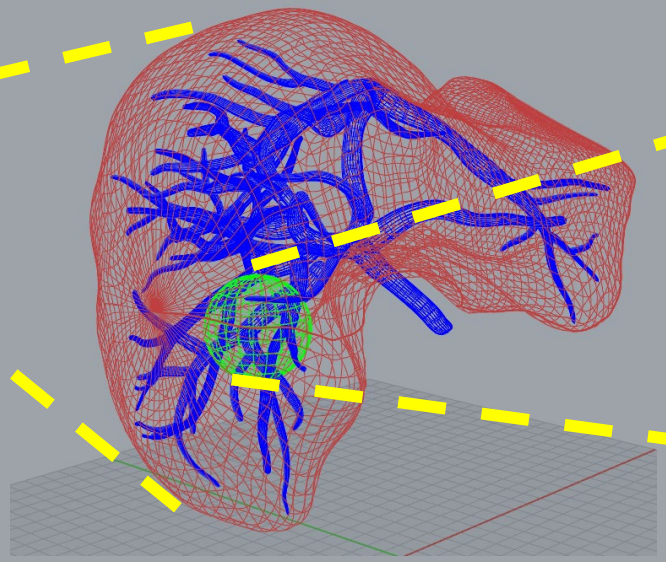
XCAT Phantom

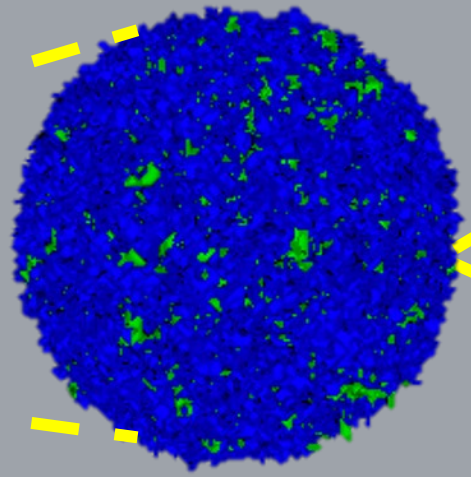
Hepatic vasculature for perfusion modeling

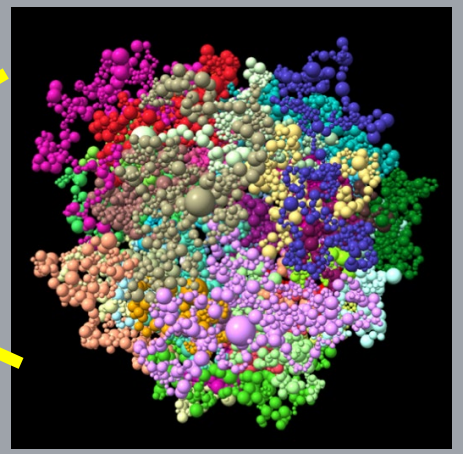
Embedded 3D tumor volume

DNA single and double strand breaks









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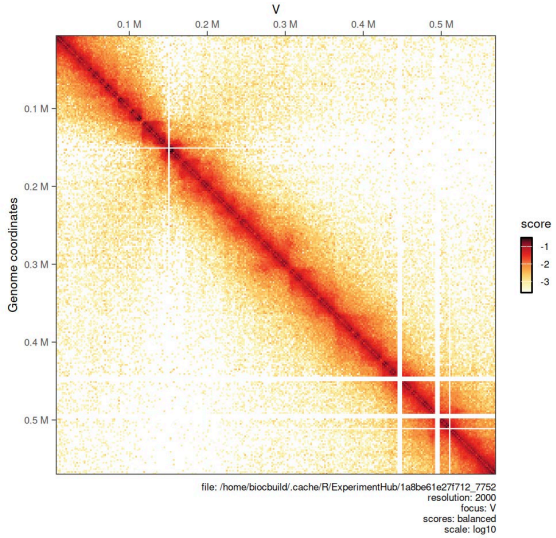
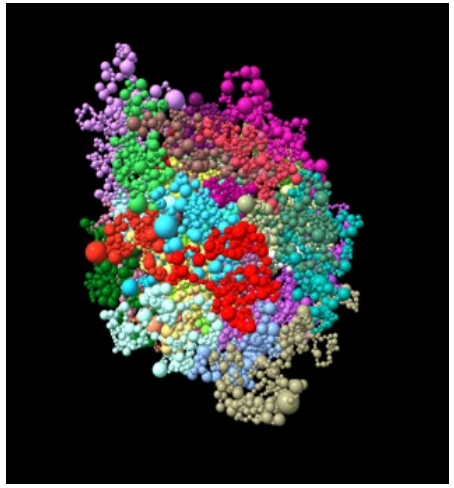
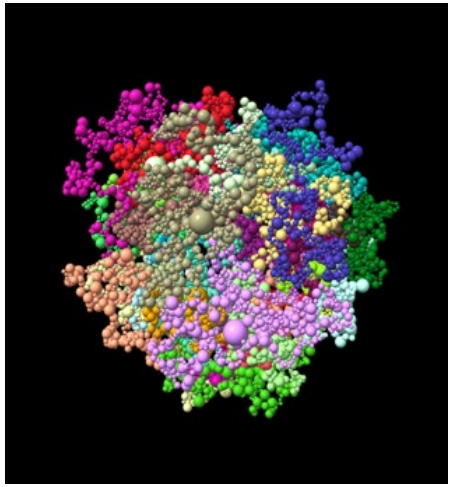
Hi-C data to 3D chromosome structures





