OAK RIDGE National Laboratory

Multiscale Digital Twins for Precision Medicine and Predictive Cell Survival Outcomes

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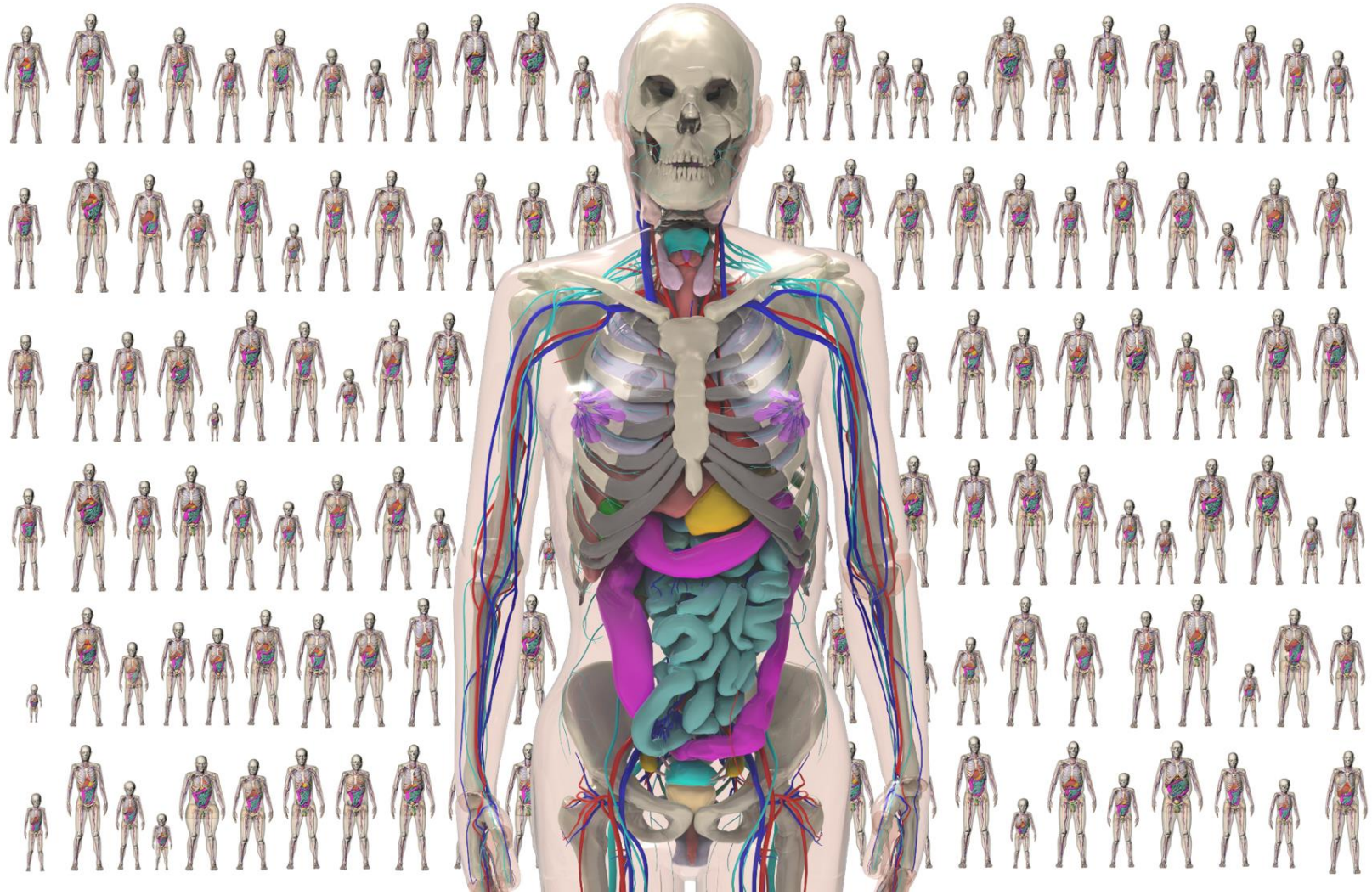
U.S. DEPARTMENT OF ENERGY

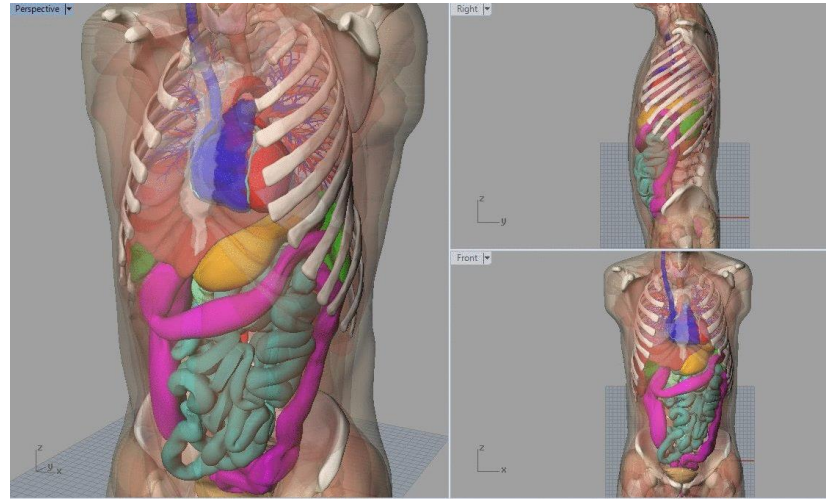
Medical digital twins that capture multiple scales

- A virtual representation of ‘you’
- Should behave like ~~a~~ the real human
- Multimodal
  - Anatomy, Physiology, Genotype Phenotype, Biology, (…)
- Multiscale
  - Molecular to whole body
  - Single human to whole population

Image from iStockphotos

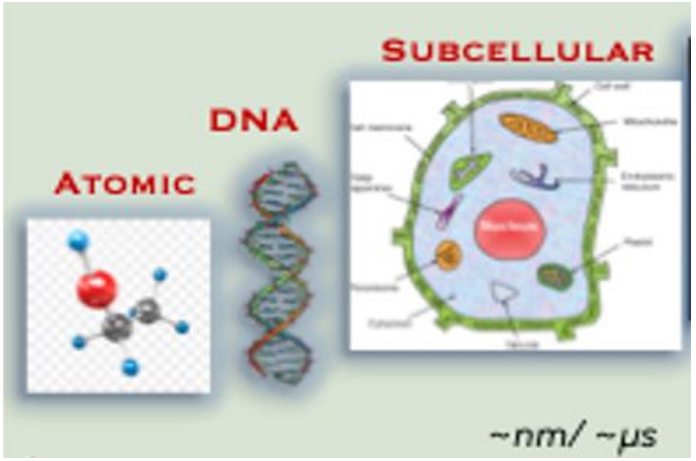
A virtual human population





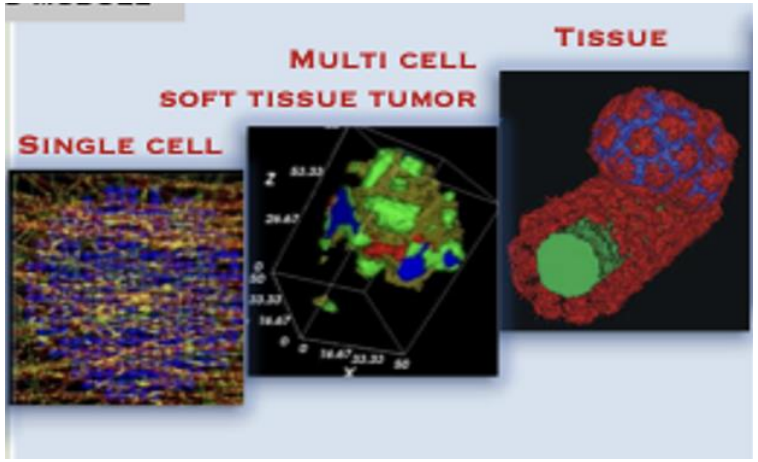
eXtended CArdiac Torso (XCAT) phantoms, E. Samei and P. Segars, Duke University

