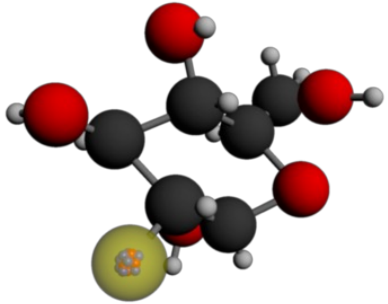
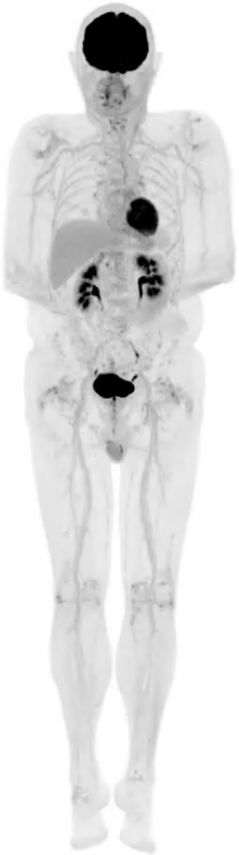
UC DAVIS
EXPLORER MOLECULAR IMAGING CENTER

Danube Symposium
Vienna, September 21/22nd, 2023

Molecular Imaging and Total-Body PET: The Basics

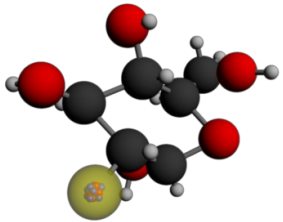




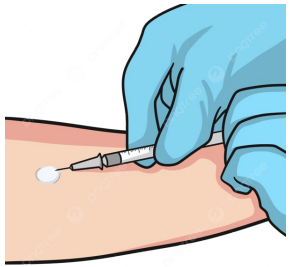
Simon R. Cherry

Departments of Biomedical Engineering and Radiology, UC Davis

Positron Emission Tomography

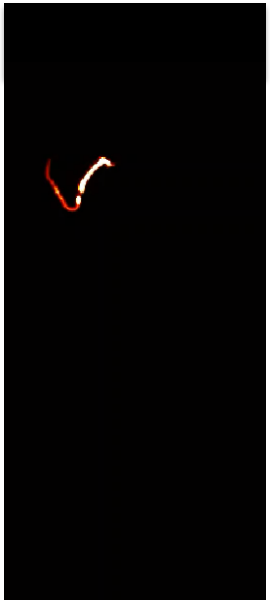


radiotracer

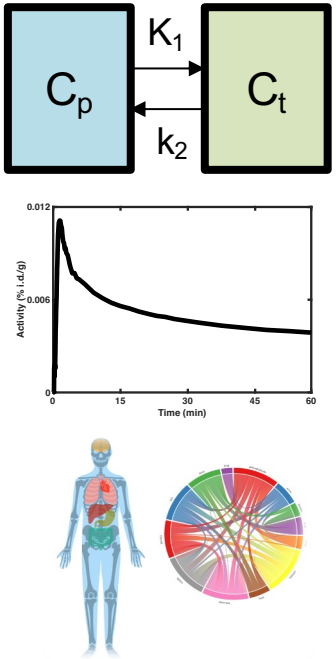


inject into subject

PET scanner

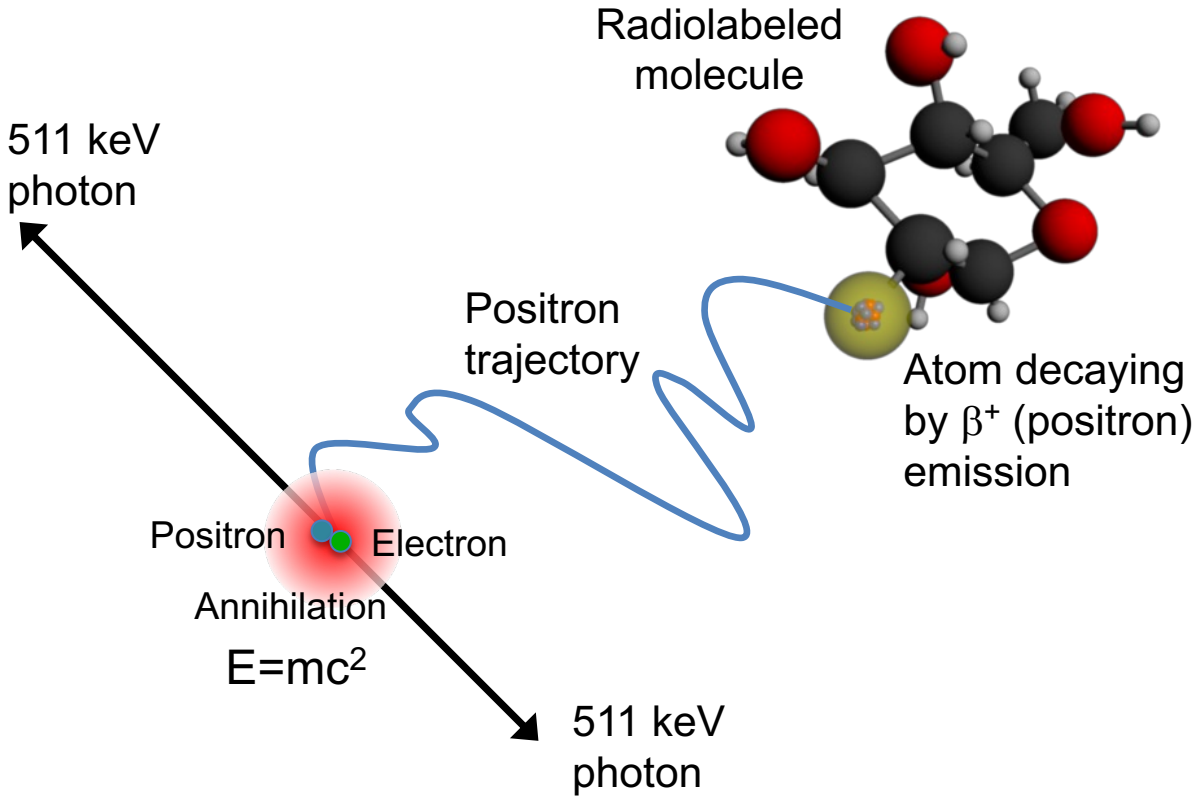


PET images

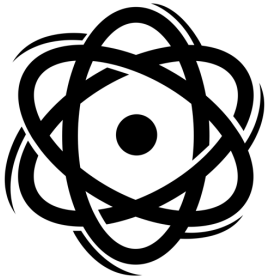


analysis

Positron Emission Tomography
A Beautiful Piece of Physics



Positron-Emitting Radionuclides

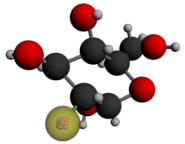


Isotope	Halflife	β^+ fraction	Max. Energy
C–11	**20.4 mins**	**0.99**	**0.96 MeV**
N–13	9.96 mins	1.00	1.20 MeV
O–15	123 secs	1.00	1.74 MeV
F–18	**110 mins**	**0.97**	**0.63 MeV**
Ga–68	**68.3 mins**	**0.88**	**1.90 MeV**
Rb–82	**78 secs**	**0.96**	**3.15 MeV**
Zr-89	**3.3 days**	**0.22**	**0.90 MeV**
I–124	4.18 days	0.22	3.16 MeV

and many others…

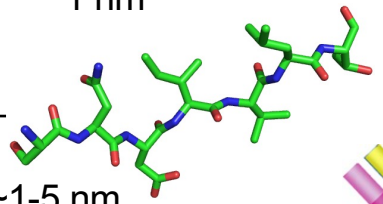
Radiolabeled Agents for PET Imaging

- **Small molecules**
  - Substrates for enzymes, receptor ligands, drugs…



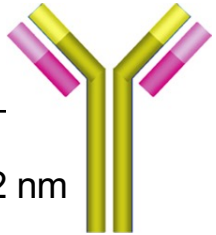
~1 nm

- **Peptides**
  - Receptor targeted, enzyme substrates…



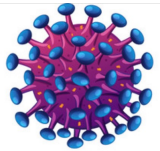
~1-5 nm

- **Antibodies**
  - Full length, minibodies, diabodies



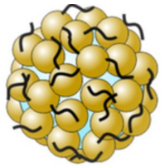
~10 x 2 nm

- **Pathogens**
  - Viruses, bacteria…



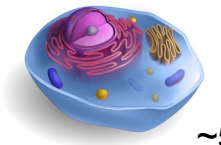
~20-200 nm

- **Particles**
  - Liposomes, lipospheres, nanoparticles…



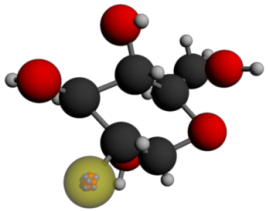
~20-100 nm

- **Cells**
  - T-cells, stem cells…



~5-100 µm

PET Radiotracers



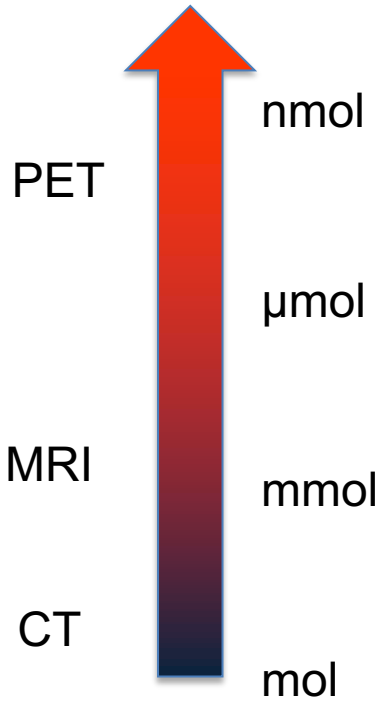
Physiology
Blood Flow $H_2{}^{15}O$, ^{11}C-butanol
Blood Volume ^{11}CO, ^{18}F-human serum albumin (HSA)

Metabolism
Oxygen $^{15}O_2$
Glucose ^{18}F-fluorodeoxygluose (FDG)
Fatty Acid ^{11}C-palmitate

Receptor/Protein Binding
Dopamine ^{11}C-raclopride
Prostate Specific Membrane Antigen (PSMA) e.g. ^{18}F-piflufolastat
CD8 (T-cells) e.g. ^{89}Zr-Df-Crefmirlimab
Beta-amyloid e.g. ^{18}F-florbetapir

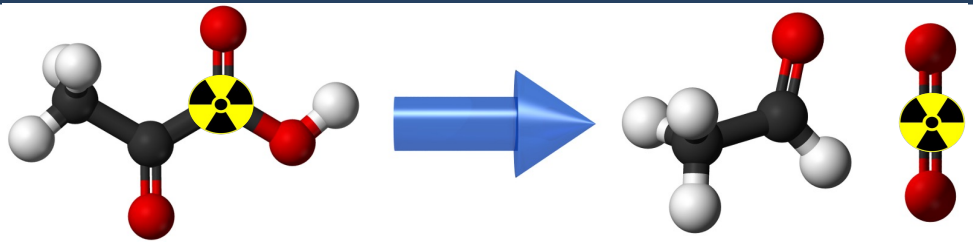
PET is Highly Sensitive

- PET radiotracers are synthesized with molar activity as high as 100-1000 GBq/μmol
- Typical administrations of small molecules are in the range 2.5 – 25 nmol (0.1 – 10 μg)
- PET is a **tracer** technique – generally no pharmacological effect
- Biodistribution may change with mass level – may want to add additional mass of cold compound