Fibroblast
BJ-5ta chromosome



Lymphoblastoid
GM12878 chromosome

Hi-C data from **Experiments** → 3D chromosome structures **G-NOME** → Radiation track simulation **TOPAS-nbio** → DNA damage output → DNA repair simulation **MEDRAS**

Andriotty et al, (Physics in Medicine & Biology – 2024)

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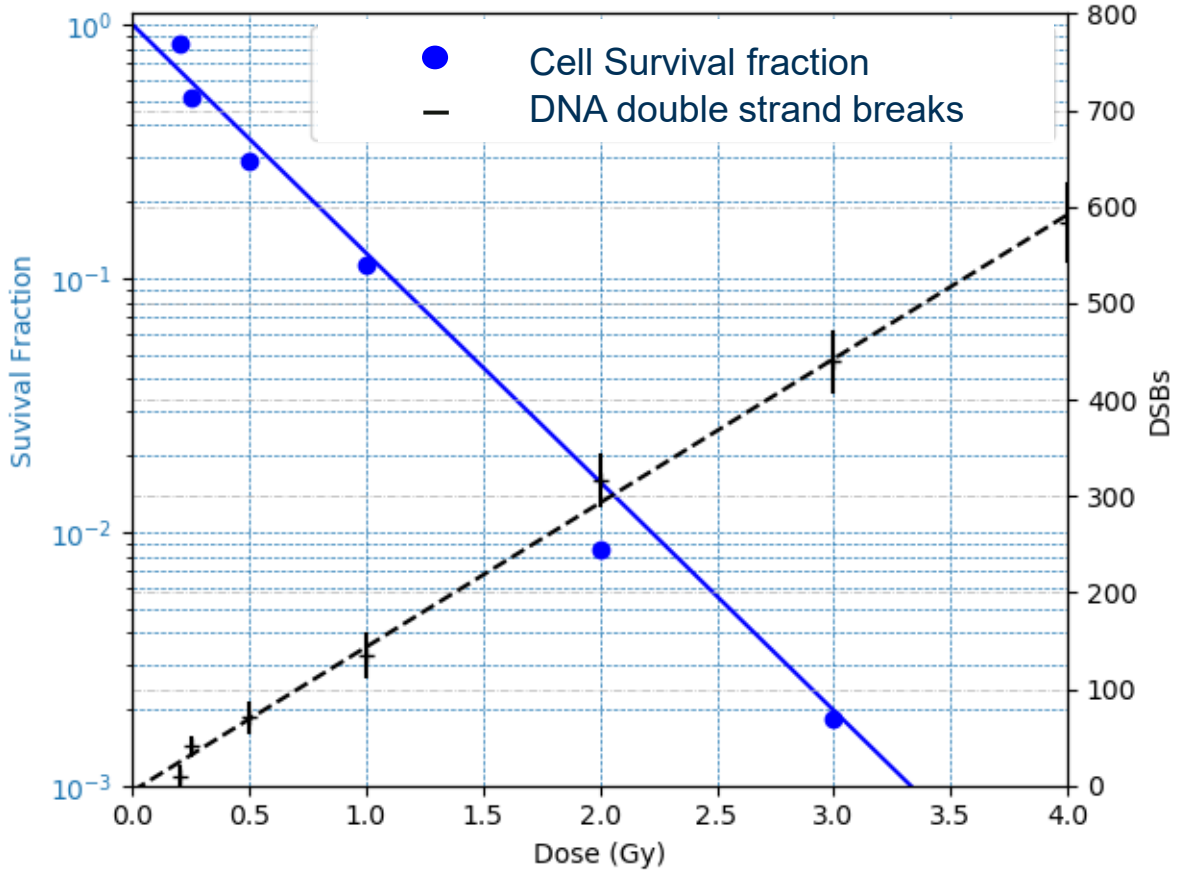
Dosimetry + Outcomes Prediction



Predicting cell survival fraction and number of double strand breaks (DSBs) as a function of radiation dose

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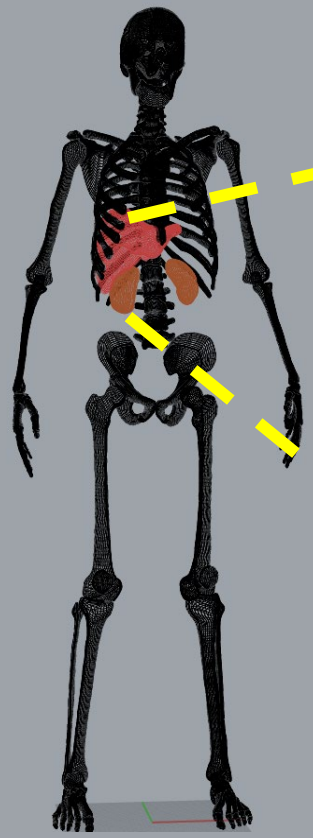
Multiscale digital twin for RPT