Integrated into a Multiscale Computational Environment



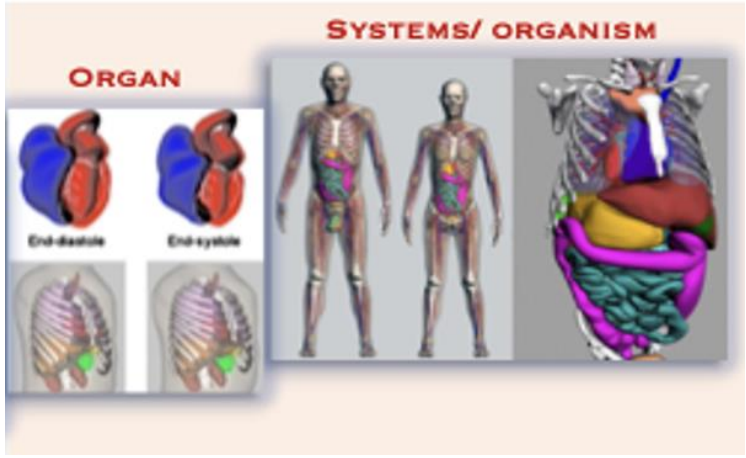
Subcellular

DNA damage, repair
Cell-specific response



Multi-cell

Inter- and intra-cellular effects
Biochemical response
Bystander effect
Multicellular tumor growth

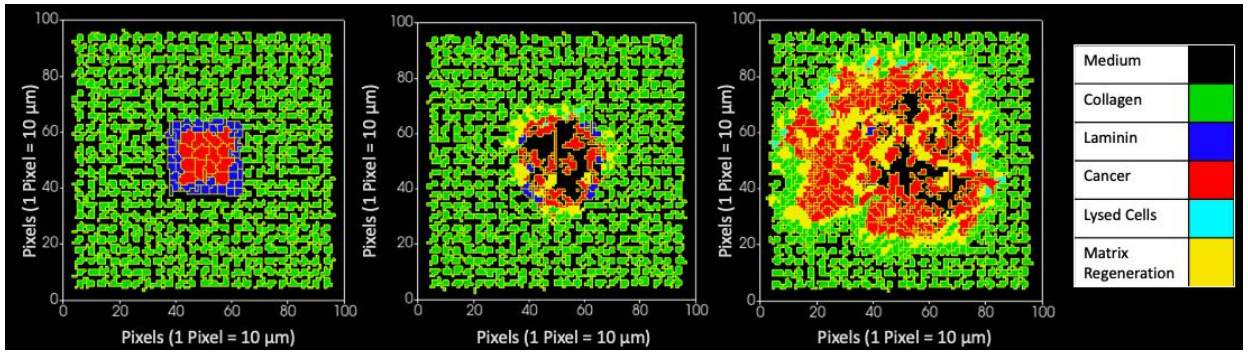


Whole body

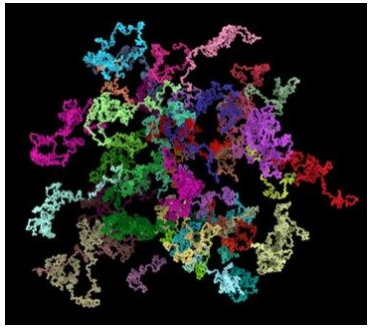
Anatomy, physiology,
Perfusion, Organ systems
Absorbed dose

Illustrative result: External beam tumor irradiation

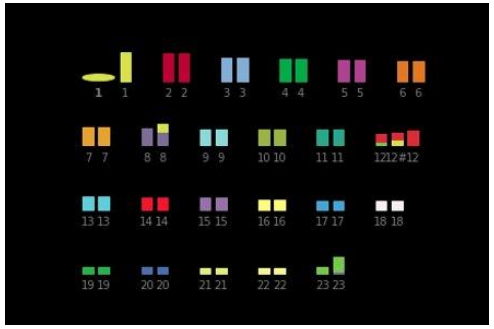
Multicell tumor growth model



Time

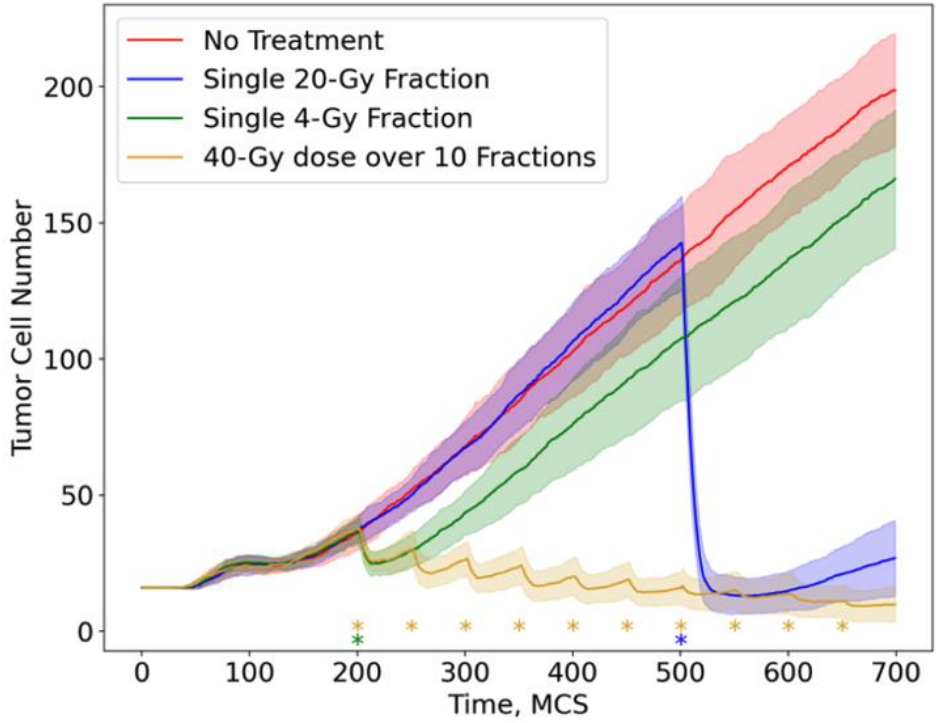


Chromatin structure



Fluorescence In Situ Hybridization (FISH) plots showing DNA misrepair

External beam irradiation protocols



Inman, Houri, Gounley, Agasthya, Kapadia, AAPM 2022

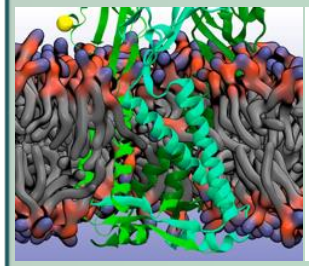
Extending digital twins to molecular domains

