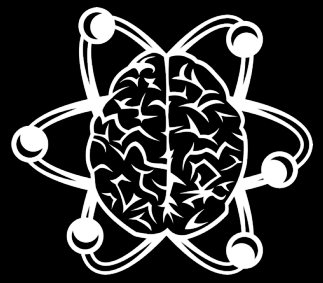
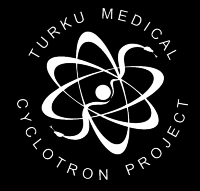


BASICS OF BIOLOGICAL MODELLING WITH PET

Turku PET Centre Brain Imaging Course 2024

Riku Klen, Turku PET Centre



About this lecture (what you should learn)

Contents of the talk

- PET imaging
- Image segmentation
- PET modelling
- Interpretation

Key terminology

- Dynamic PET
- TAC
- Compartment model
- Patlak plot
- Logan plot
- Parametric imaging

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Why do we need modelling?

- PET images can contain millions of pixels (or voxels)
  - Big data
- PET images are 3D (static) or 4D (dynamic)
  - Hard to visualise
- Analysis is complex
  - Automation helps (a little)
- Conclusions are difficult to make
  - Modelling helps (a lot)
- Modelling is needed to extract important information

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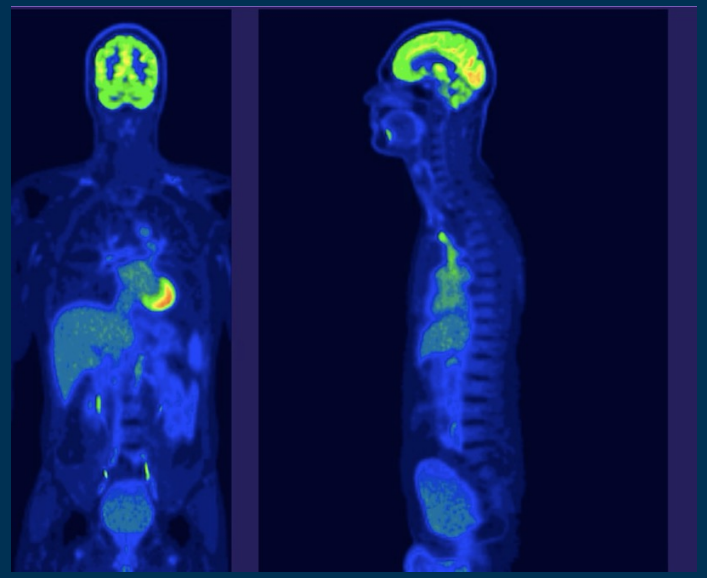
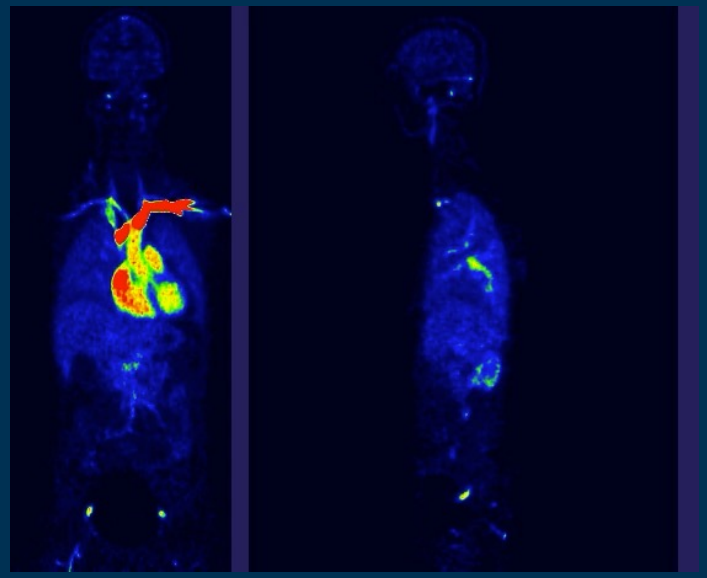
Static and dynamic imaging