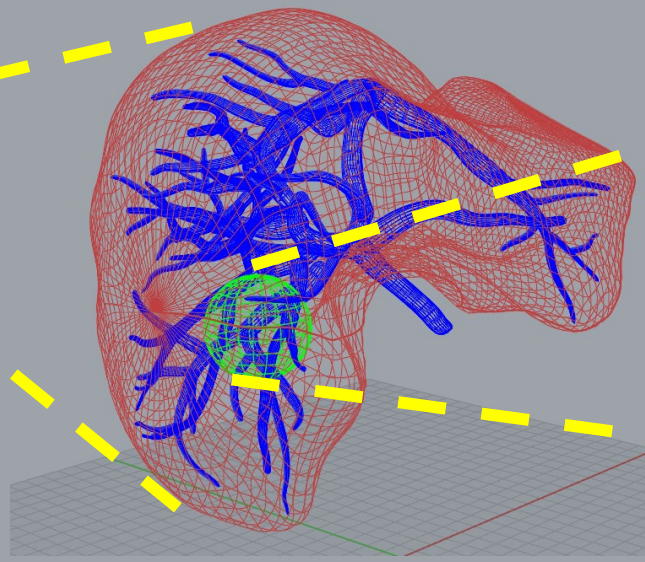
XCAT Phantom

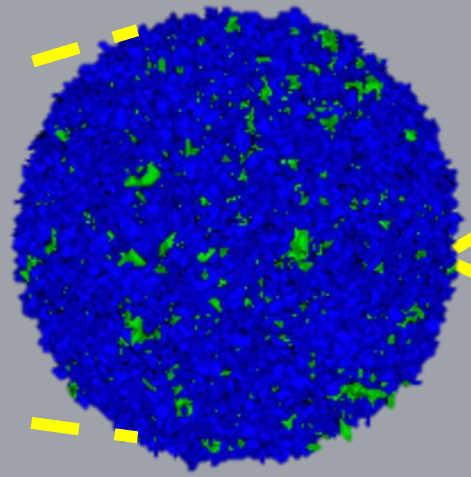
Hepatic vasculature for perfusion modeling