NMR

Cryo-EM

X-rays

Thermodynamics & Kinetics

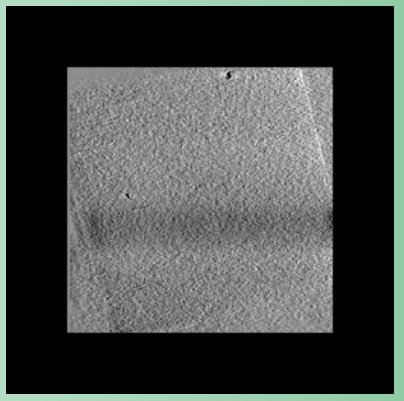


Molecular Dynamics

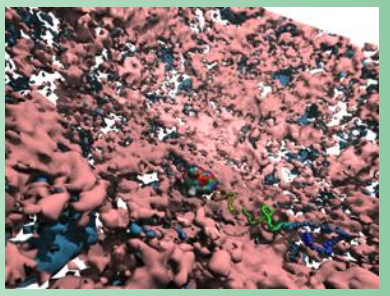
Enhanced Sampling

$\sim nm/\sim \mu s$

Tomogram



Subcellular Diffusion

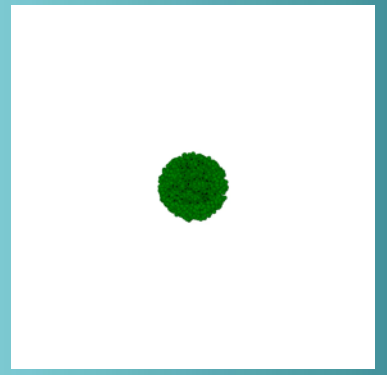


Diffusion Kinetics

$\sim \mu m/\sim ms$

Live-cell Imaging

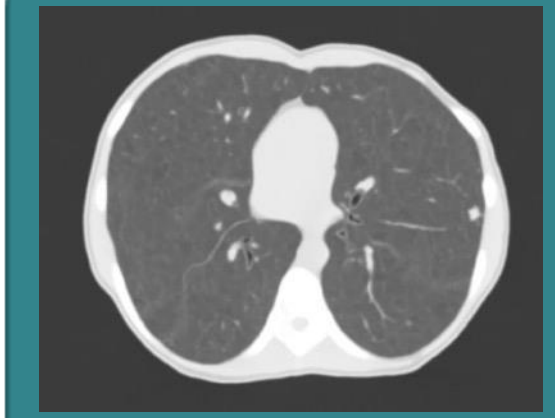
Systems Biology



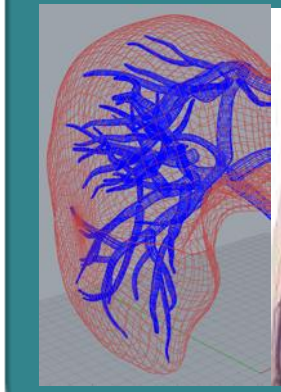
Multicellular Simulations

$\sim mm/\sim s$

CT Scans



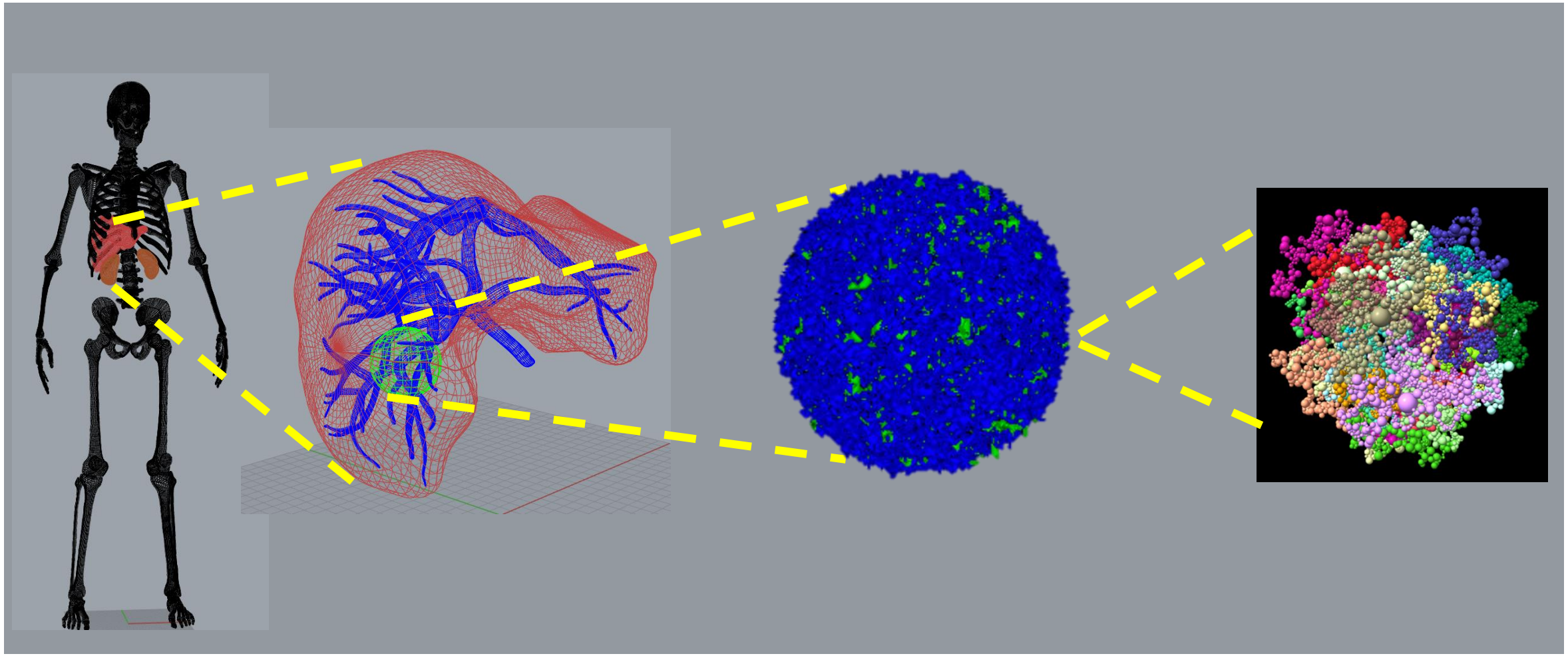
Physiology



XCAT Phantom

$\sim cm/\sim min$

Radiopharmaceutical therapy modeling



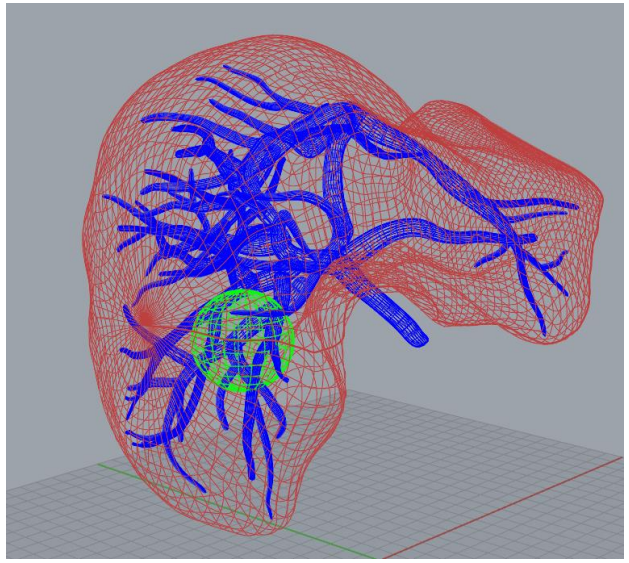
XCAT Phantom

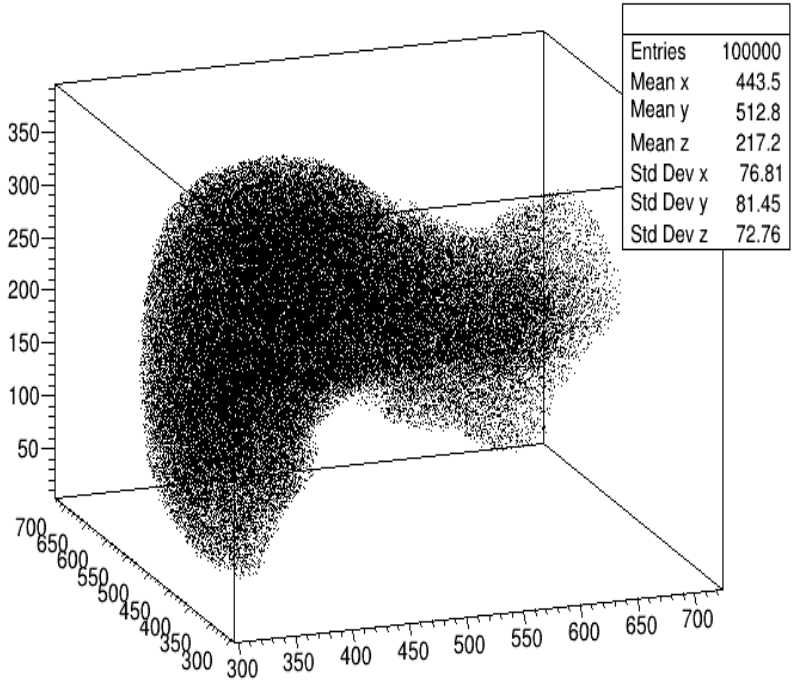
Hepatic vasculature
for open FOAM

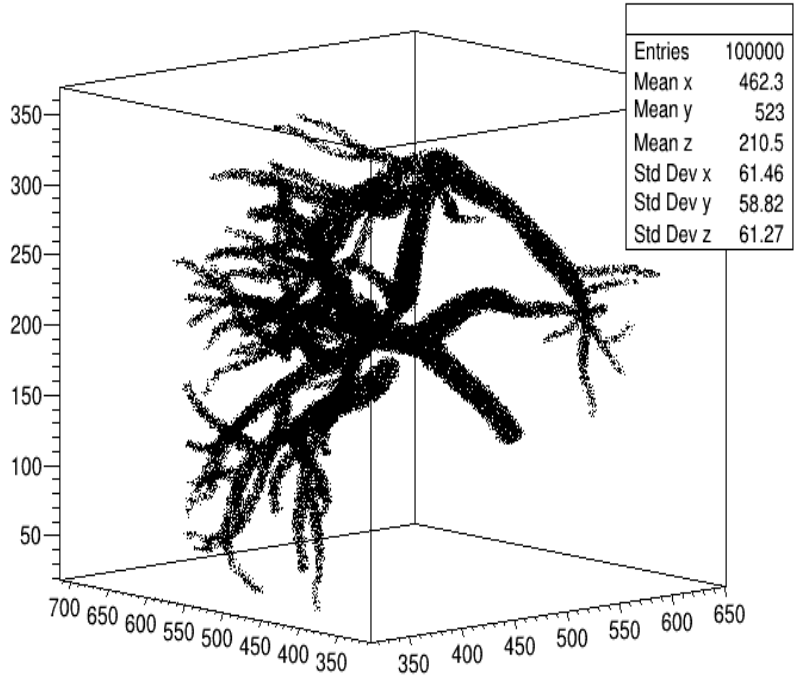
Embedded 3D
tumor volume

Embedded 3D
chromatin structure

Radionuclide flow throughout the organ using CFD







Ac225 spatial distribution reconstruction in the liver volume (left) and liver vasculature (right)