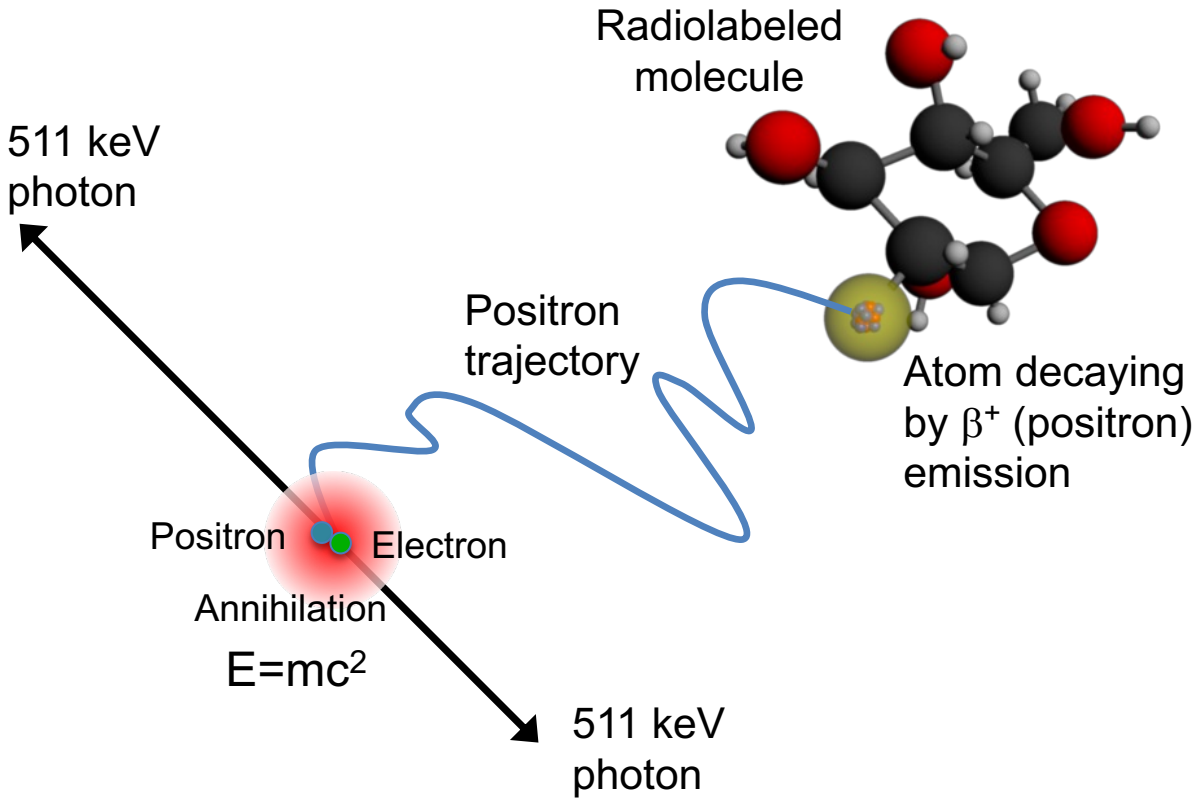
Luurtsema et al, *EJNMMI Radiopharmacy and Chemistry* 6; 34 (2021)

One Important Caveat – Metabolites!



- PET images the distribution of the **radioisotope**
- PET cannot distinguish radiolabeled metabolites from parent compound
- Important to know fate of radiotracer in the body over the imaging time
- Careful tracer design (native vs analog)
- May require metabolite correction/analysis to properly interpret images

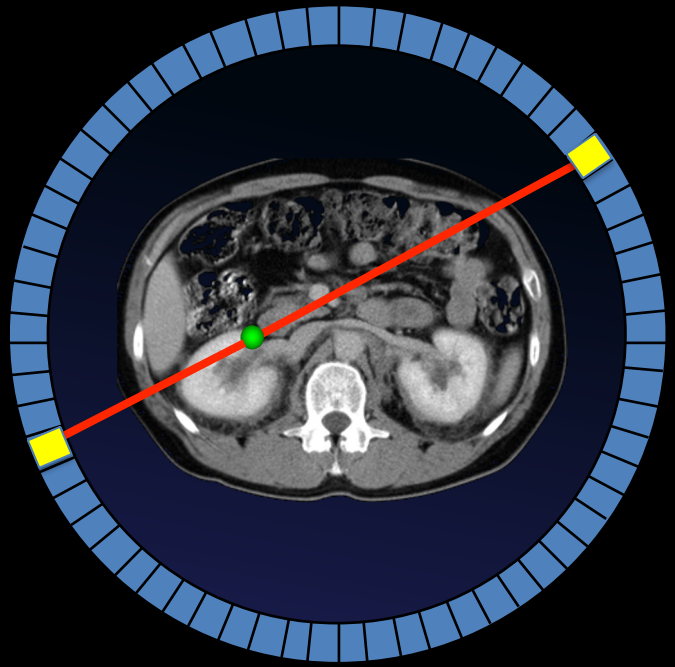
Positron Emission Tomography



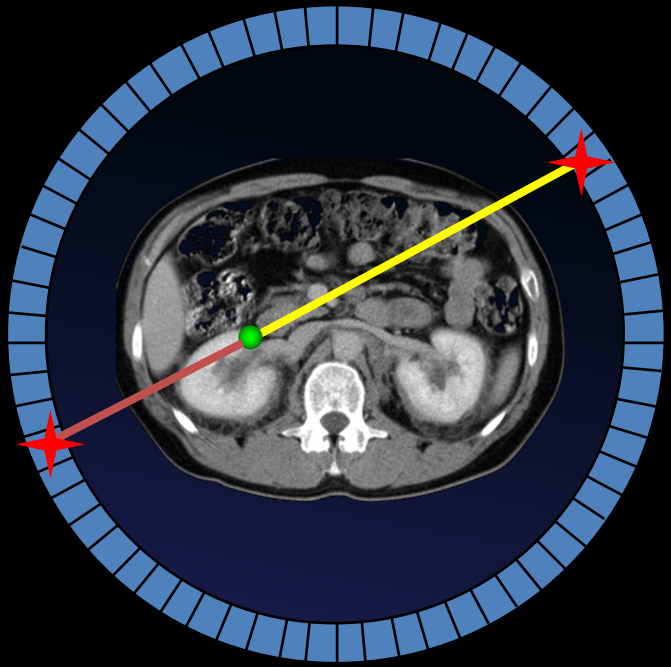
PET Scanner

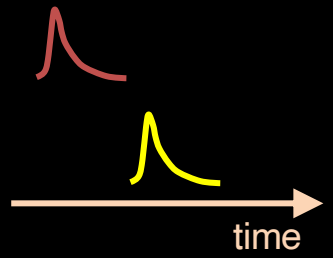
Rings of scintillation detectors

Very dense material to effectively absorb 511 keV photons

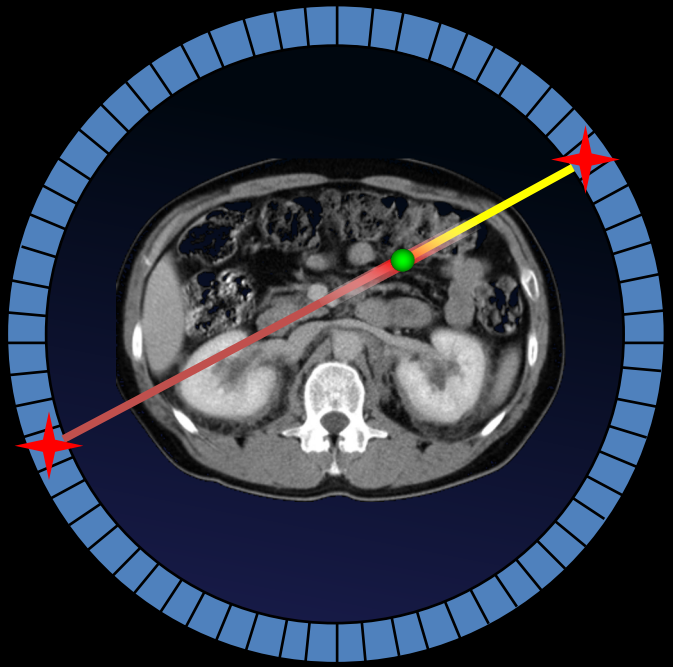


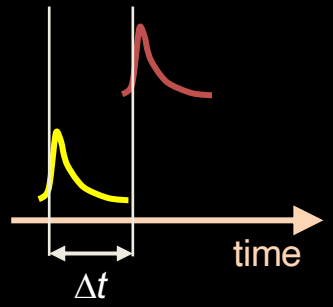
Time of Flight PET





Time of Flight PET





$$\Delta x = \frac{c\,\Delta t}{2}$$

Timing resolution

Δt = ~200 ps

Δx = 3 cm

Time of flight information not sufficient to directly localize events

Image Reconstruction

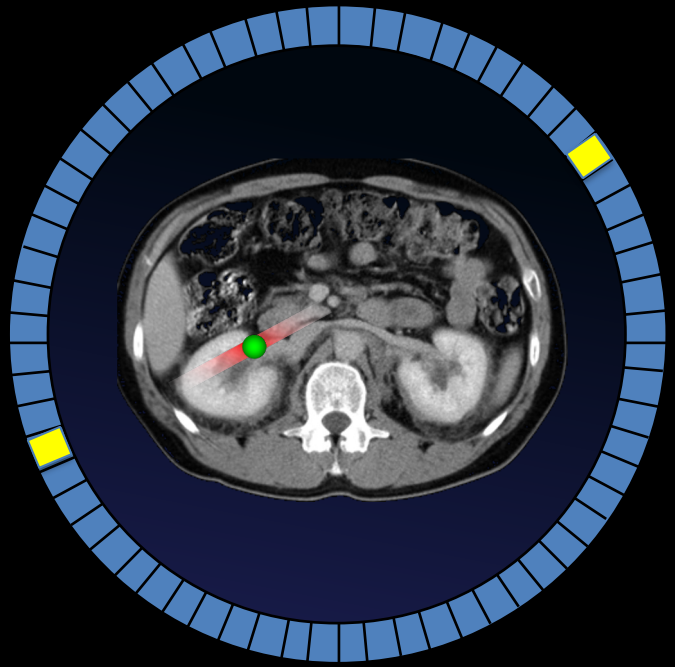
Sophisticated iterative methods

List mode time-of-flight

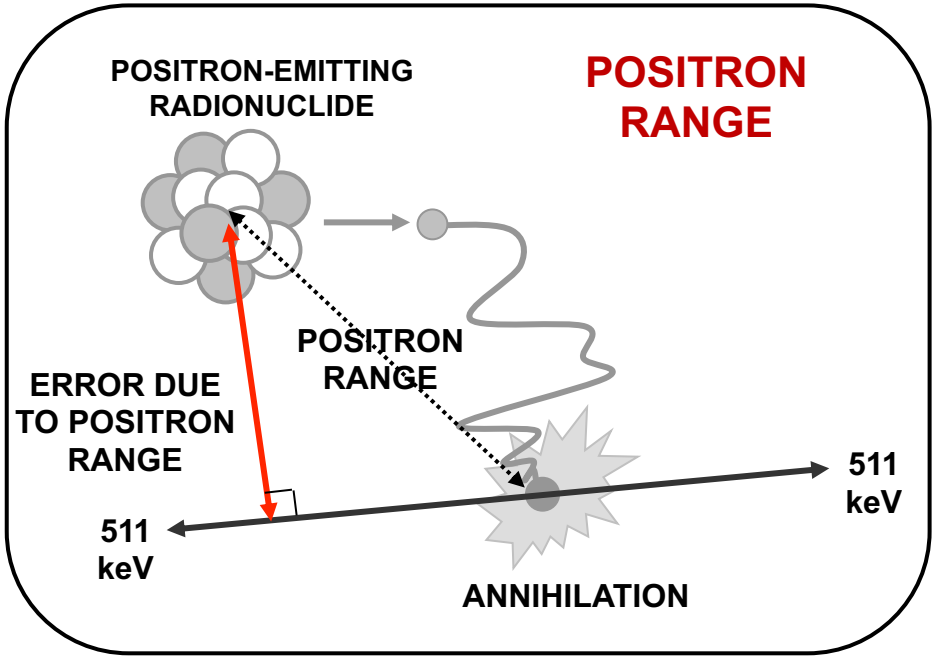
Ordered subsets, expectation maximization (OSEM)