Static PET imaging



40 minutes

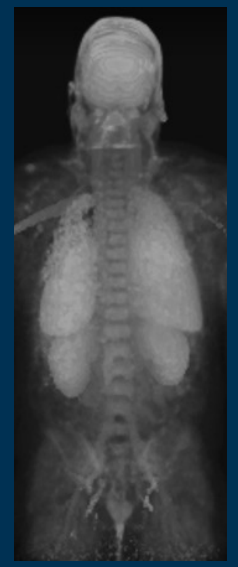
Dynamic PET imaging



40 minutes, 13 frames

Image analysis

X. Chen et al.: A deep learning-based auto-segmentation system for organs-at-risk on whole-body computed tomography images for radiation therapy. Radiotherapy and Oncology (2021), 170, 175-184.



Segmentation, modelling

These example images were provided by Prof. Kirsi Virtanen.

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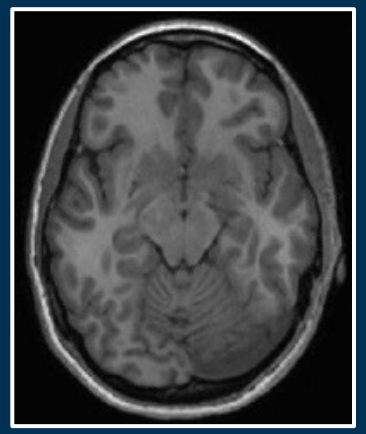
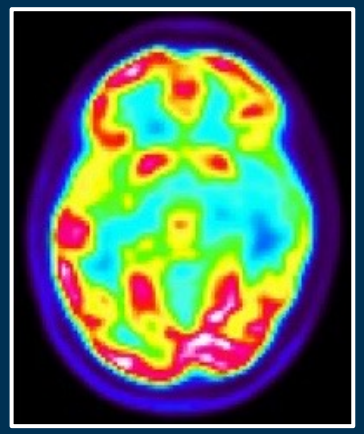
Why PET imaging?

To understand how organism functions



MRI



PET

Clinical motivation

- Locate diseases, e.g. cancer
- Find malfunctions, e.g. ischemia

Understanding physiology

- Neuroimaging, e.g. emotions
- Metabolic imaging, e.g. brown fat

Research

- Drug development, e.g. distribution

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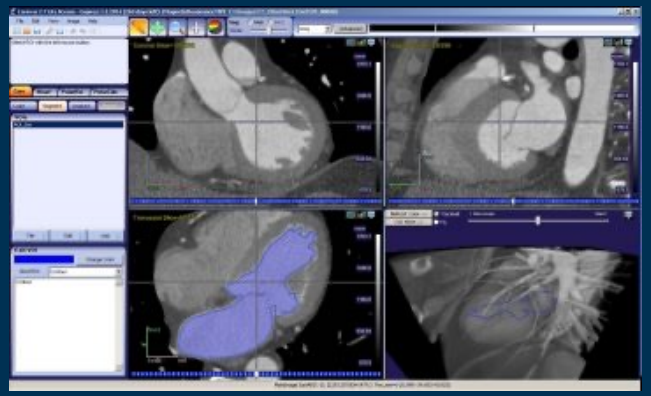
An example of PET image analysis

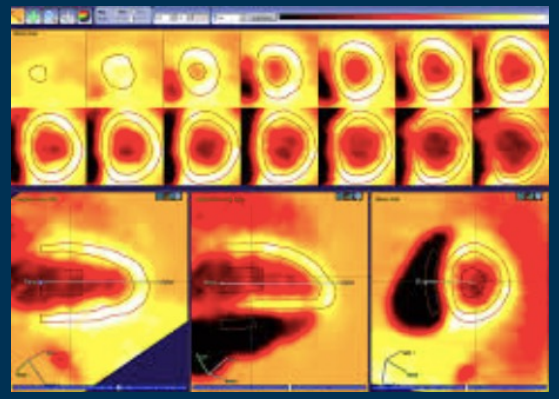
Total body O-15-water PET imaging

- PET image size: 440 x 440 x 380 x 24 ~ 1.8 billion voxels
  - Time series of 24 images (3D)
- Hard to visualise – even harder to analyse manually
- Automatic analysis steps needed