Modeling goals in radiopharmaceutical therapy

CELL TARGET SPECIFICITY

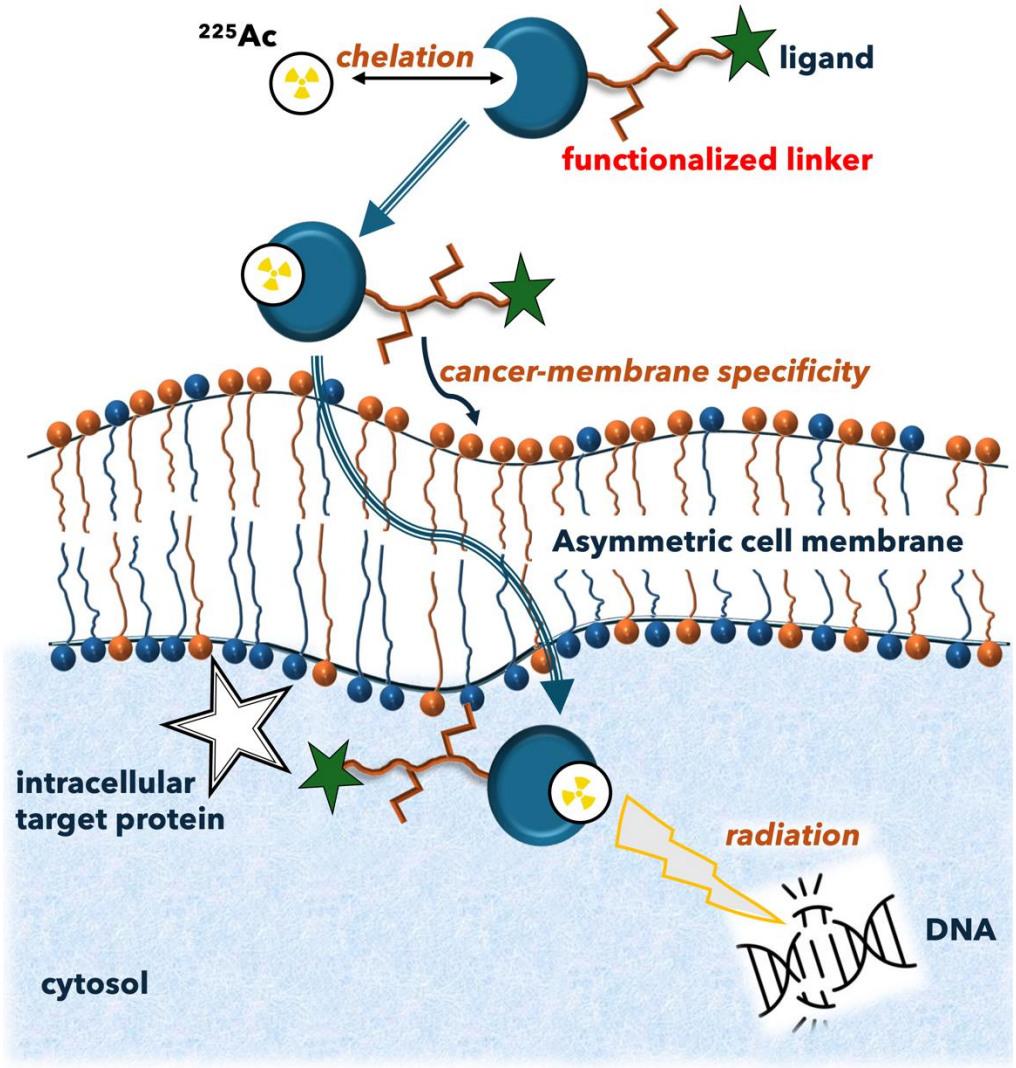
CELLULAR BARRIERS

TARGETING COMPLEX PROCESSES IN CELLS

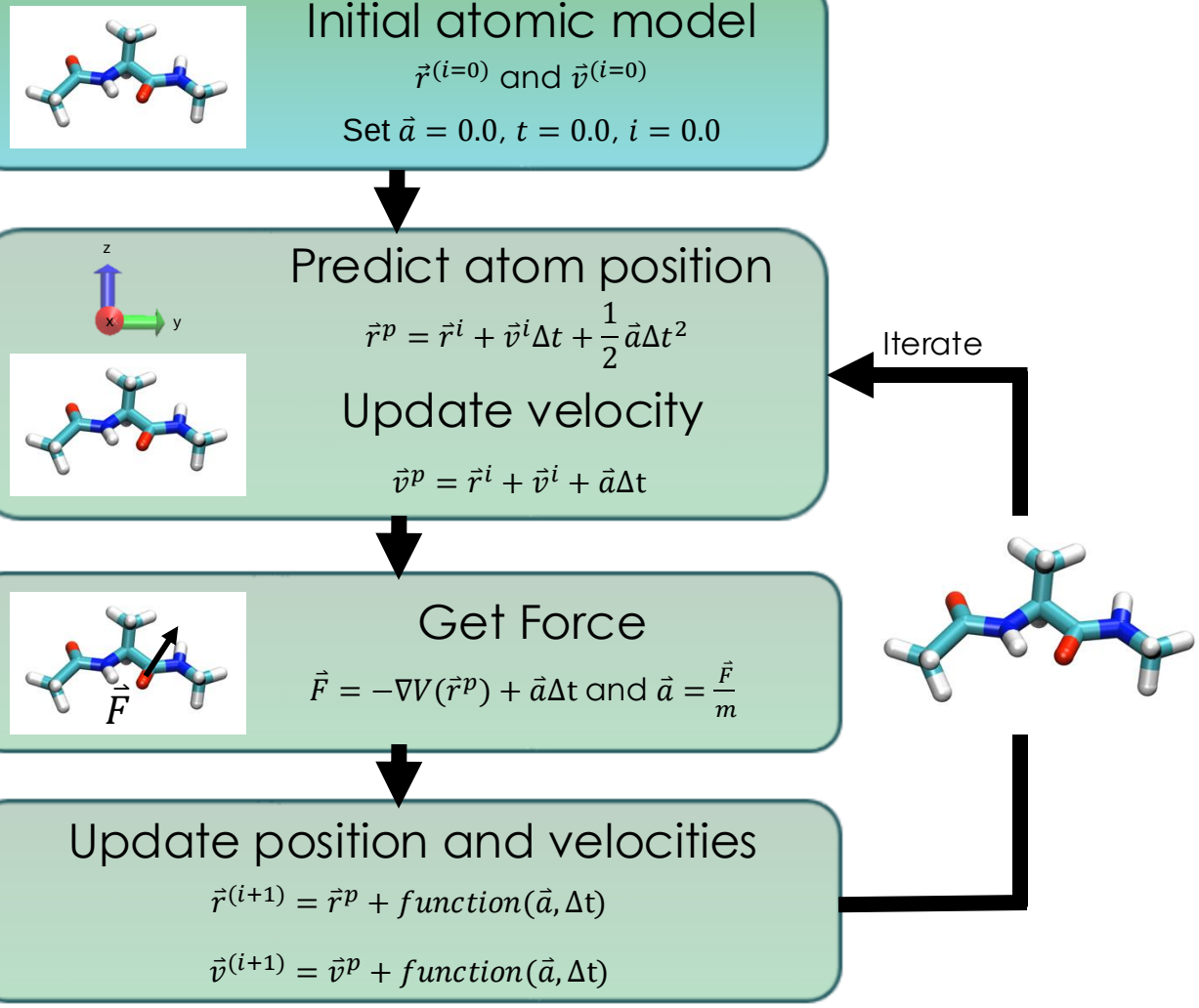
CANCER CELL SHUTDOWN