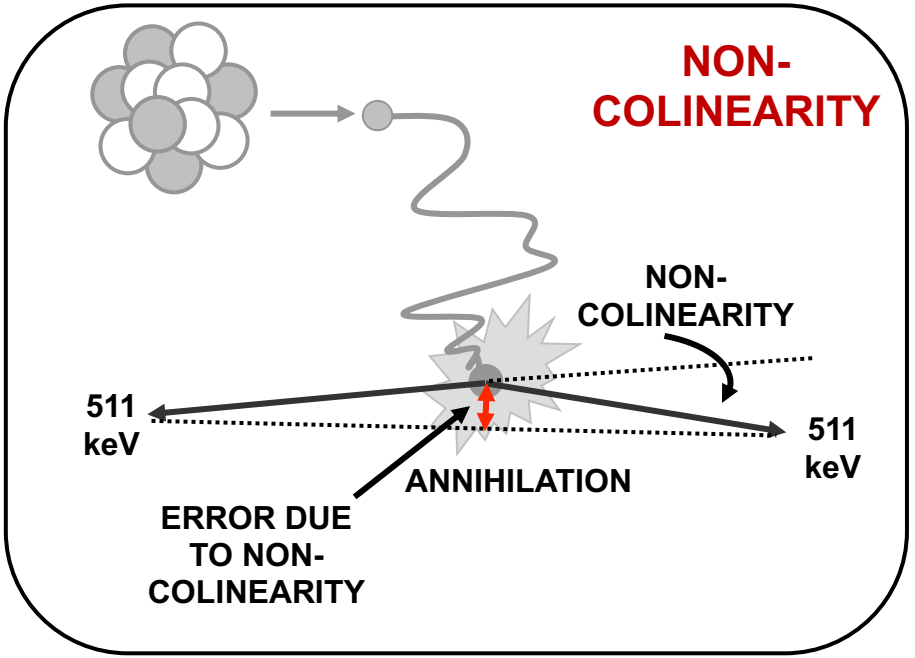
Point spread function (PSF) modeling may be applied

Post smoothing may be applied



The Spatial Resolution of PET is Limited





Whole-body imaging ~ 2 mm

Brain imaging ~ 1 mm

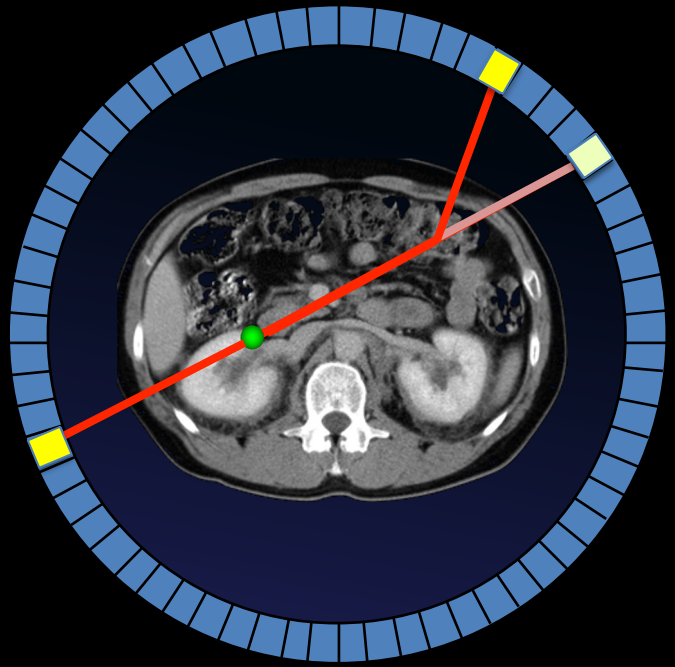
Data Corrections

Detector efficiency

Accidental (random) events

System deadtime

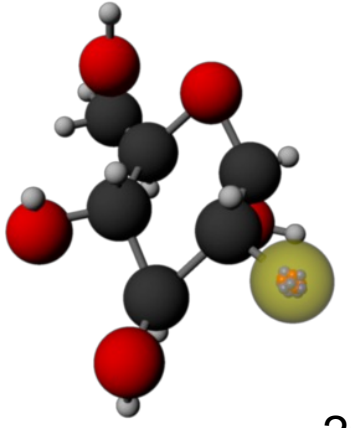
Photon attenuation and scatter
(using CT or MRI information)



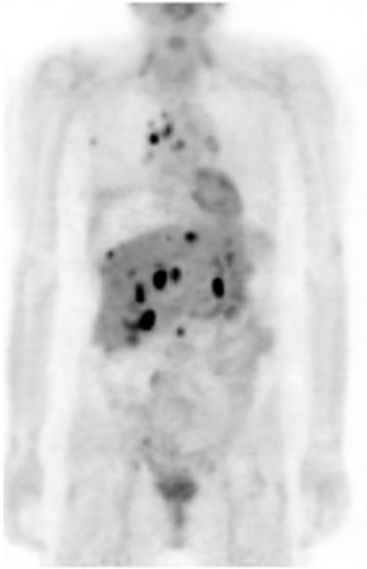
Clinical Use of PET Scanning

17 FDA approved PET tracers

[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)



~20 mins

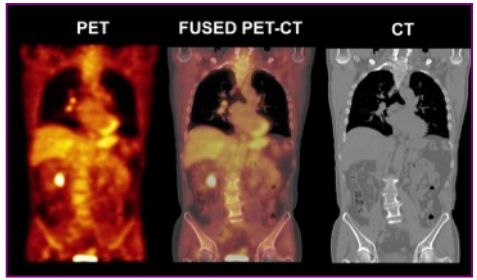


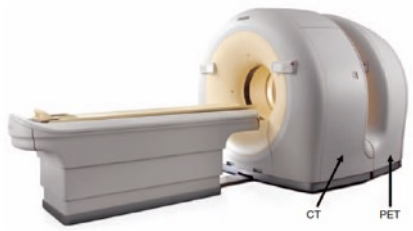
Clinical Use (2016 figures):

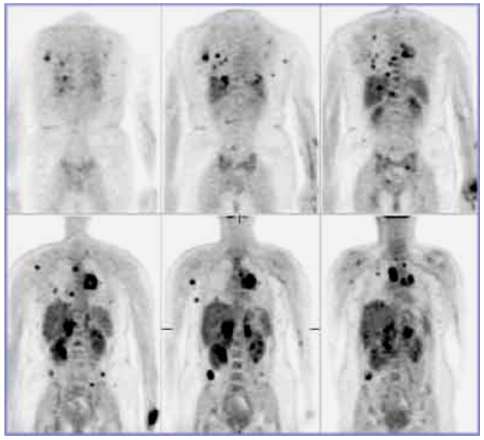
5.76 million scans per year at ~5,700 sites in the world

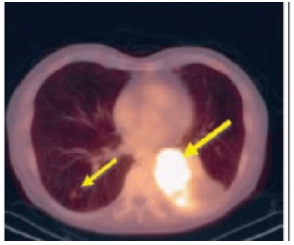
Oncology: staging, response to therapy
Cardiology: perfusion, viability
Neurology: amyloid imaging in AD

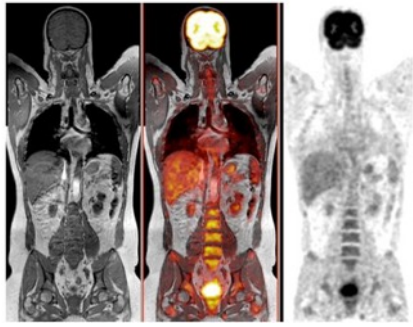
PET/CT and PET/MR Scanners

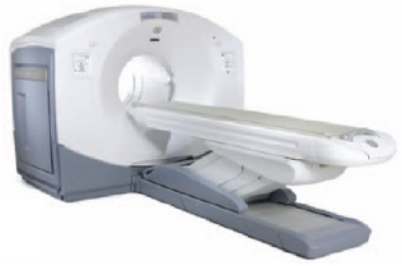


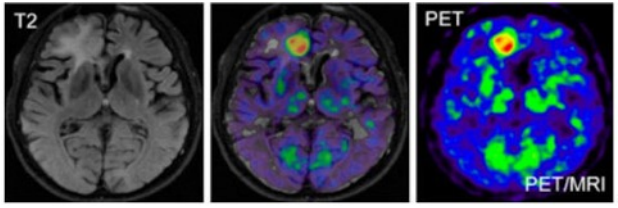


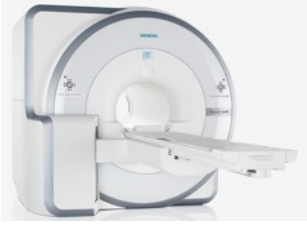












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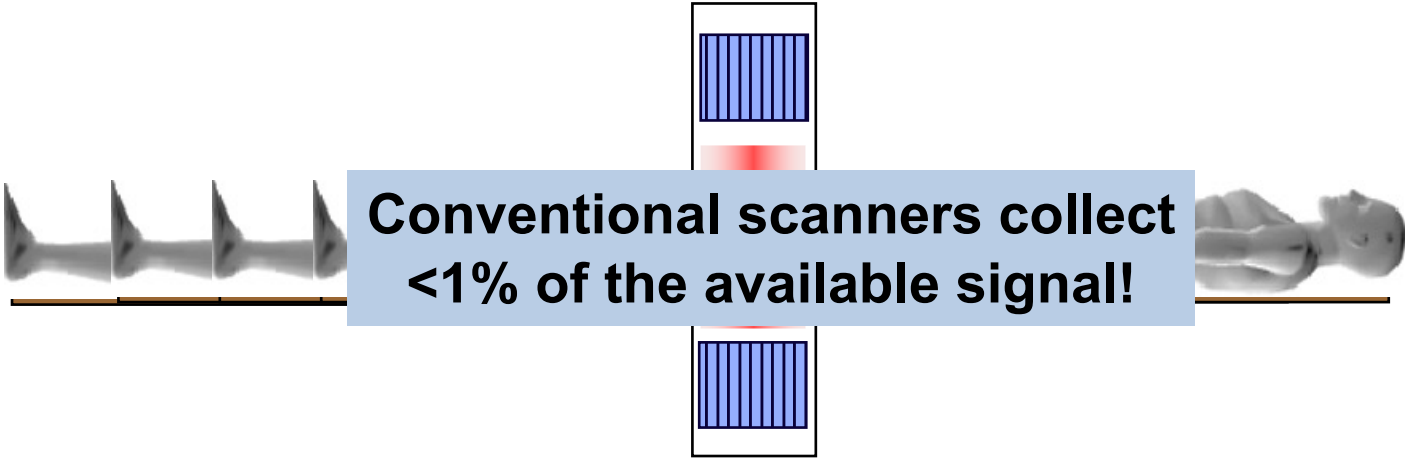
Signal Collection in PET



- PET provides the most sensitive non-invasive molecular assay of the human body
- All PET studies are limited by low signal, radiation dose, or both

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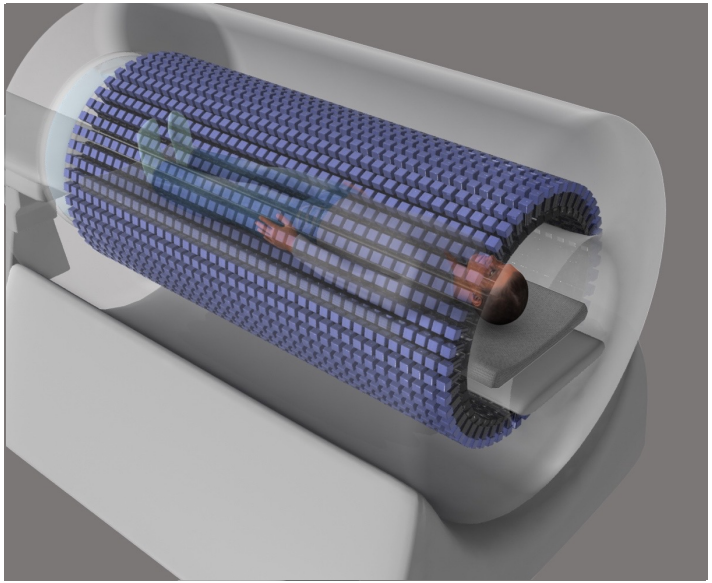
Total-Body PET



Total-Body PET/CT Scanner

Opportunities:

- All organs/tissues in field of view
- High geometric collection efficiency
- Leads to ~20-60 fold higher signal for whole-body imaging

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uEXPLORER Scanner

UNITED IMAGING

Performance:

174 kcps/MBq sensitivity*
(<20 kcps/MBq industry standard)