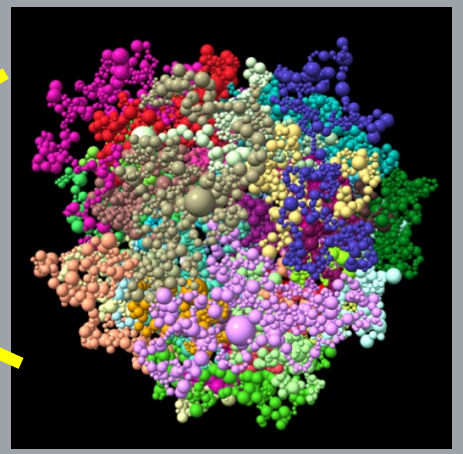
Embedded 3D tumor volume

DNA single and double strand breaks









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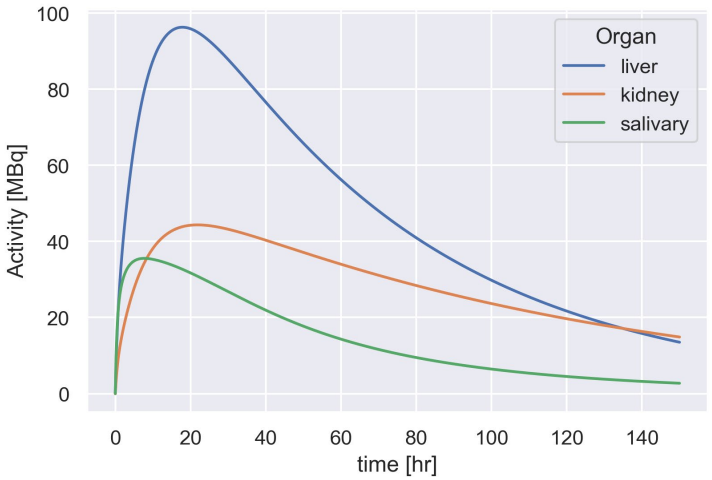
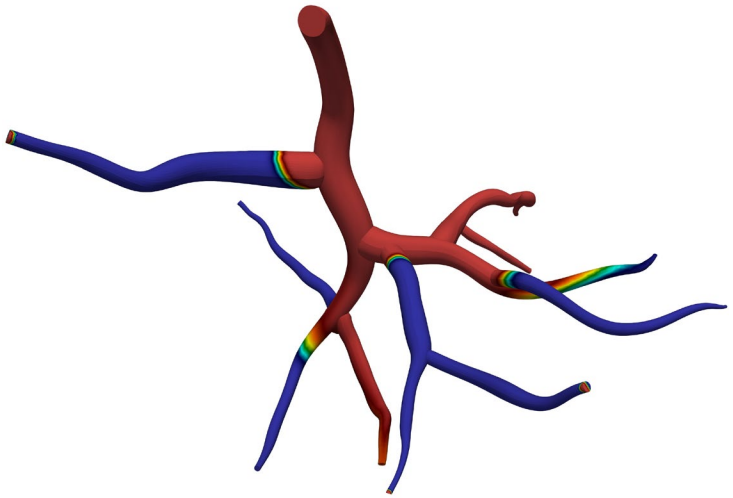
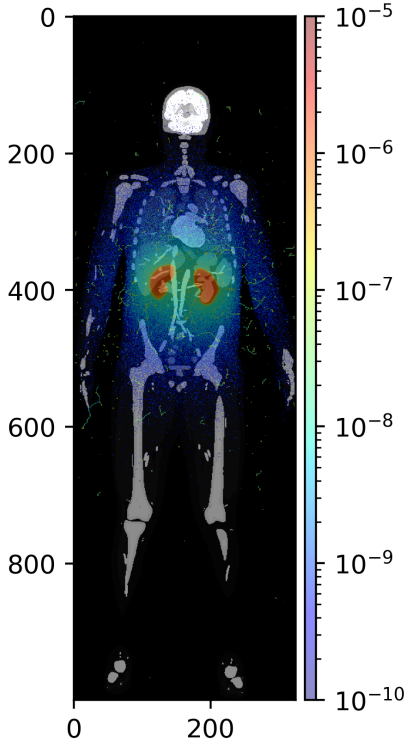
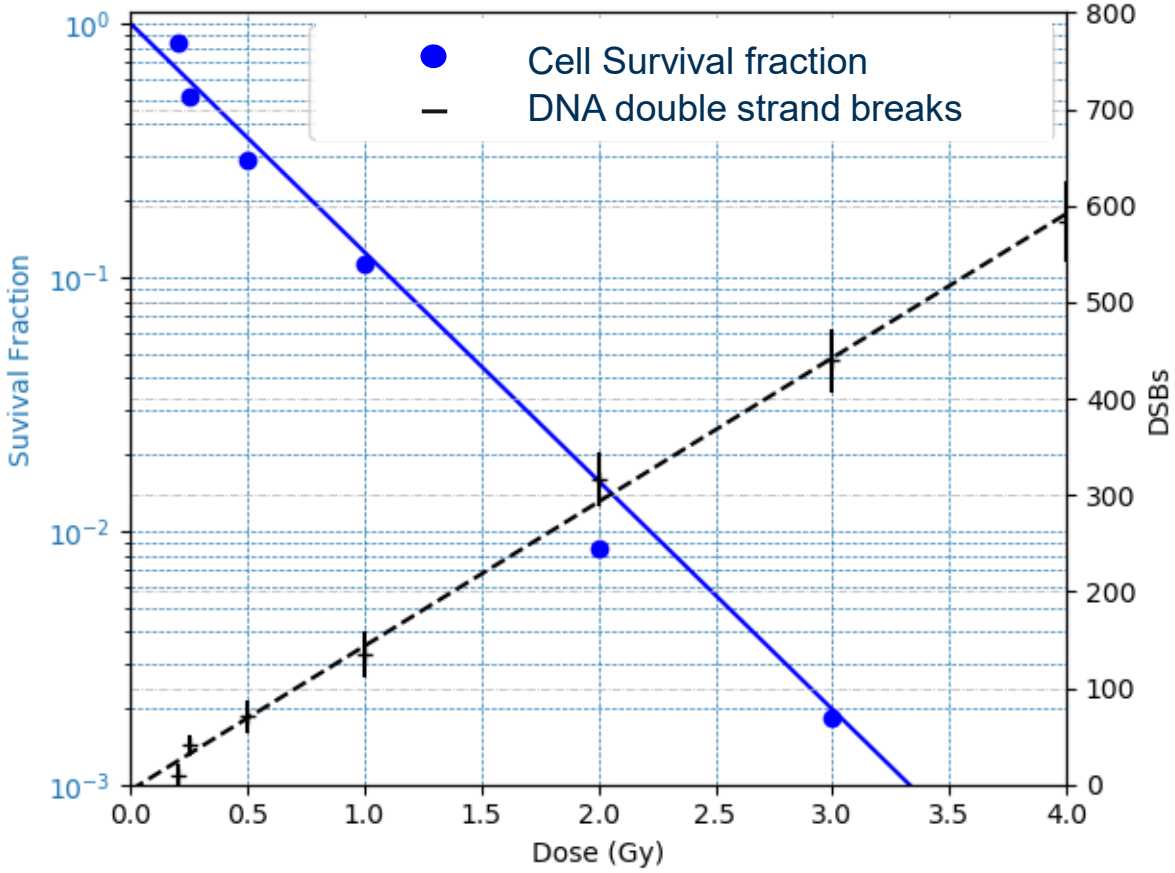
Multiscale digital twin for RPT - outcomes