EXPEDITED DEVELOPMENT

IN-SILICO PIPELINE



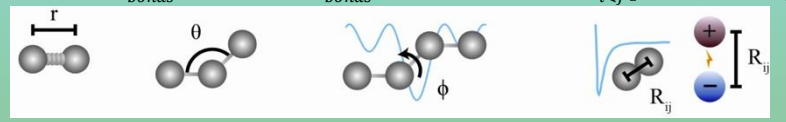
Molecular Dynamics



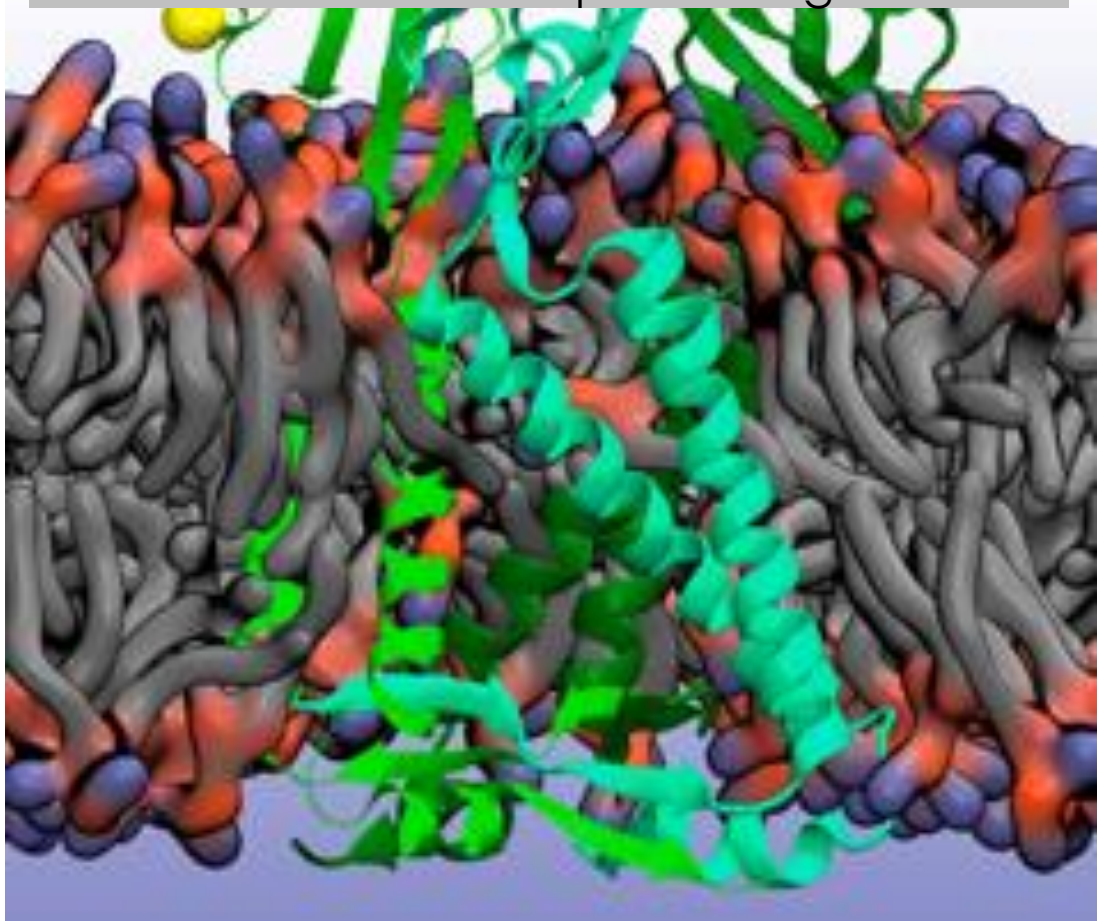
Interaction Energy

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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