2.9 mm spatial resolution*

509 psecs time of flight

11.7% energy resolution

*NEMA NU 2-2018 protocol

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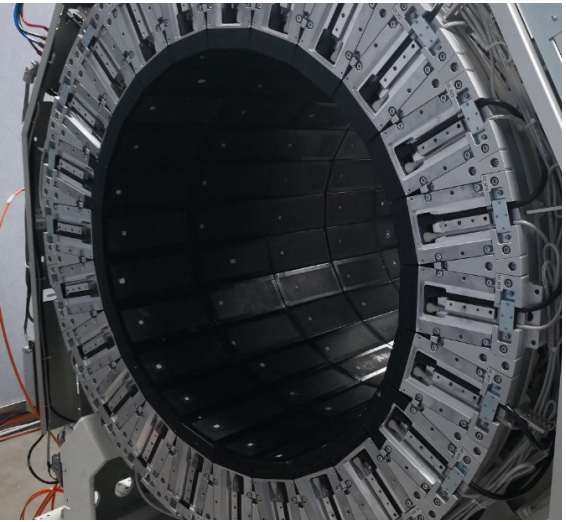
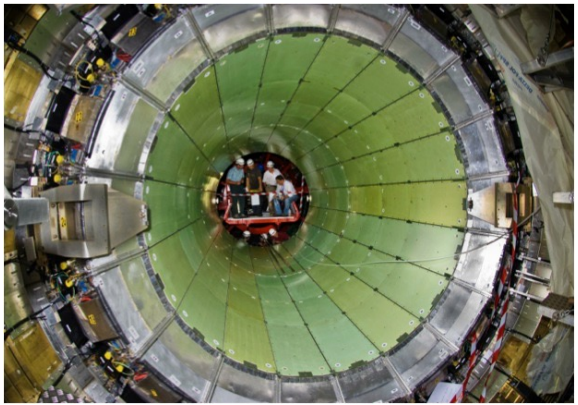
EXPLORER vs CMS EM Calorimeter





# of crystals: 564,480
# of photodetectors: 53,760
# of electronic channels: 53,760
Mass: ~11,000 kg

# of crystals: 75,848
# of photodetectors: 137,048
# of electronic channels: 75,848
Mass: ~100,000 kg

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Capabilities of Total-Body PET

High quality imaging

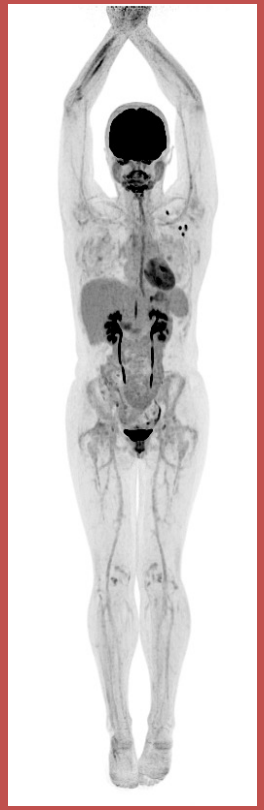


Image quickly: 30 sec scan

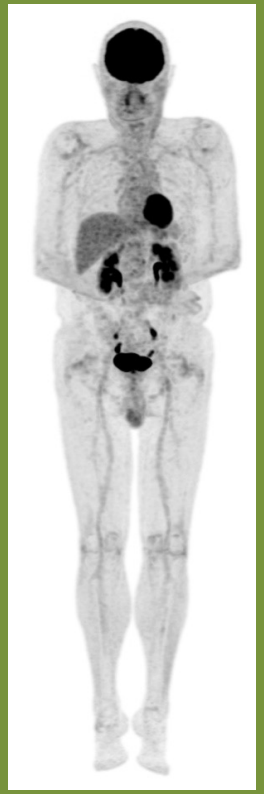
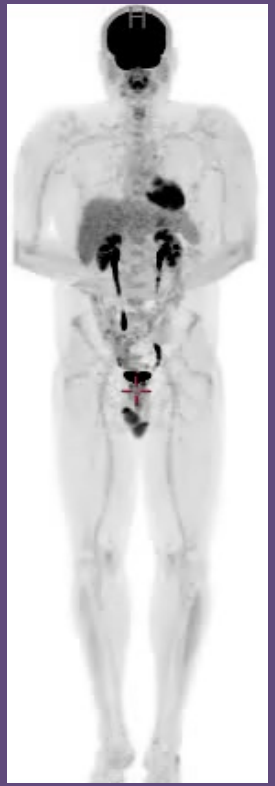


Image gently: 18 MBq dose



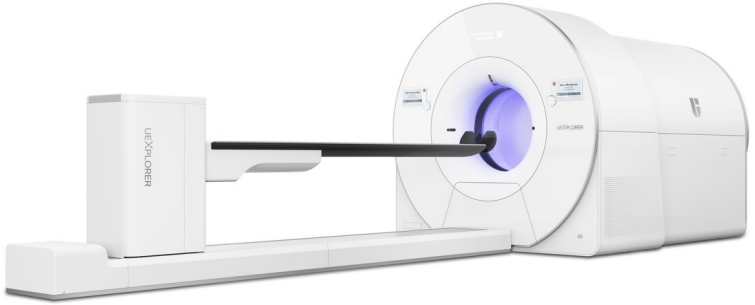
Total-Body and Long PET Scanners

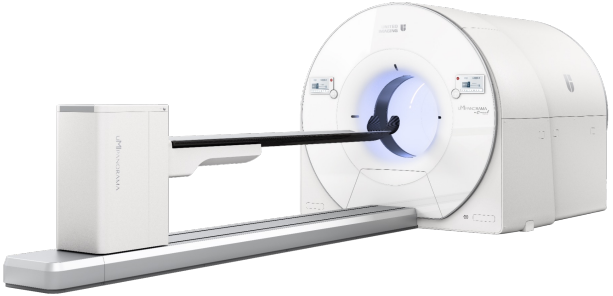
United Imaging uEXPLORER (194 cm)

~3 mm spatial resolution

total-body coverage

~500 ps time-of-flight





United Imaging Panorama GS (148 cm)

~200 ps time-of-flight

Siemens Vision Quadra (106 cm)

~220 ps time-of-flight

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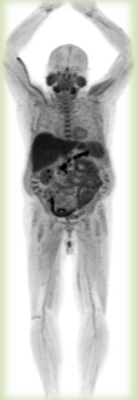
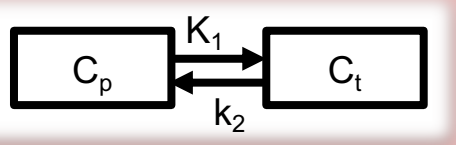
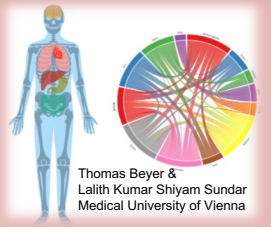
Total-Body PET: A Scientific Measurement Instrument

Scanner
Calibration/QC
Normalization
Attenuation
Scatter
Randoms
Deadtime
Background/Other γ's



Subject
Motion
Dietary Prep
Time of Day
Room Temperature
Exercise, Stress





Modeling/Analysis
Motion Correction
Segmentation, AI tools
Biological Understanding
TB Kinetic Modeling
Connectomics

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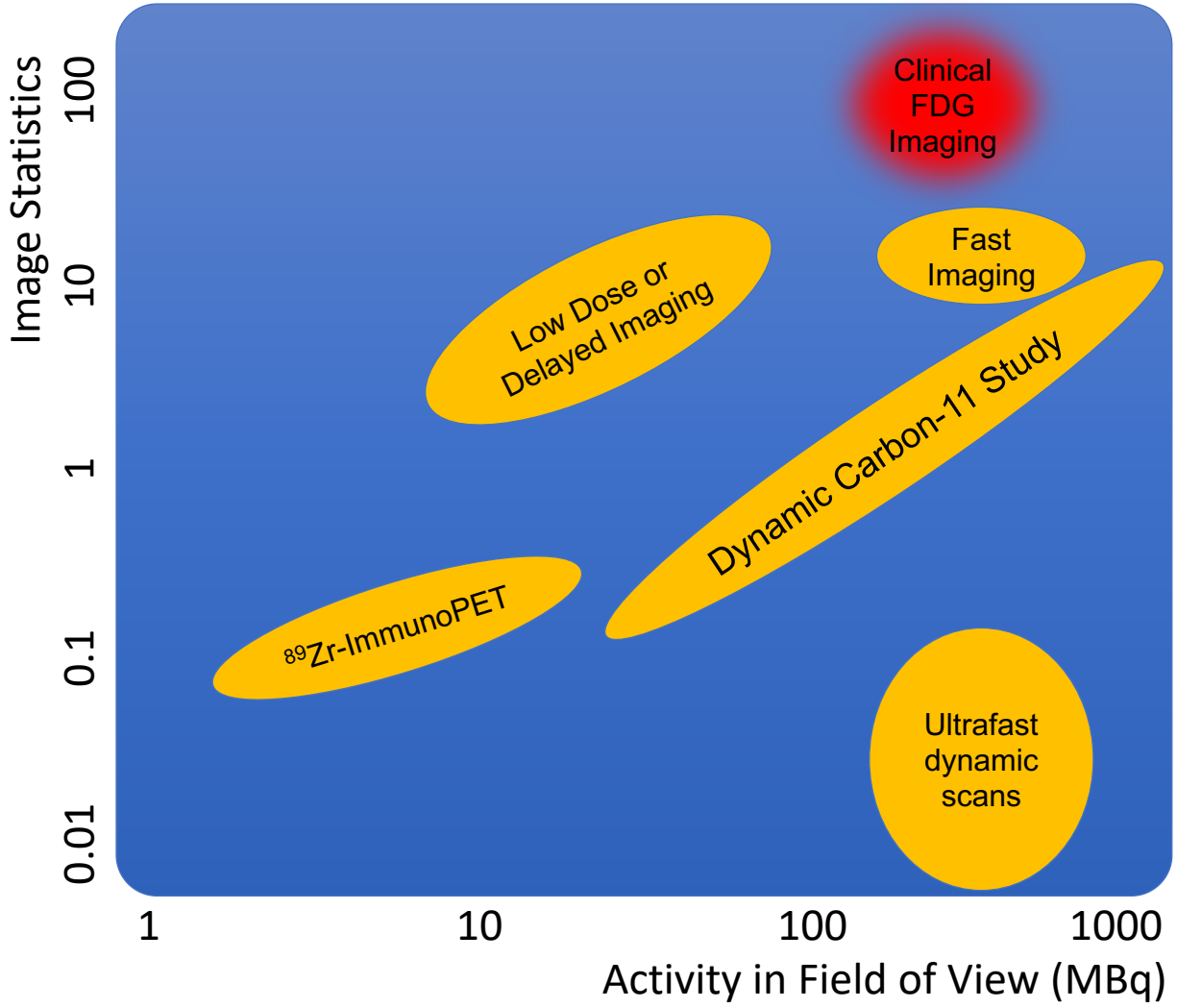
Challenge:

Need to be accurate and precise over 3-4 orders of magnitude!