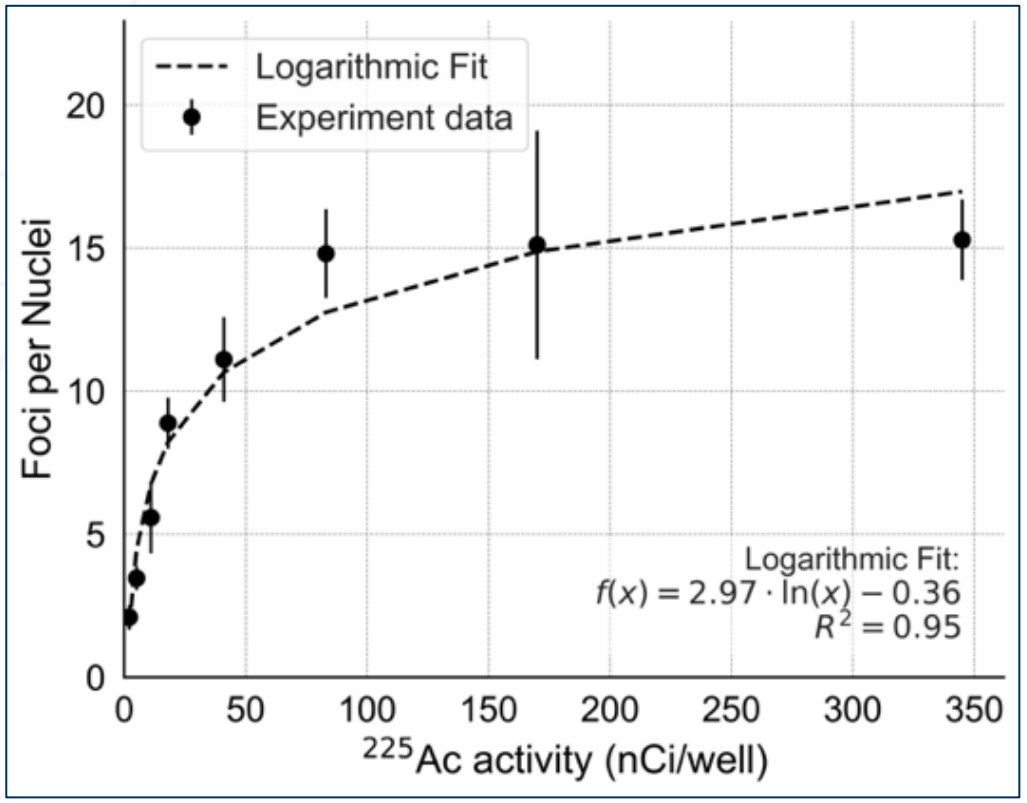


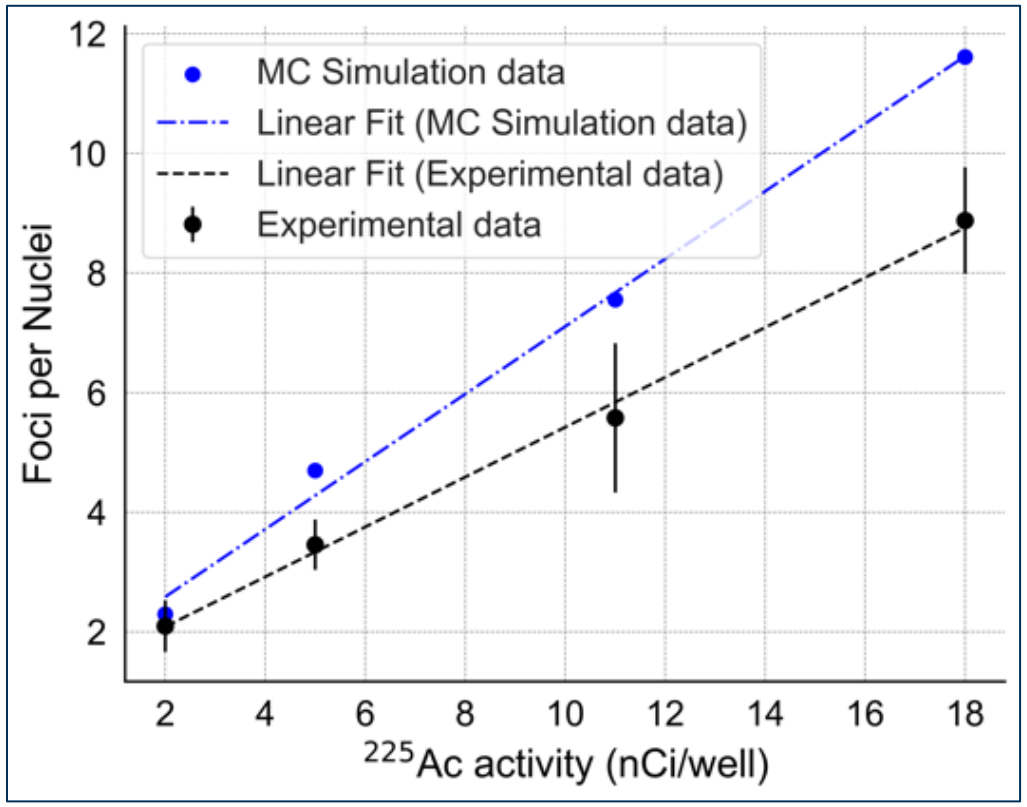


The complexity of multiscale VVUQ – Ongoing work

- Integrating across temporal and spatial scales
- Interactions between physics, biology and chemistry
- UQ propagation across scales
- Data requirements – Experiments across scales
- Computational costs and surrogate modeling
- Patient specific parameters