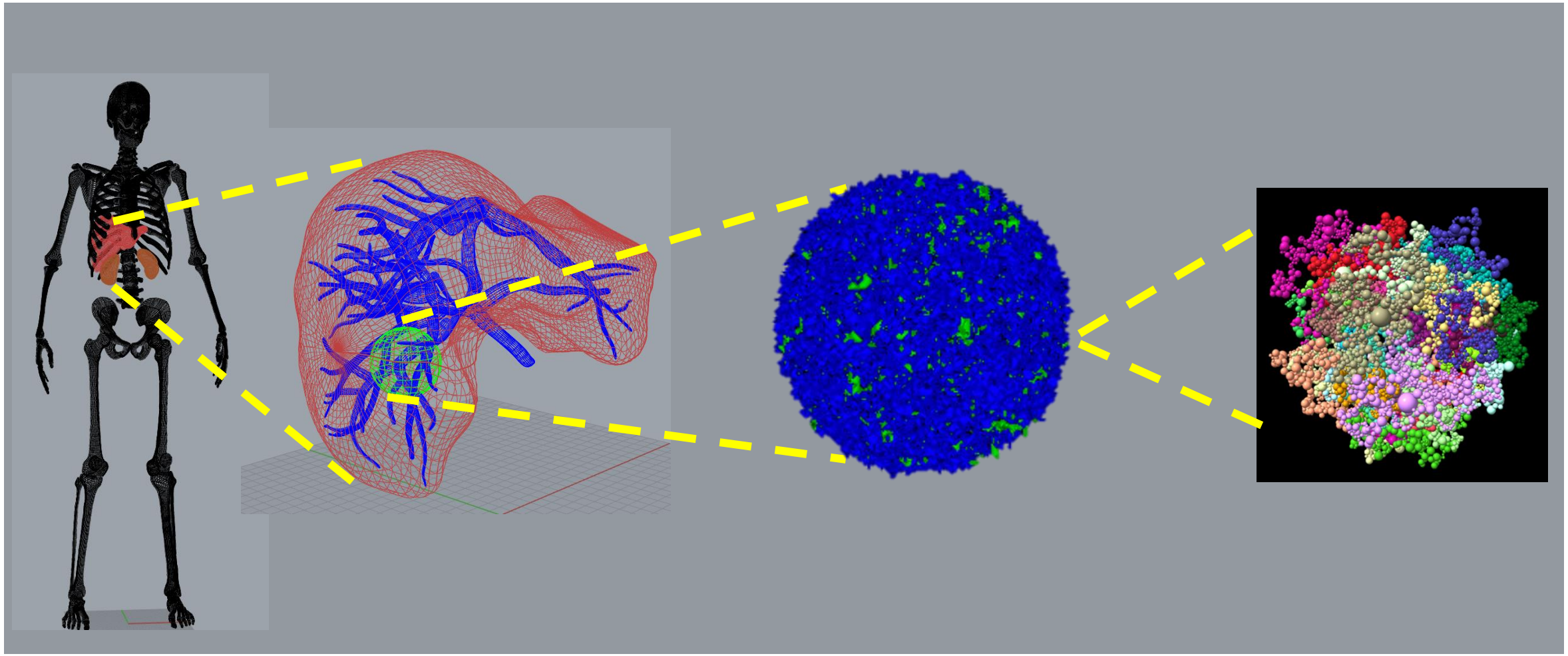
Radiopharmaceutical therapy modeling



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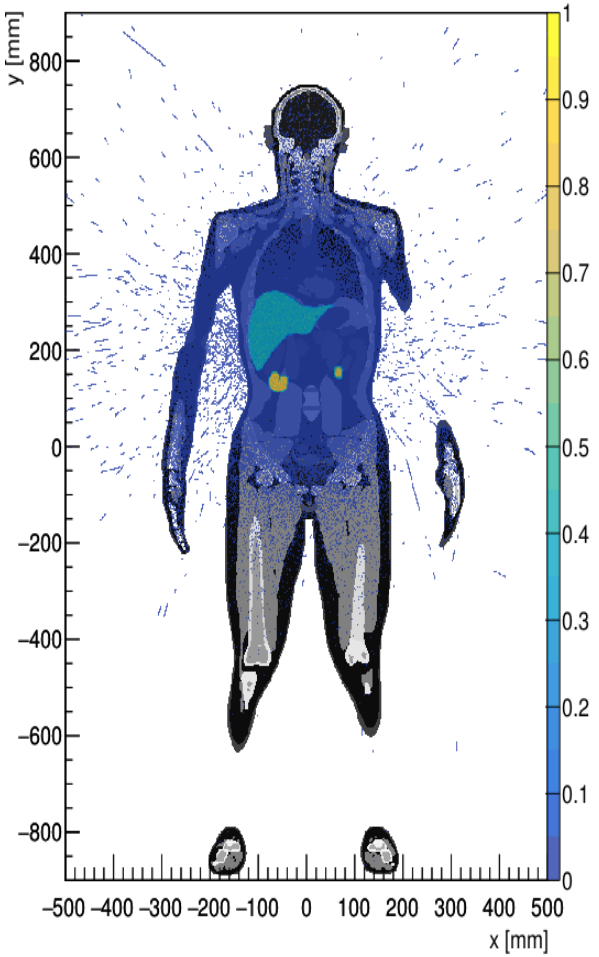
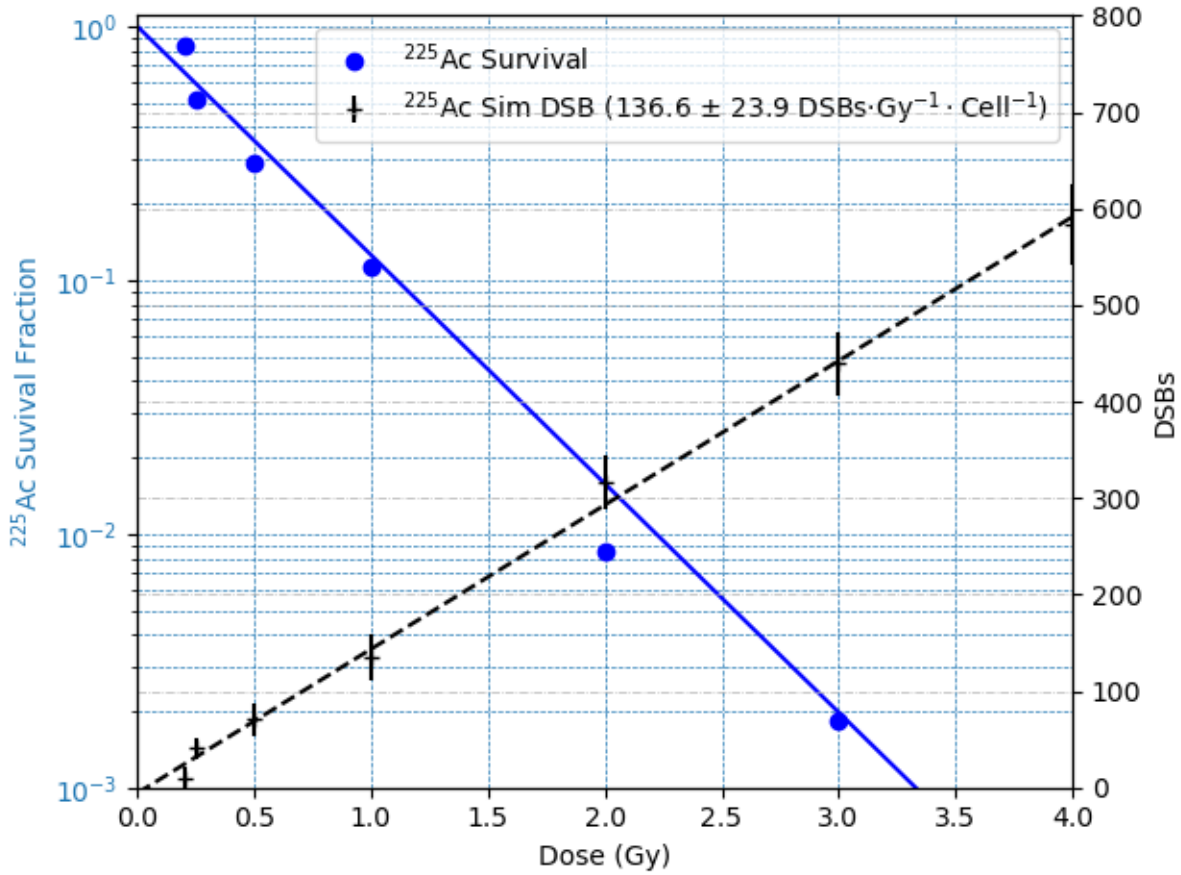