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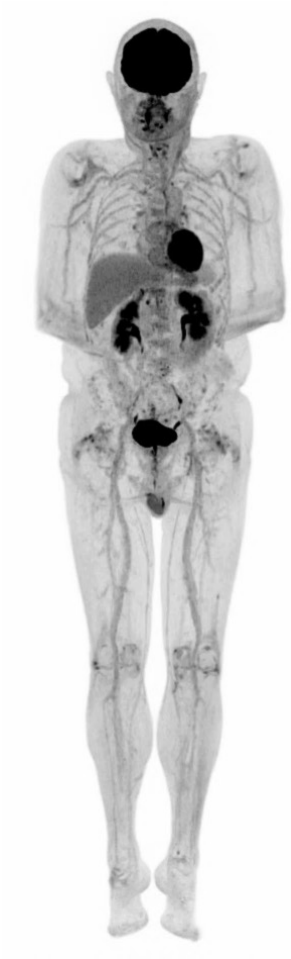
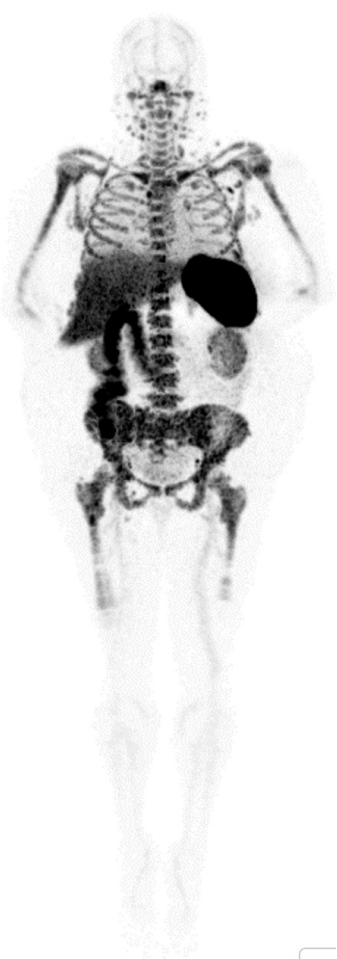
Challenge:

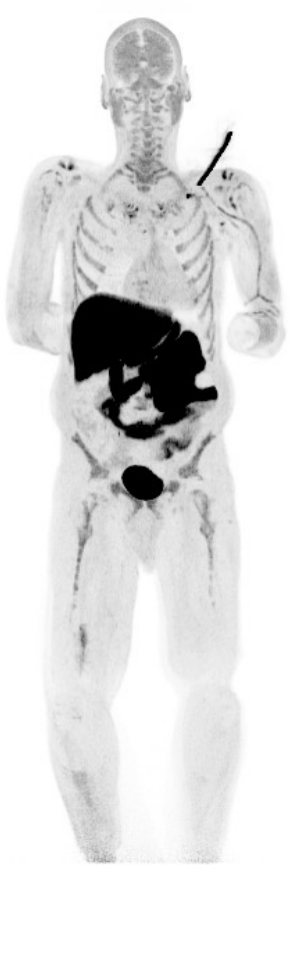
Distribution varies over time and with different tracers



^{18}F-FDG



^{89}Zr-Df-Crefmirlimab



^{18}F-Florbetaben

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Challenge:

Subject volume can vary by > 10x

10 kg – 150 kg

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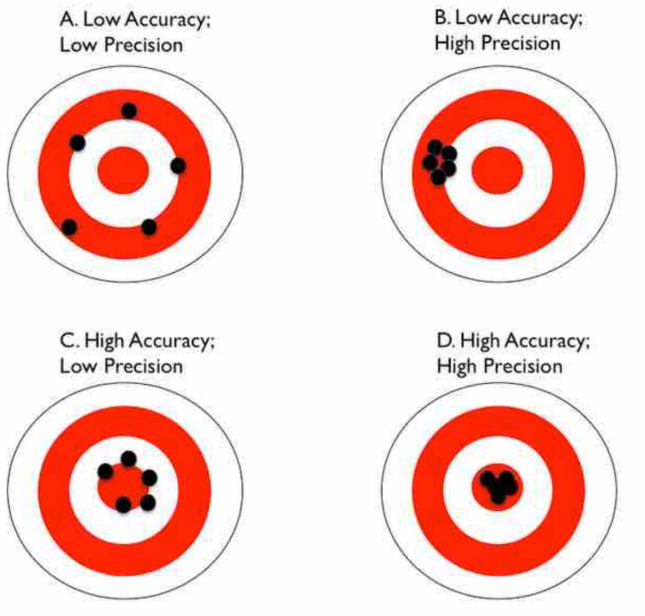
Quantitative Accuracy and Precision

- PET measures radiotracer concentration (kBq/cc)

- Precision (# of counts)
- Accuracy (data corrections)

- How good is it? ~ 5-10%
  - (ignoring biological variability)

- How good can it be?



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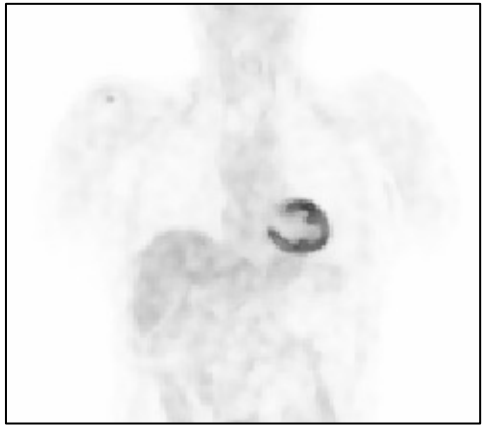
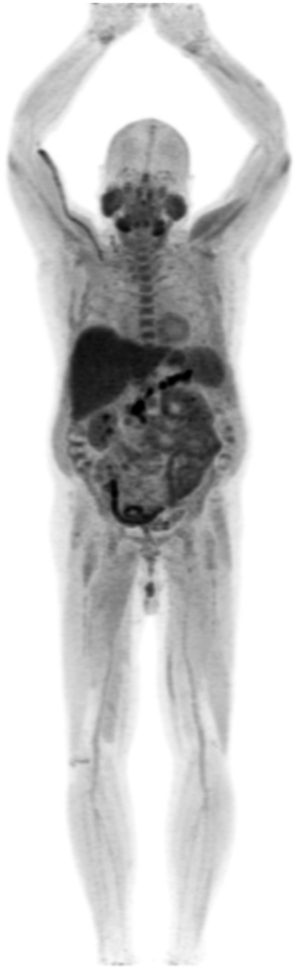
Challenge:

Motion occurs during scanning





Xuezhu Zhang, Eric Berg and Yasser Abdelhafez

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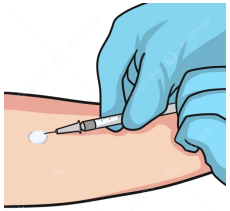
Static vs Dynamic Imaging

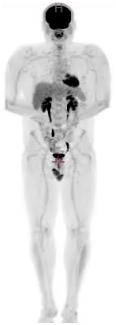
Static imaging



inject

wait

scan

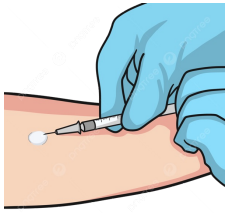


image

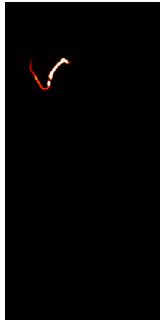
- Simple
- Short time in scanner

Dynamic imaging

+



position subject in scanner, imaging starts just before injection



time series of images

- More time in scanner
- More information

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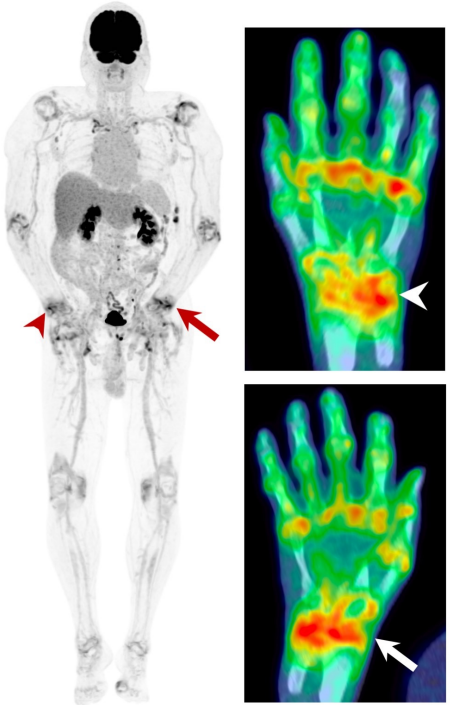
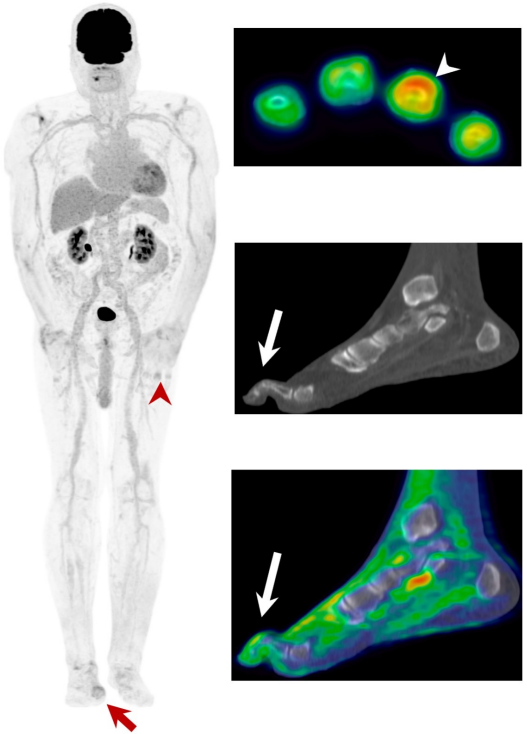
Total-Body PET in Arthritis

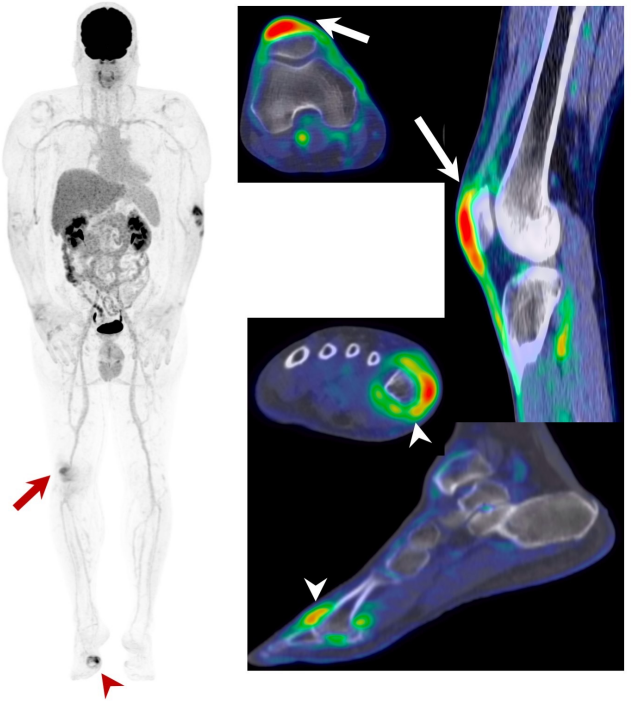
Psoriatic Arthritis



Rheumatoid Arthritis



Osteoarthritis



Yasser Abdelhafez and Abhijit Chaudhari

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Metrics from Static Scans

- **Standardized Uptake Value (SUV)**

$$\text{SUV (g/ml)} = \frac{C_{tissue}(\text{kBq/ml})}{A(\text{kBq}) / w(\text{g})}$$

Sensitive to uptake time, tracer delivery, scanner/dose calibrator calibration etc.
10-15% variability in within-subject test-retest studies

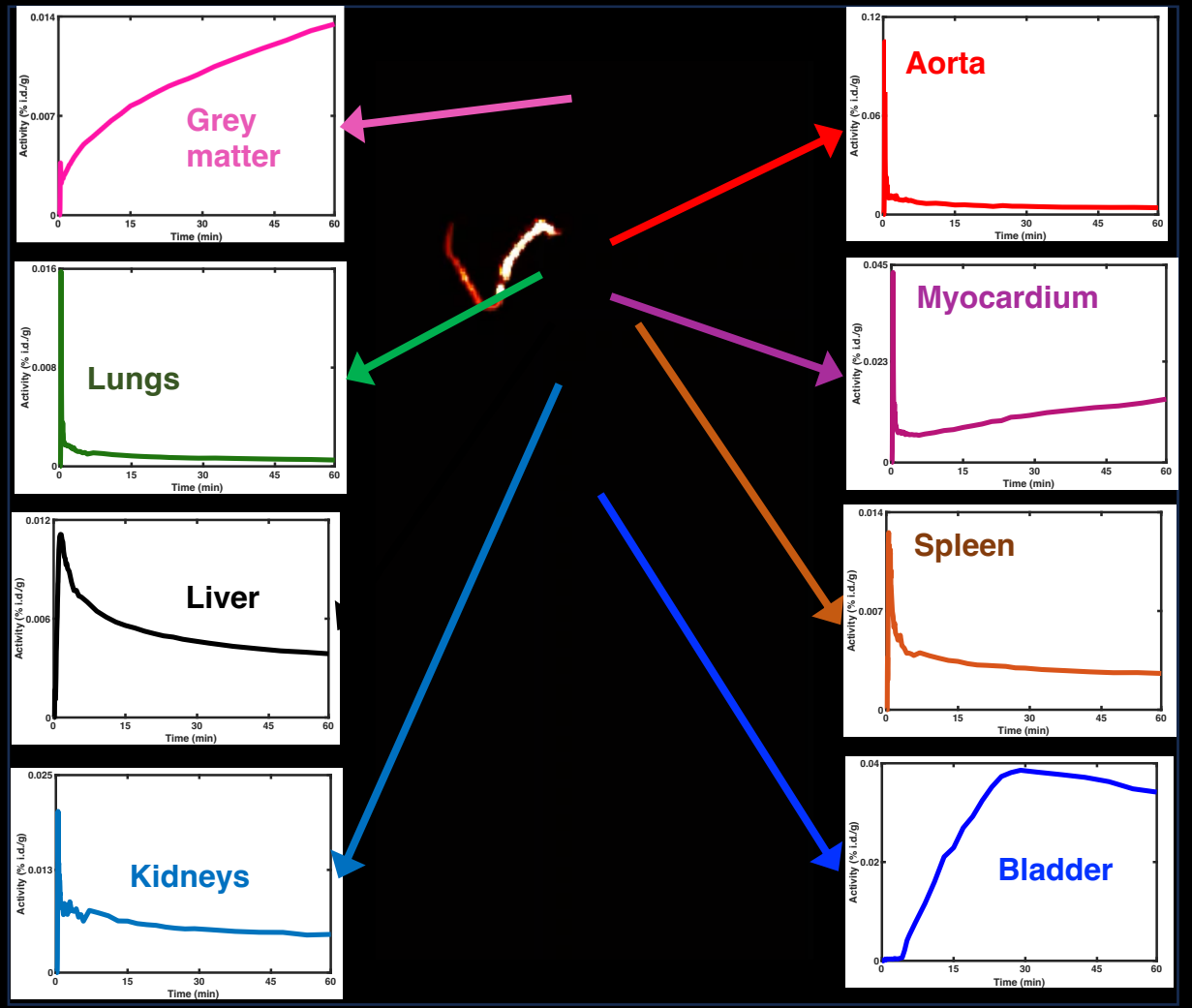
- **Standardized Uptake Value Ratio (SUVR)**