Comparing live cell experiments against digital twin





Tiwari et al, AAPM 2024

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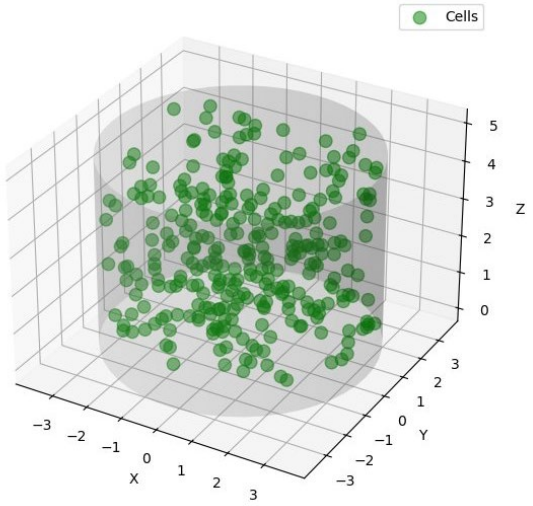
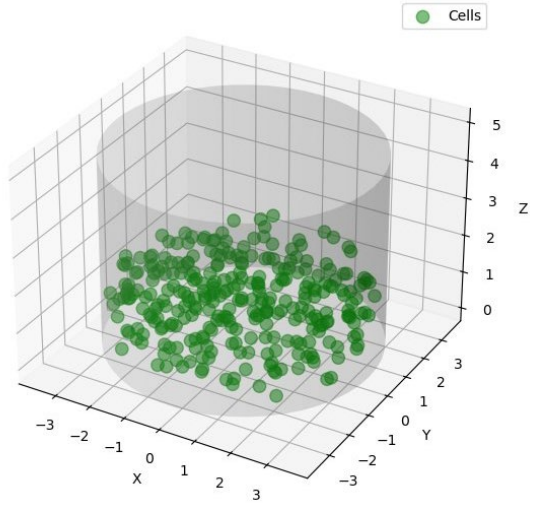
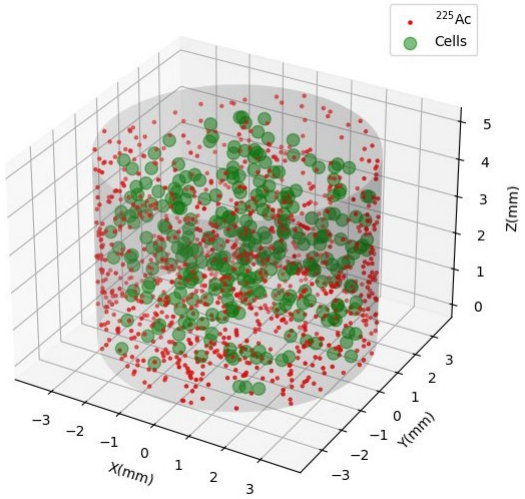
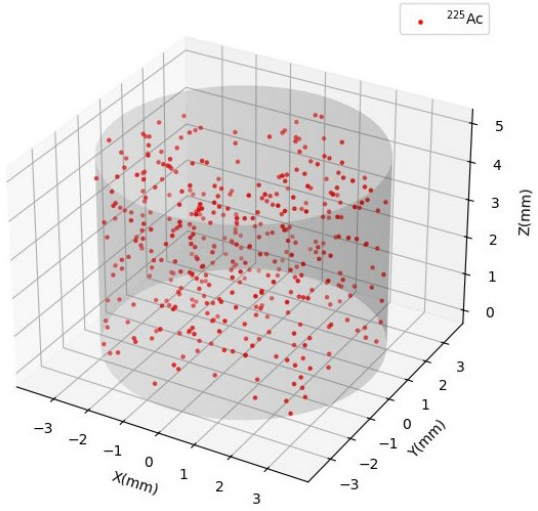
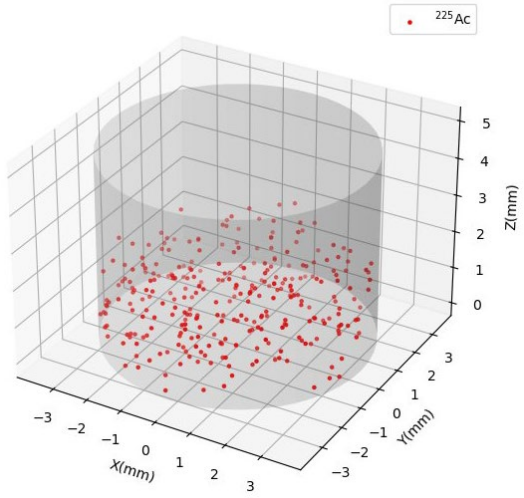
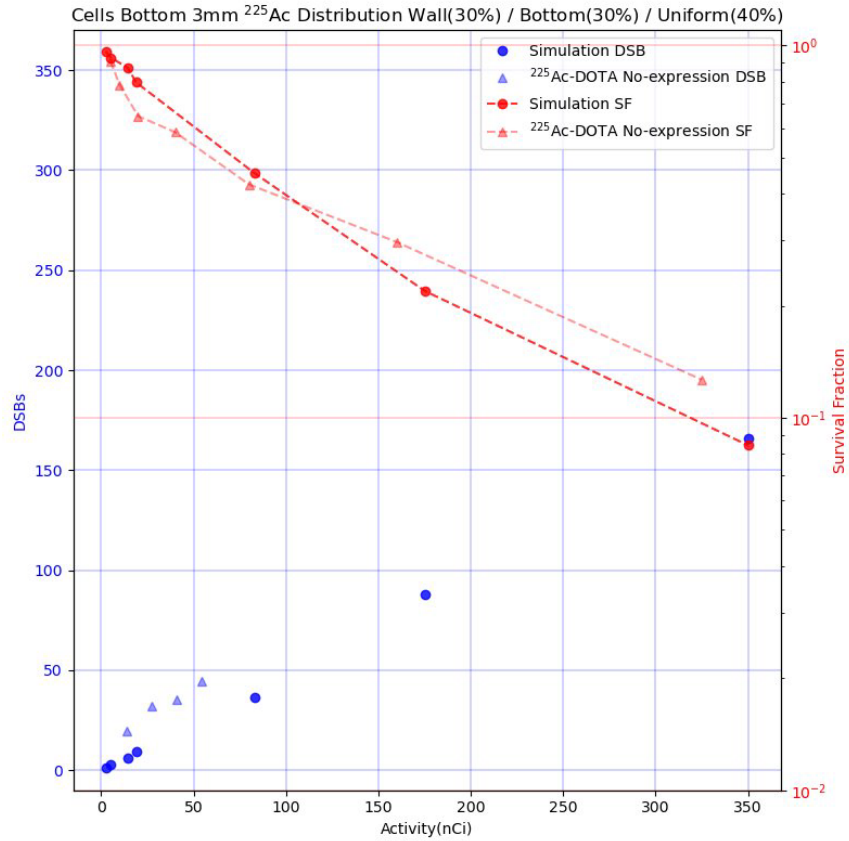

Cells
X
Y
Z


Cells
X
Y
Z


225Ac
Cells
X(mm)
Y(mm)
Z(mm)


225Ac
X(mm)
Y(mm)
Z(mm)


225Ac
X(mm)
Y(mm)
Z(mm)


Cells Bottom 3mm 225Ac Distribution Wall(30%) / Bottom(30%) / Uniform(40%)
Simulation DSB
225Ac-DOTA No-expression DSB
Simulation SF
225Ac-DOTA No-expression SF
DSBs
Survival Fraction
Activity(nCi)