3D dose map of Ac-225



Predicting cell survival and double strand breaks (DSB) as a function of alpha-particle dose

Radionuclide exposures outcomes using 177Lu and 90Y

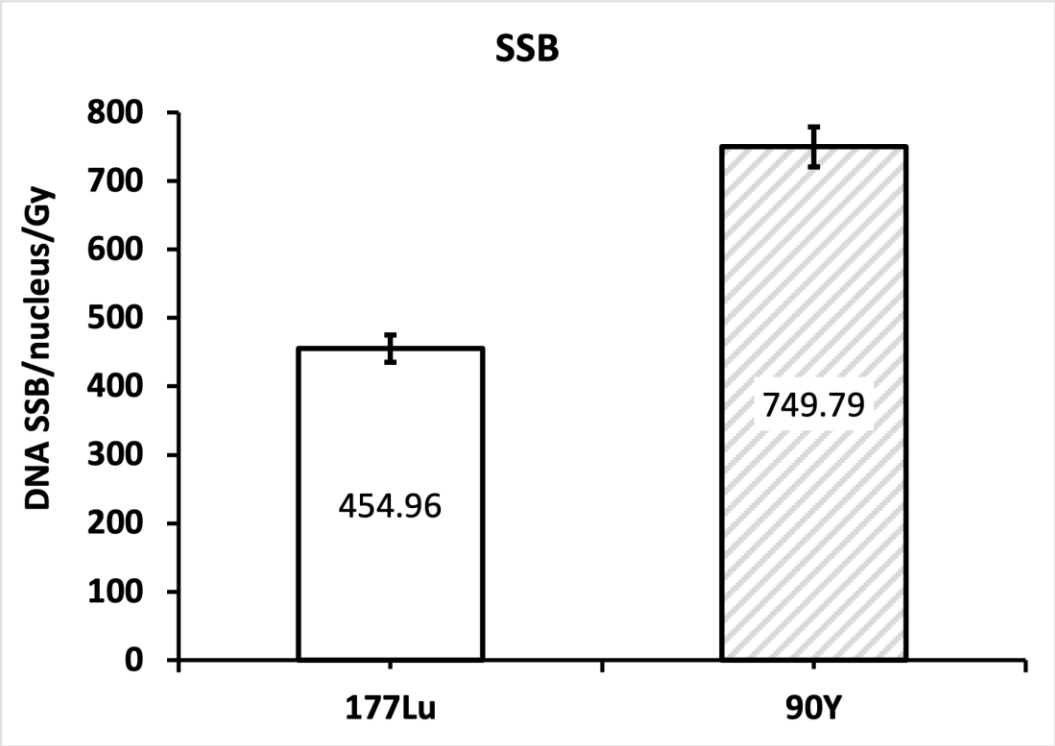


Fig 1: Comparison of single strand breaks for two therapeutic radionuclides ^{177}Lu and ^{90}Y