$$SUVR = SUV_{tissue}/SUV_{reference}$$

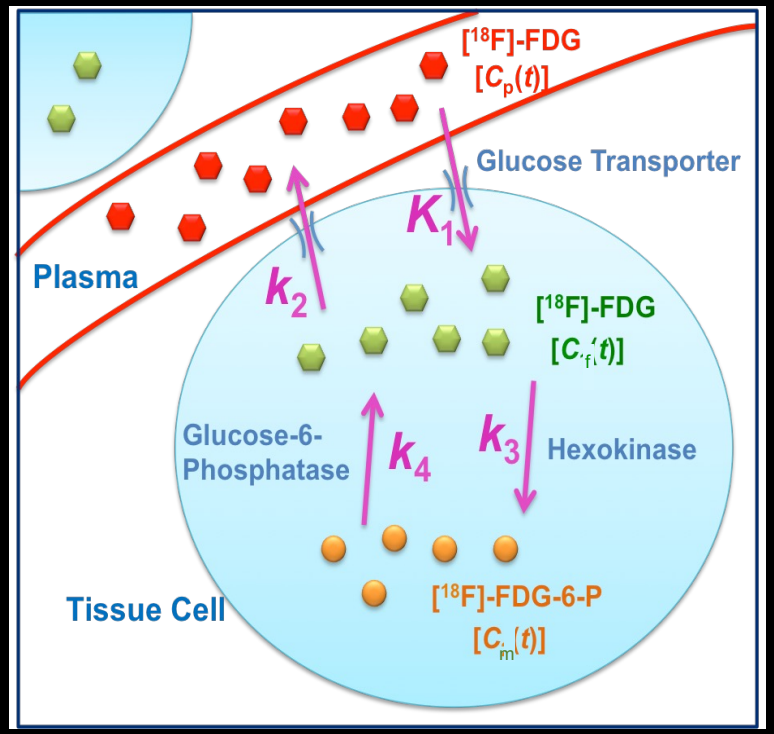
Boellaard, J Nucl Med 2009;50:115–120

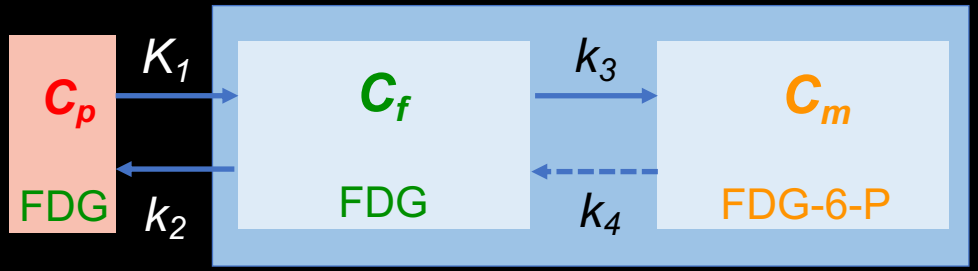
Total-Body Dynamic Imaging

Time-activity curves (TACs)



Total-Body Kinetic Modeling





$$\frac{dC_f}{dt} = K_1 C_p - (k_2 + k_3) C_f + k_4 C_m$$

$$\frac{dC_m}{dt} = k_3 C_f - k_4 C_m$$

$$C_{PET}(t) = (1 - v_b)(C_f(t) + C_m(t)) + v_b C_p(t)$$

Guobao Wang, UC Davis

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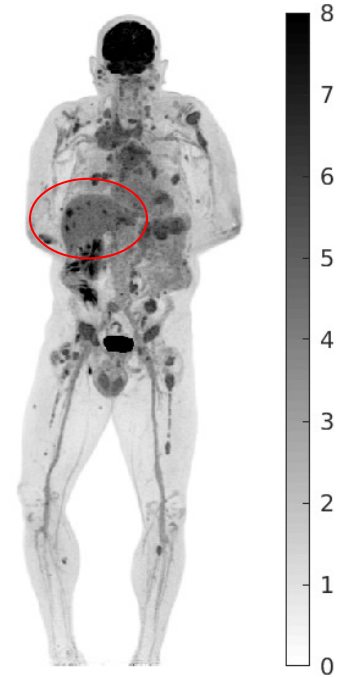
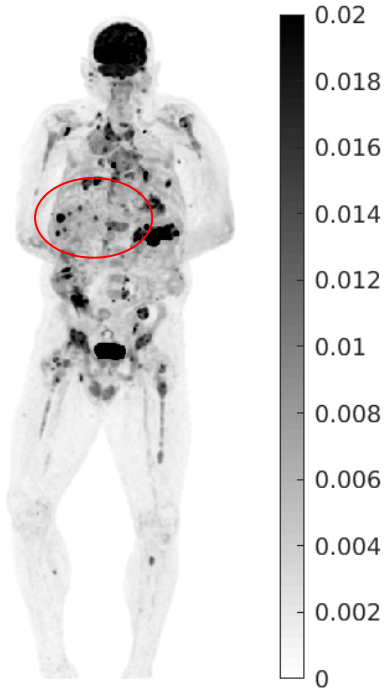
Parametric Imaging with ^{18}F-FDG

SUV (g/ml)

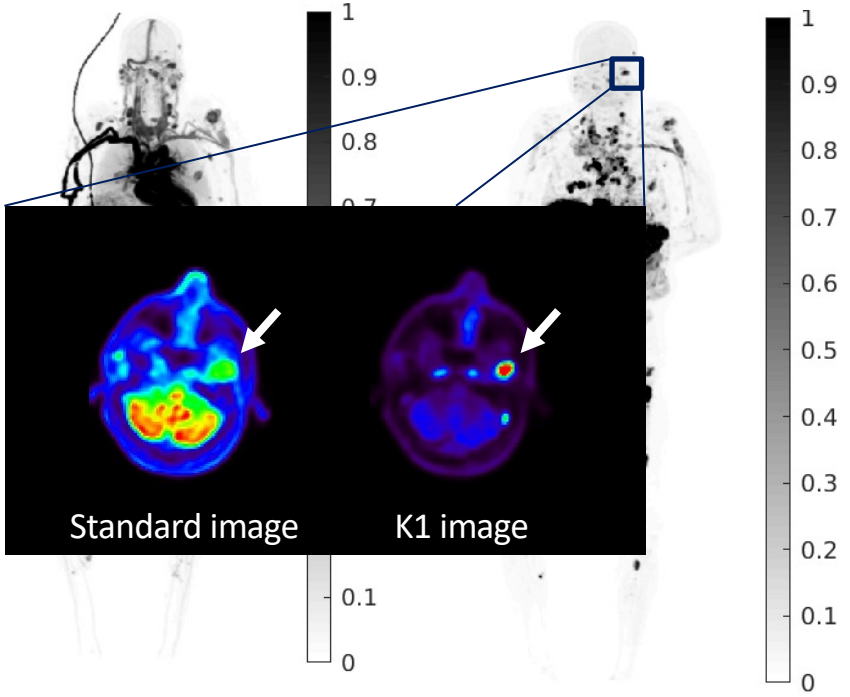


K_i: Overall FDG influx rate (ml/g/min)



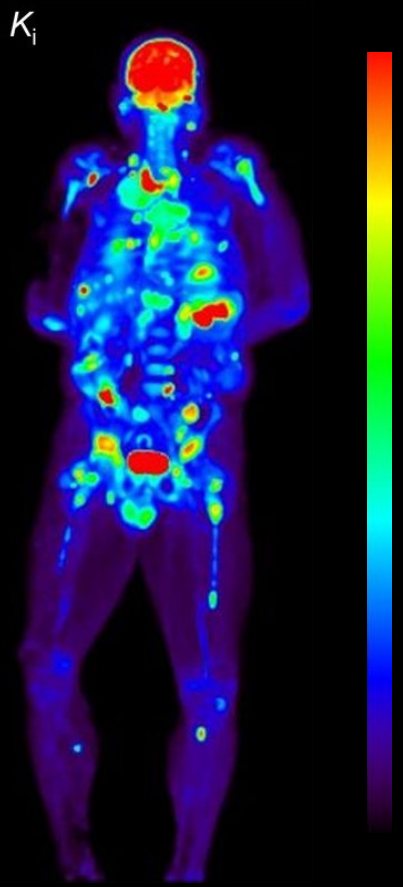
v_b: fractional blood volume

K_1: glucose transport rate (ml/g/min)



Courtesy of Dr. Guobao Wang, UC Davis

Challenges and Limitations in Kinetic Modeling



- Delay and dispersion of the blood input function
- Input function measures C_{wb} not C_p
- Model selection and special cases
  - Blood, liver, lungs etc…
- Correcting for metabolites
- Selecting appropriate model complexity
  - What can the data support?
  - Identifiability analysis
- Effects of motion

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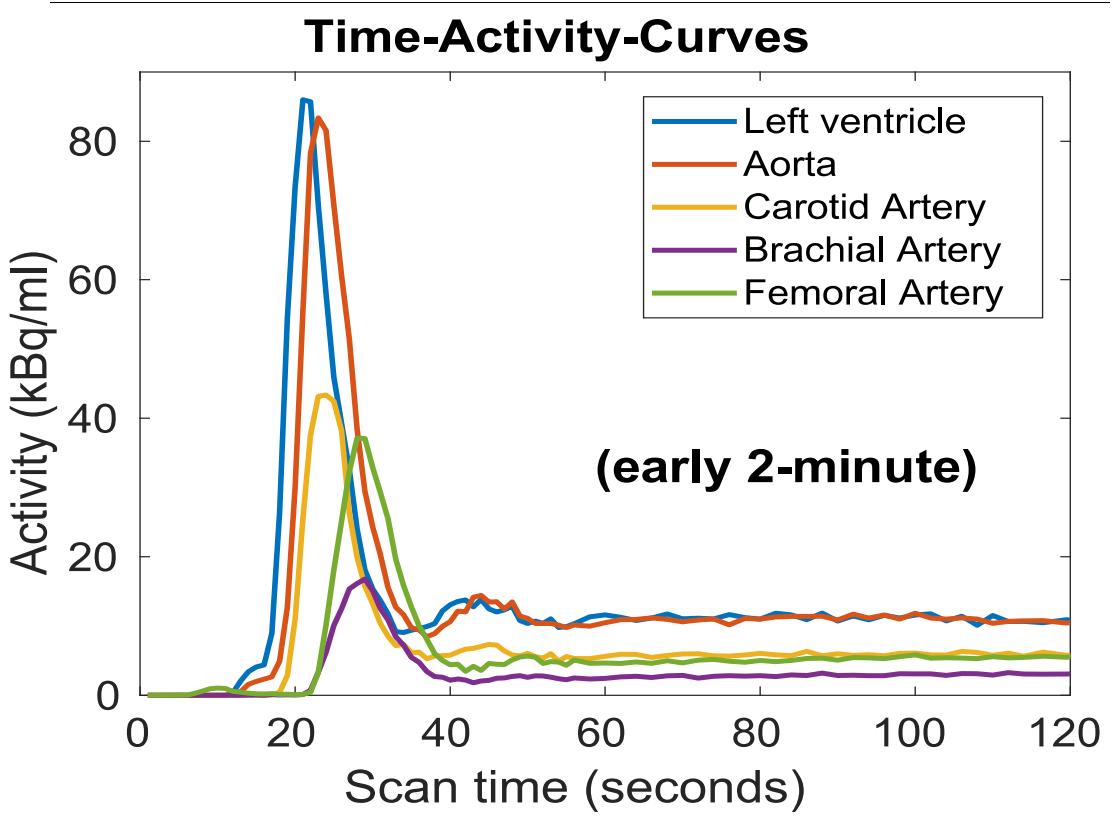
Image-Derived Input Function