Future work

- Patient and disease specific multiscale tumor modeling
- AI-driven surrogate models to reduce computational complexity
- RPT virtual clinical trials
- Biochemistry modeling

Synthetic CT data generation – population scale

- Total virtual patients: 491
- Total simulations: 10,140
- Total data produced: 125 TB
- Time per simulation: 35-100 mins, average 45 min
- Total time on a standard compute server: 317 days (four Summit nodes)
- Total real-world time on Summit: 2 weeks

Dataset	Adult Lung Lesions	Pediatric Lung Lesions			Optimization		
Dataset		80 kV	100 kV	120 kV	Lung Lesions	COPD	Liver Lesions
# patients (total # of phantoms)	40 (120)	57 (171)			67	67	66
Scanner type	EID, PCCT	EID	EID, PCCT	EID	EID	EID	EID
Tube voltages	100, 120 , 140 kV	80 kV	100 kV	120 kV	80, 100, 120, 140 kV		
Tube currents (mAs)	25, 50, 75, 100, 125 mAs	75, 100, 125 mAs	50, 75, 100, 125 mAs	25, 50, 75, 100, 125 mAs	20, 80, 150 mAs		
Simulation count	4320	684	1710	1026	804	804	792
Total	4320	3420			2400		
Final total	10140						

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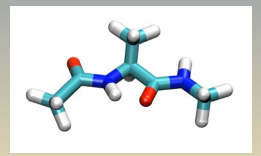
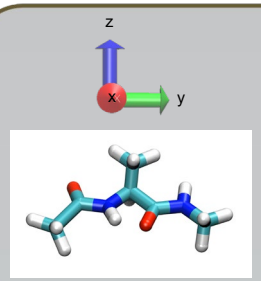
Molecular Dynamics



Initial atomic model

$\vec{r}^{(i=0)}$ and $\vec{v}^{(i=0)}$

Set $\vec{a} = 0.0$, $t = 0.0$, $i = 0.0$

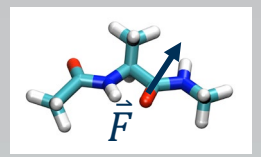


Predict atom position

$$\vec{r}^{p} = \vec{r}^{i} + \vec{v}^{i}\Delta t + \frac{1}{2}\vec{a}\Delta t^{2}$$

Update velocity

$$\vec{v}^{p} = \vec{r}^{i} + \vec{v}^{i} + \vec{a}\Delta \mathrm{t}$$



Get Force

$$\vec{F} = -\nabla V(\vec{r}^{p}) + \vec{a}\Delta \mathrm{t} \text{ and } \vec{a} = \frac{\vec{F}}{m}$$