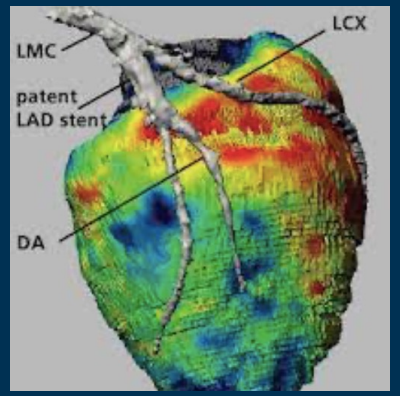
Visualisation

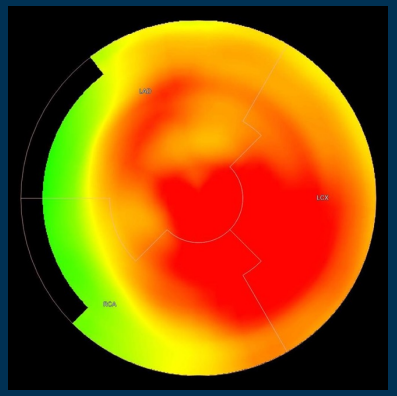


Segmentation



Modelling





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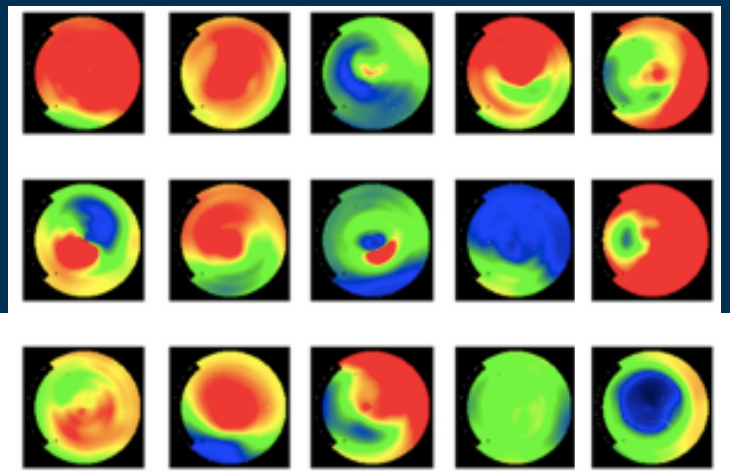
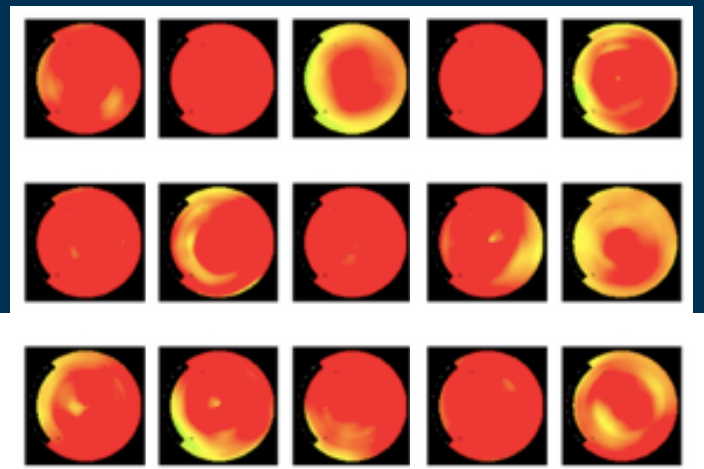
An example of PET image analysis

Total body O-15-water PET imaging

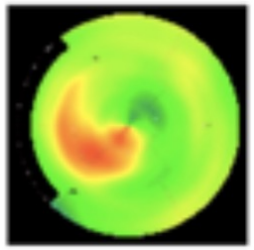
Ischemia



No ischemia



?