Input function shows both **delay** and **dispersion** with distance from the left ventricle

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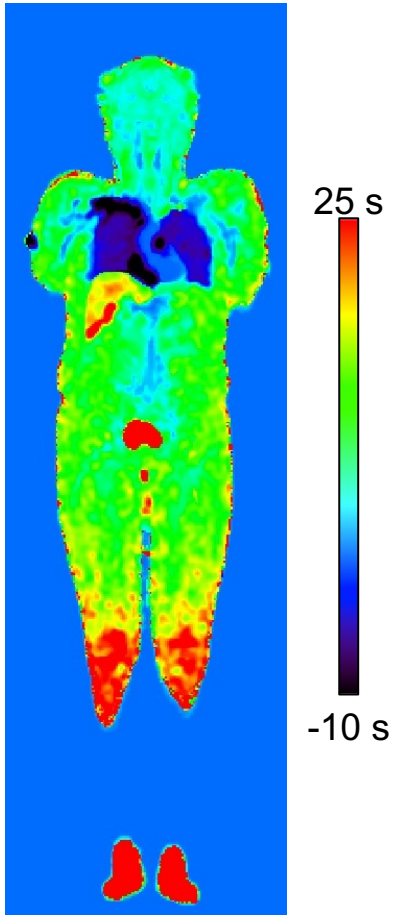
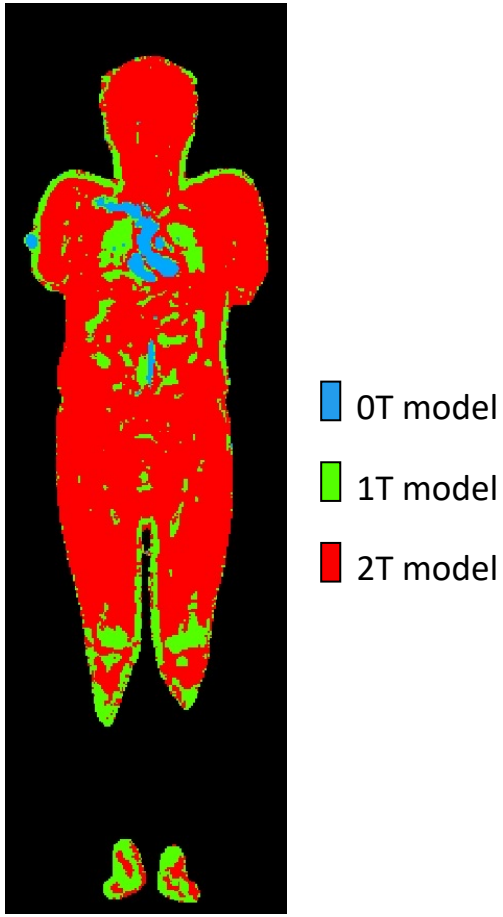
Time delay and model selection maps

Yiran Wang, UC Davis

Time delay



Kinetic model selection



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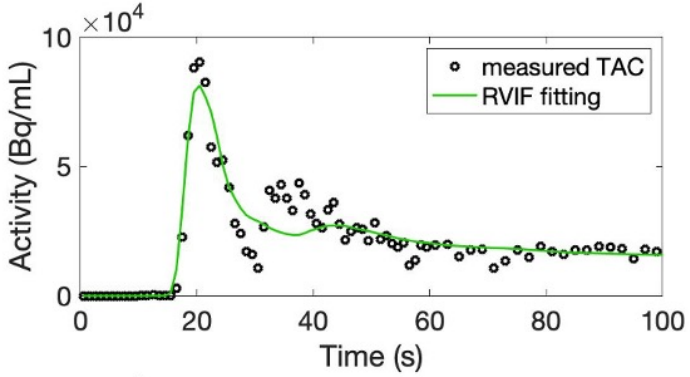
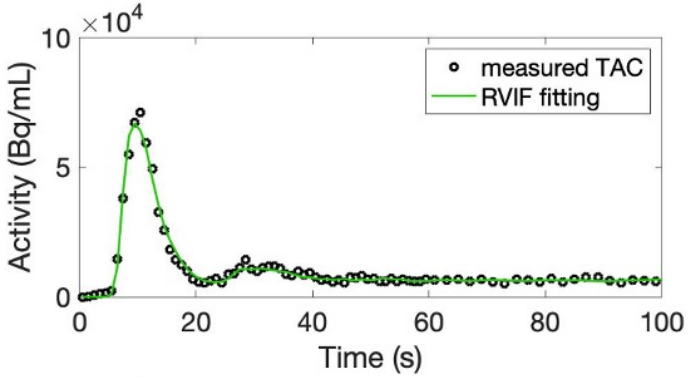
Dual Blood Input Function - Lung