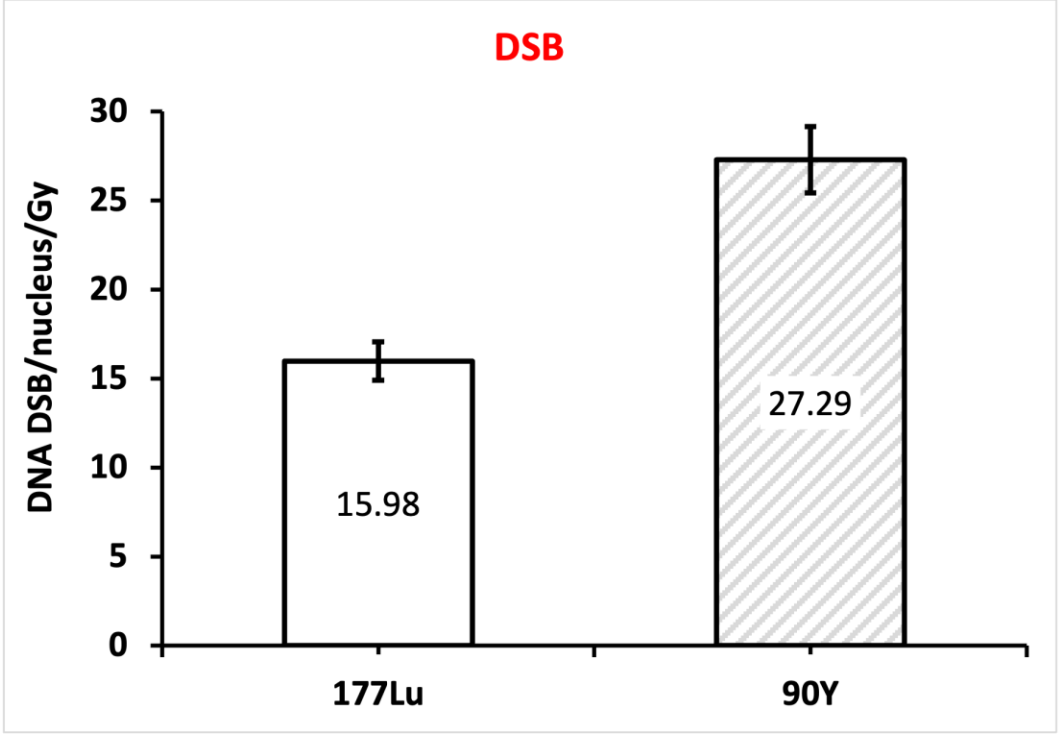
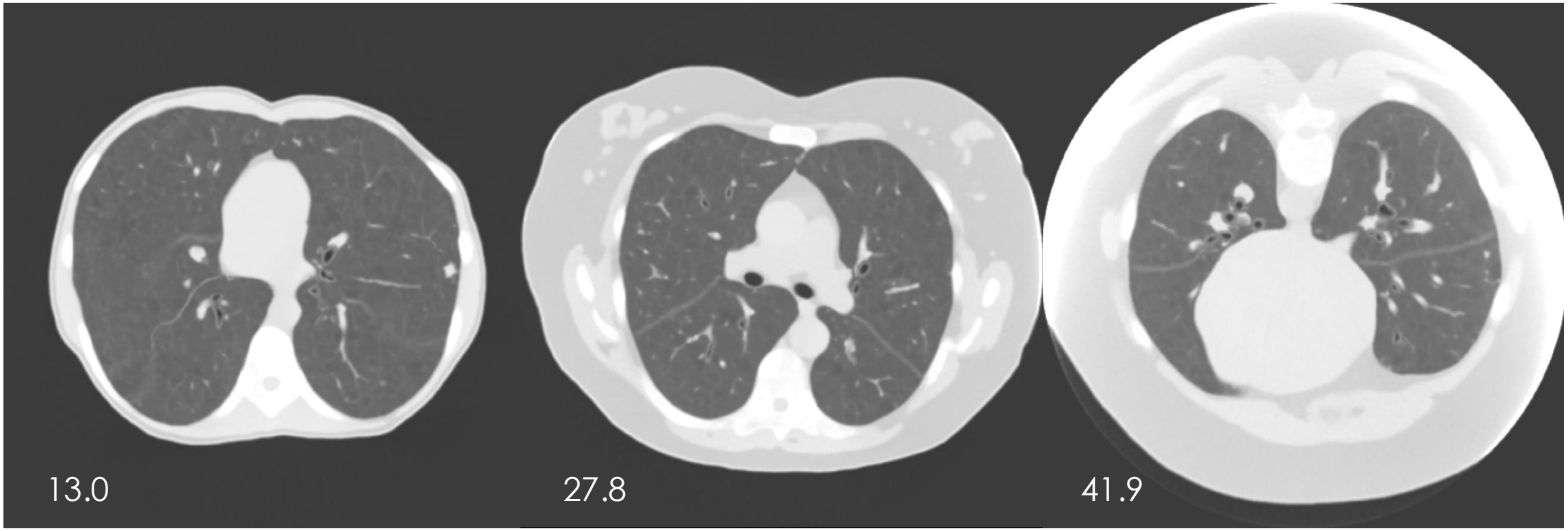


Fig 2: Comparison of double strand breaks for two therapeutic radionuclides ^{177}Lu and ^{90}Y

Computational speedup and acceleration

- Accelerate simulations
  - High-performance computing
  - AI methods
  - GPU acceleration
  - Simulation time in minutes, not days
- DOE leadership computing systems
  - Frontier (Oak Ridge)
  - Aurora (Argonne)

Synthetic data generation – Virtual CT scans



Synthetic CT scans generated for three virtual XCAT patients with different BMI values (shown)

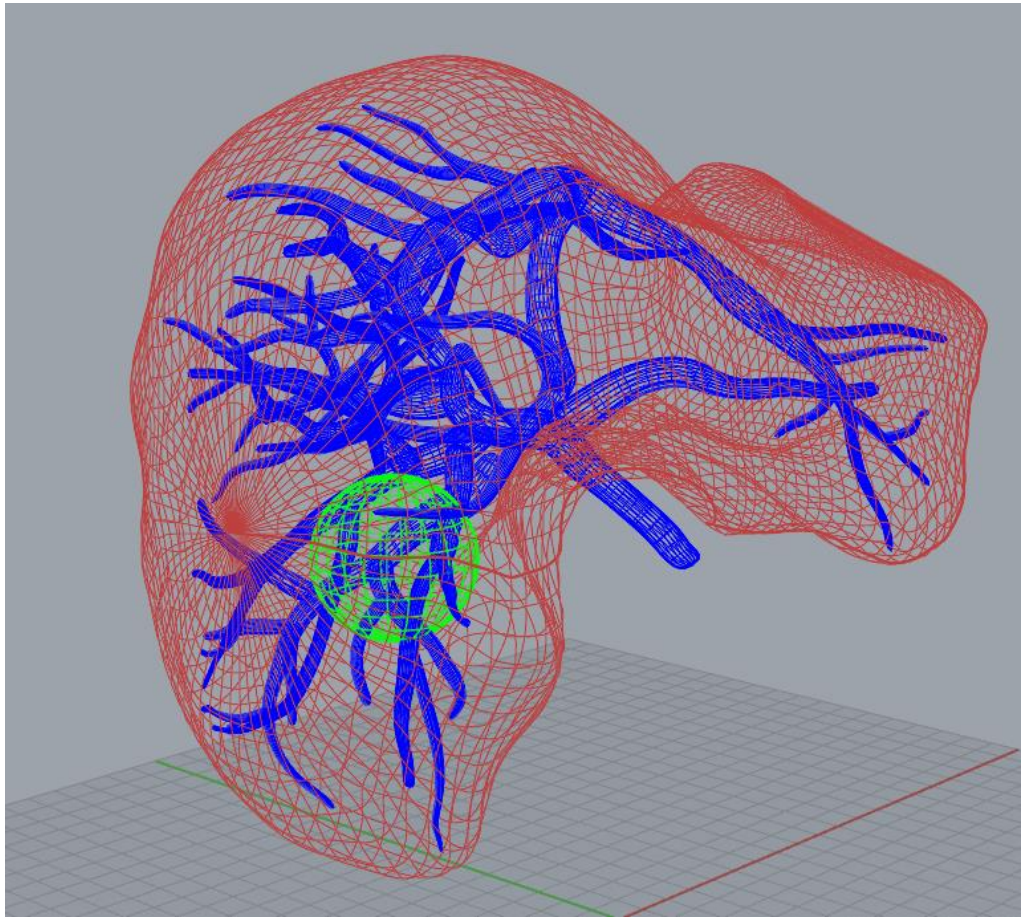
Where do we go next?

- Multimodal data integration
  - Data from multiple modalities and at multiple scales
  - Whole body (CT, MRI), perfusion and vascular flow, microscopy
  - Genotype and phenotype data
- Clinical validation
  - Extend beyond cellular irradiation in controlled environments
  - Clinical outcomes data

XCAT Phantoms, Duke University

Where do we go next?

- Integration with other digital twin systems
  - Evaluation of composite effects on human health
- Enable discoveries in medicine
  - Drug discovery
  - Chemotherapeutics
  - Combinatorial treatments



Thank you

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Thank you

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