Update position and velocities

$$\vec{r}^{(i+1)} = \vec{r}^{p} + function(\vec{a}, \Delta \mathrm{t})$$

$$\vec{v}^{(i+1)} = \vec{v}^{p} + function(\vec{a}, \Delta \mathrm{t})$$

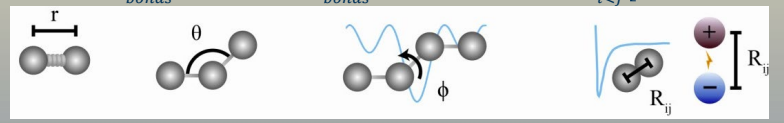
Iterate

$\vec{F}$

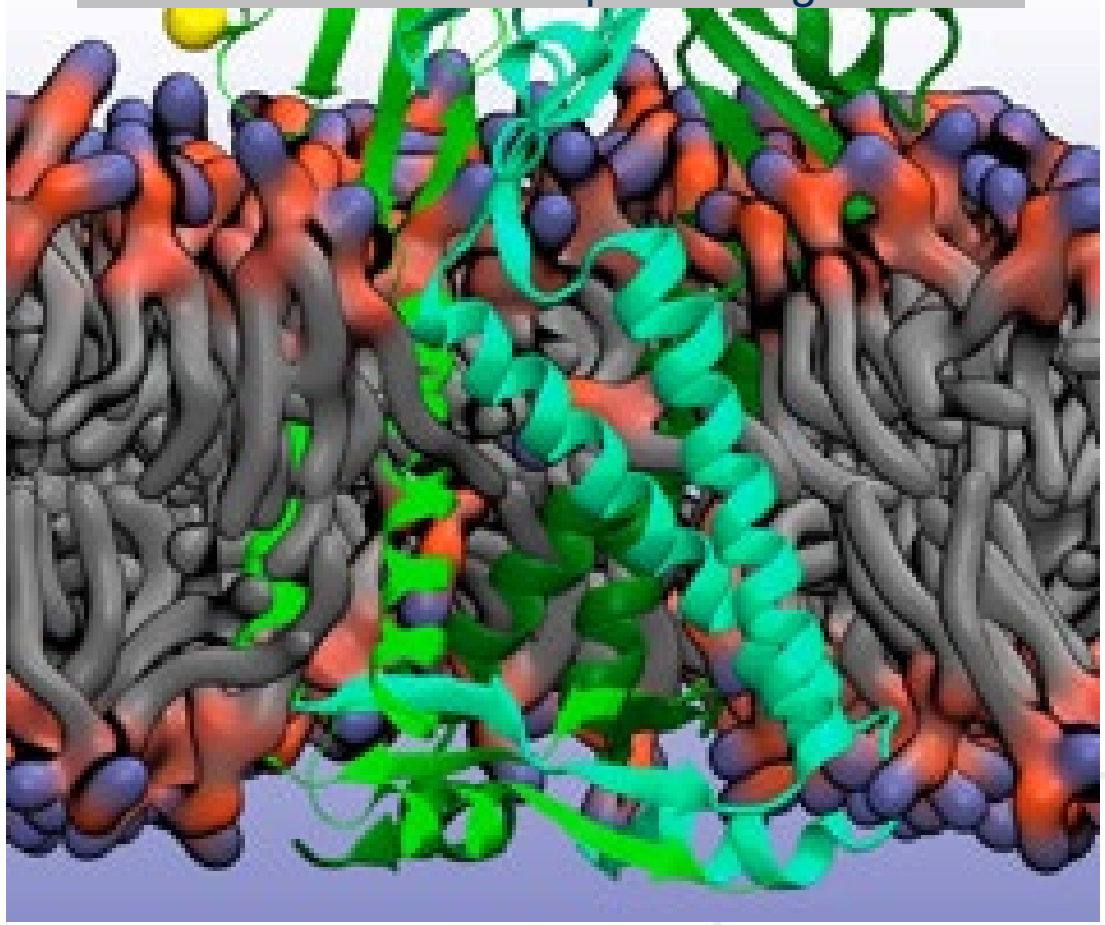
Interaction Energy

bonded | non-bonded

$$V = \sum_{bonds} K_r(r - r_{eq})^2 + \sum_{bonds} K_\theta(\theta - \theta_{eq})^2 + \sum_{bonds} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\epsilon R_{ij}}\right]$$



Simulation of Ca^{2+} transport through channel



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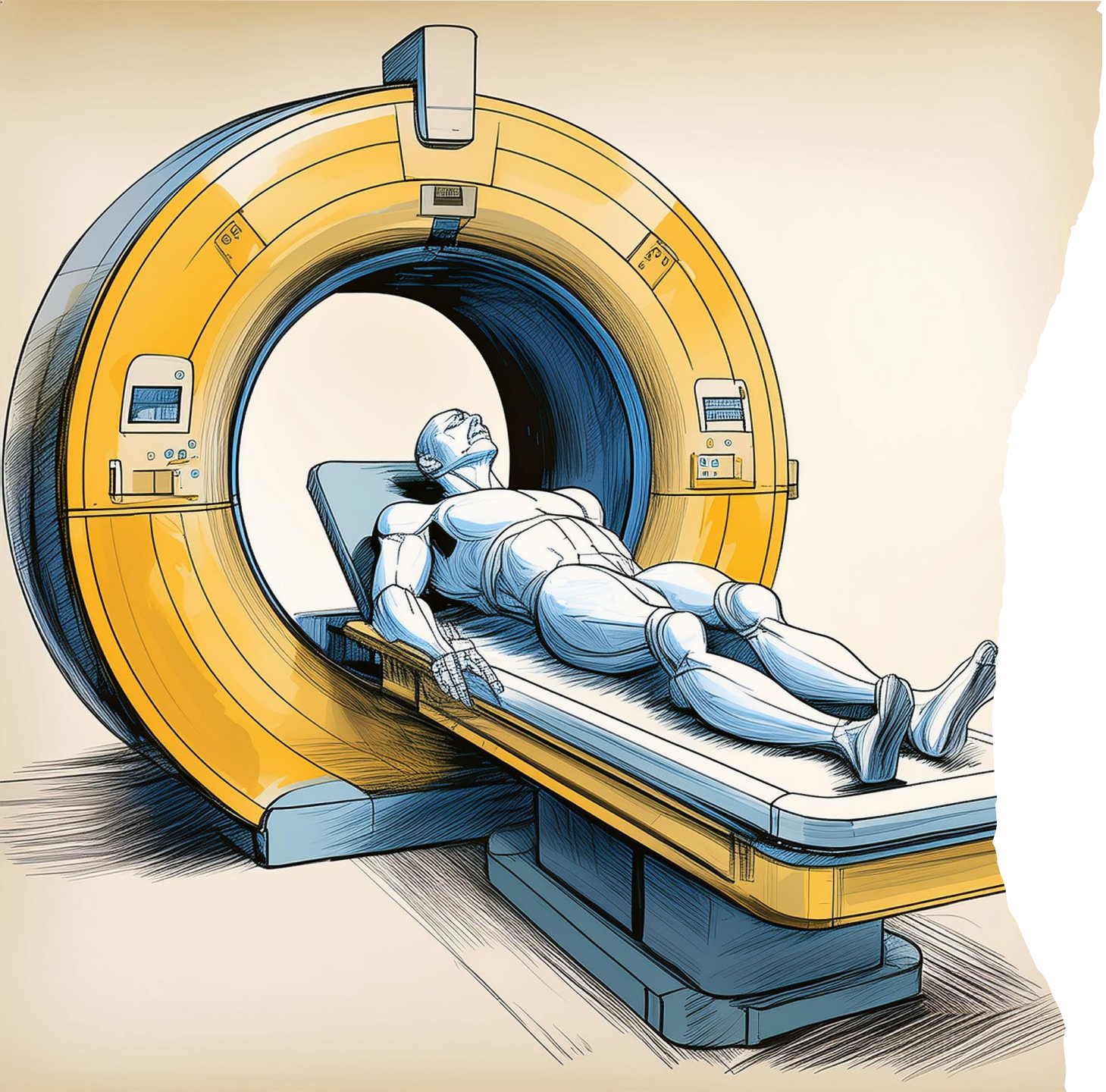

Thank you

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