Lung tumor TAC fitting

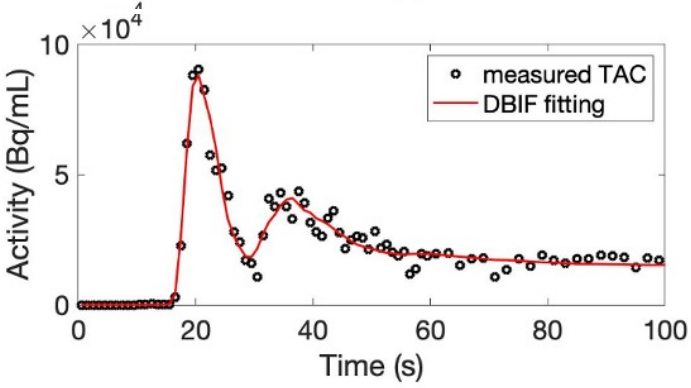
Normal lung tissue TAC fitting

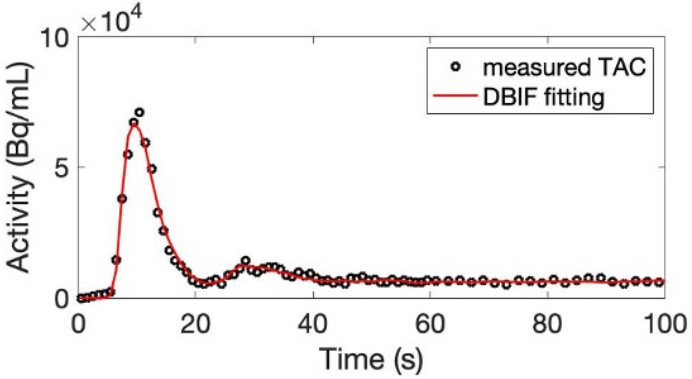
RVIF



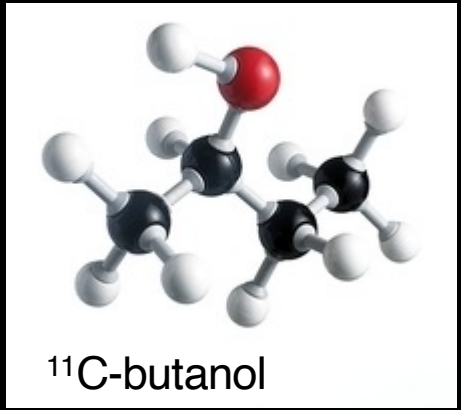


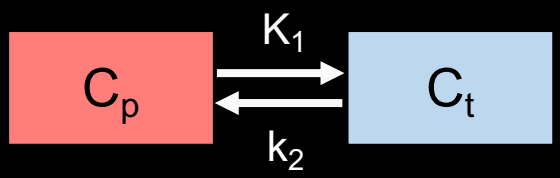
DBIF

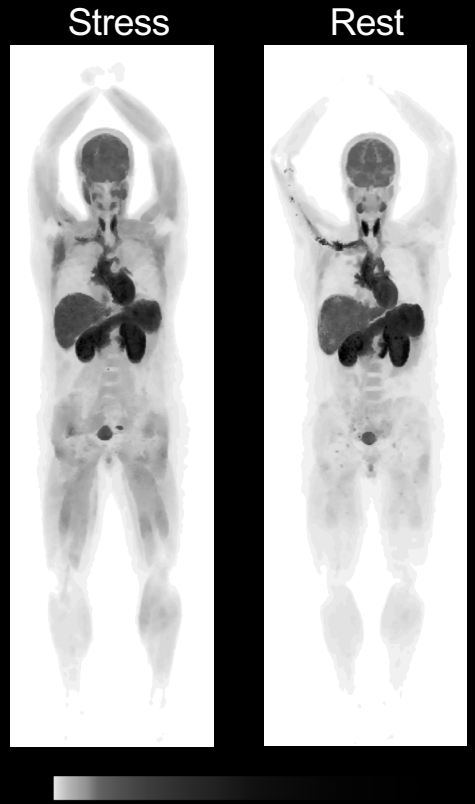


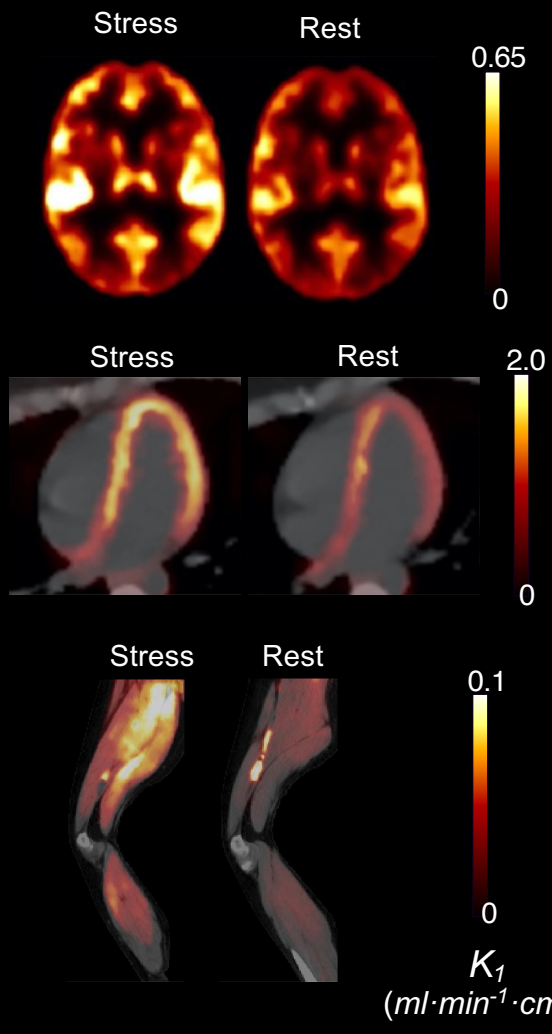


Total-Body Perfusion Imaging



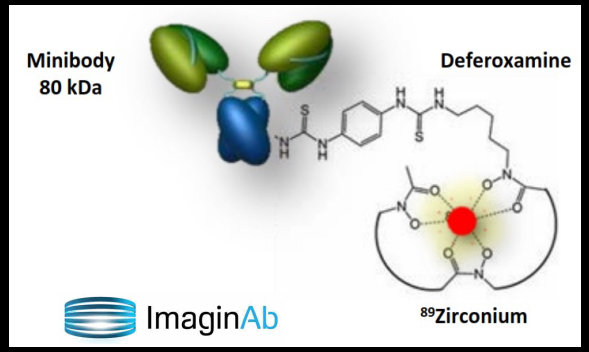






Elizabeth Li, UC Davis/UPenn

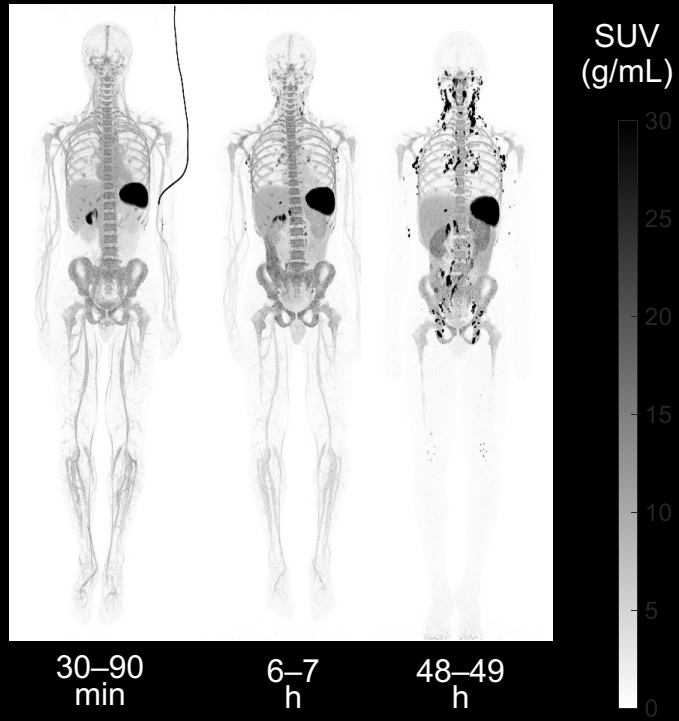
Targeted Imaging of CD8+ T cells

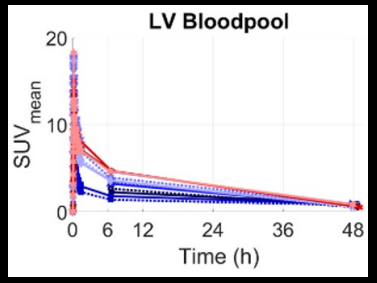


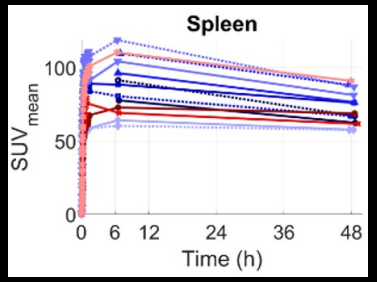
Crefmirlimab is a minibody with high affinity to **human CD8**

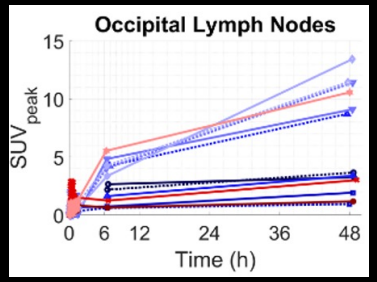
0.5 mCi (18 MBq) of
^{89}Zr-Df-Crefmirlimab-Berdoxam

Control
M, 25 y/o, BMI 21









New models needed!

Negar Omidvari, UC Davis

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Considerations in Study Design

- Radiotracer selection
- **Subject selection**
- Imaging protocol (static/dynamic)
- Reconstruction protocol
- Analysis methods

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Function is Highly Variable

- Brain anatomy[1]
  - Grey matter volume
  - Between-subject variability: 8.9%

- Brain function[2]
  - Cerebral perfusion
  - Between-subject variability: 16.2%
  - Within-subject variability: 4.8%

1. Nobis et al, Neuroimage 2019; 23: 101904
2. Henriksen et al, J Magn Reson Imaging 2012; 35: 1290-1299.

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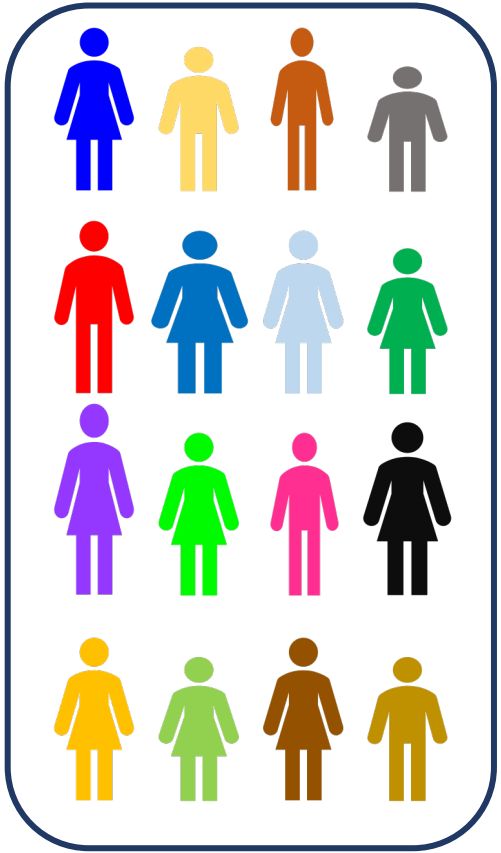
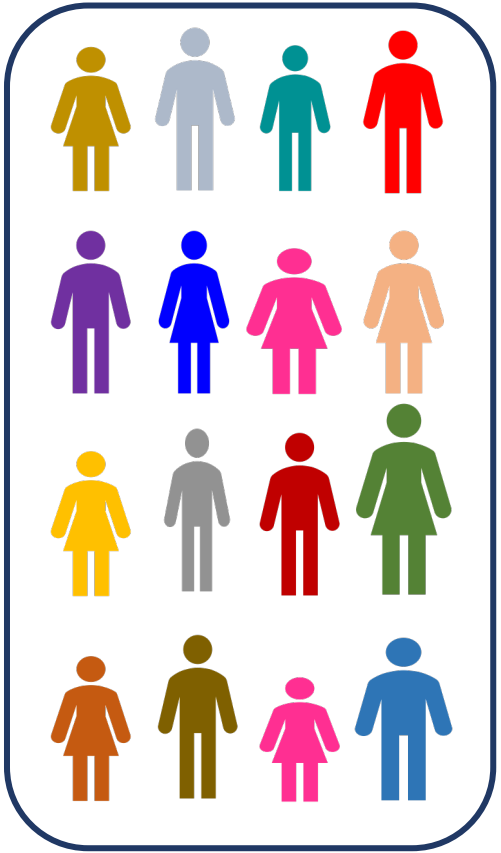
Across-subject Design



Control Group



Disease Group

Requires large numbers of subjects

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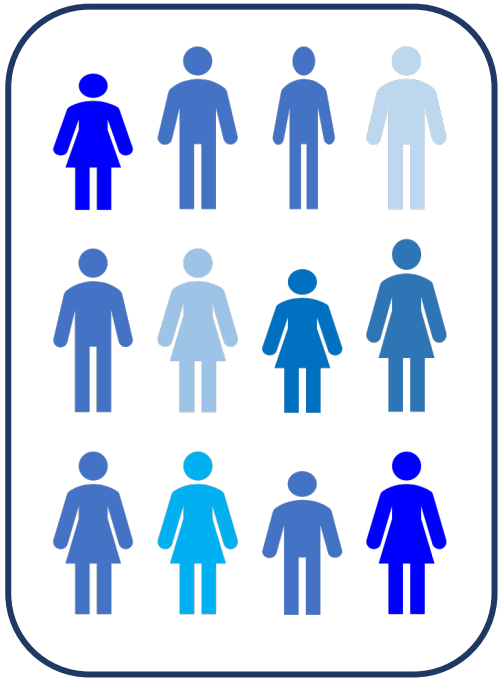
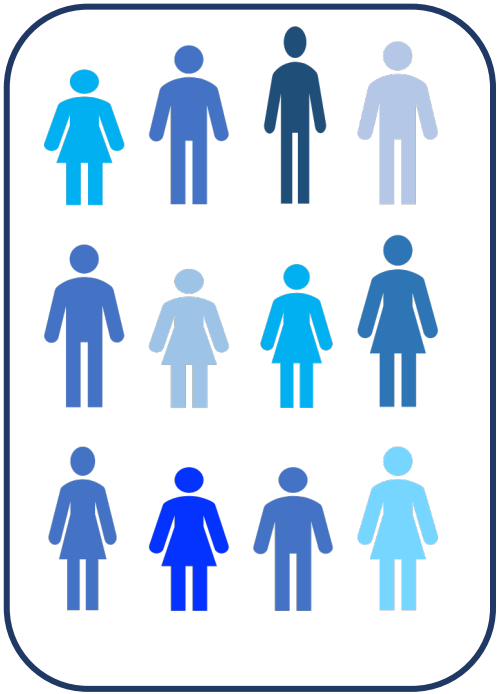
Matched Across-subject Design

gender, age, BMI, ethnicity, etc…



Control Group



Disease Group

Reduce number of subjects
Cohorts may be less diverse and representative

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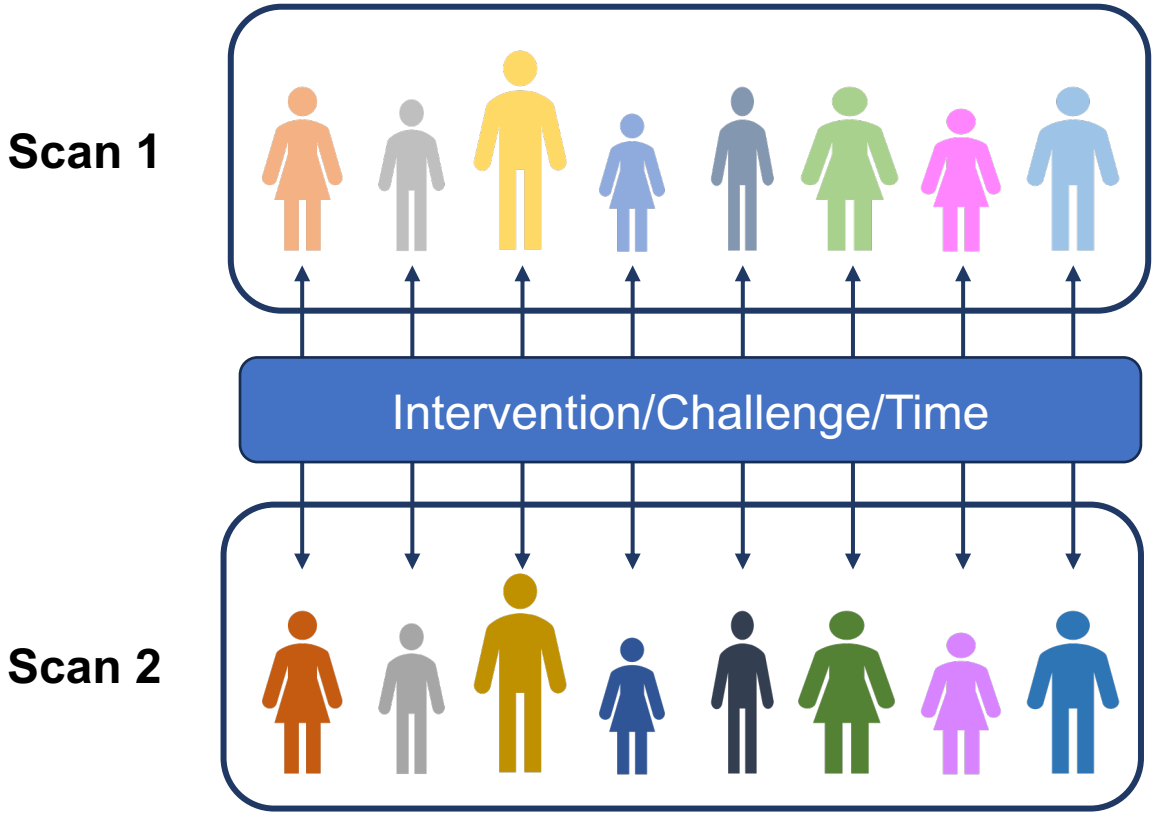
Within-subject Design



Each subject serves as their own control

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Summary

- PET is a highly sensitive technique that can quantitatively measure physiology, metabolism and molecular targets.
- Advanced total-body PET scanners enable radiotracer pharmacokinetics to be measured in the entire human body with good signal-to-noise ratio.
- Total-body PET offers new opportunities for studying the human body as a system in health and disease