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PET imaging flow

Radioactive tracer

- Various different tracer for different purposes, e.g. radioactive water for blood flow, glucose (FDG) for metabolism
- Produced with cyclotrone and radiochemistry lab
- Injection (or inhale)

PET imaging

- Duration from a couple of minutes to tens of minutes
- Patient lays still
- Typically with CT or MRI

Image analysis

- Segmentation
- Visual inspection
- Modelling
- Results

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Image segmentation

ADD FIG HERE

Manual segmentation

- 2D tools (e.g. paintbrush)
- Tedious & subjective (low repetitive)
- Human control

Semi-automatic segmentation

- 2D or 3D tools (e.g. region grow algorithm)
- Less tedious & subjective
- Some human control

Automatic segmentation

- 2D, 3D or 4D methods (e.g. deep learning)
- Fast & objective (repetitive)
- No human control

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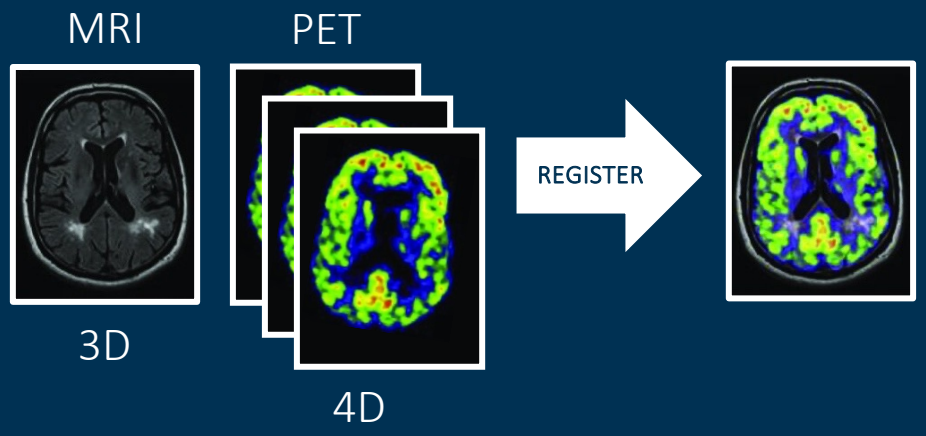
PET-MRI image segmentation in neuroimaging

Automatic PET-MRI registration

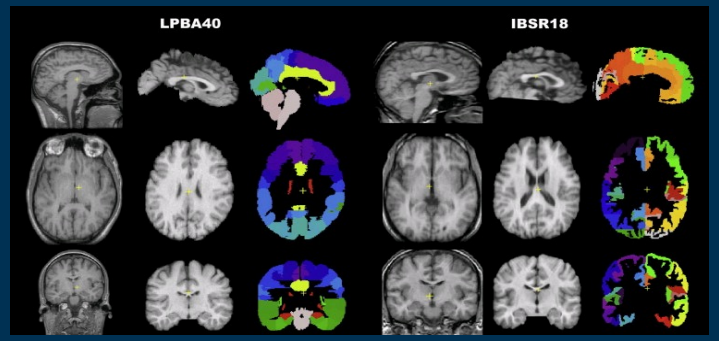
- Dynamic PET and MRI images are registered



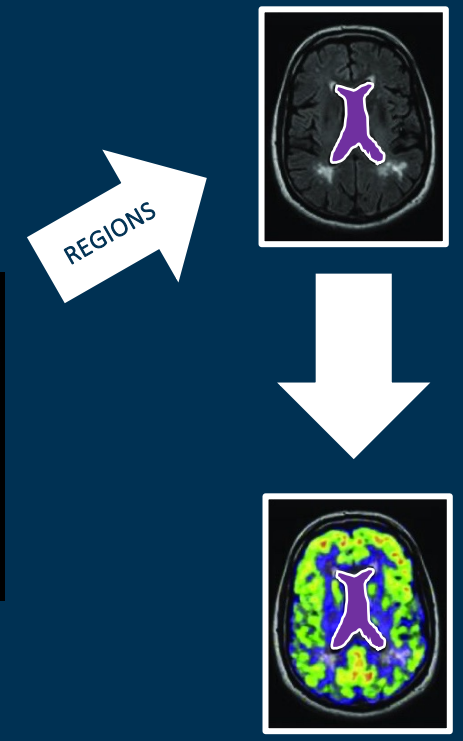
Automatic MRI segmentation

- Manually segmented MRI templates

MRI brain template



https://www.fil.ion.ucl.ac.uk/spm/



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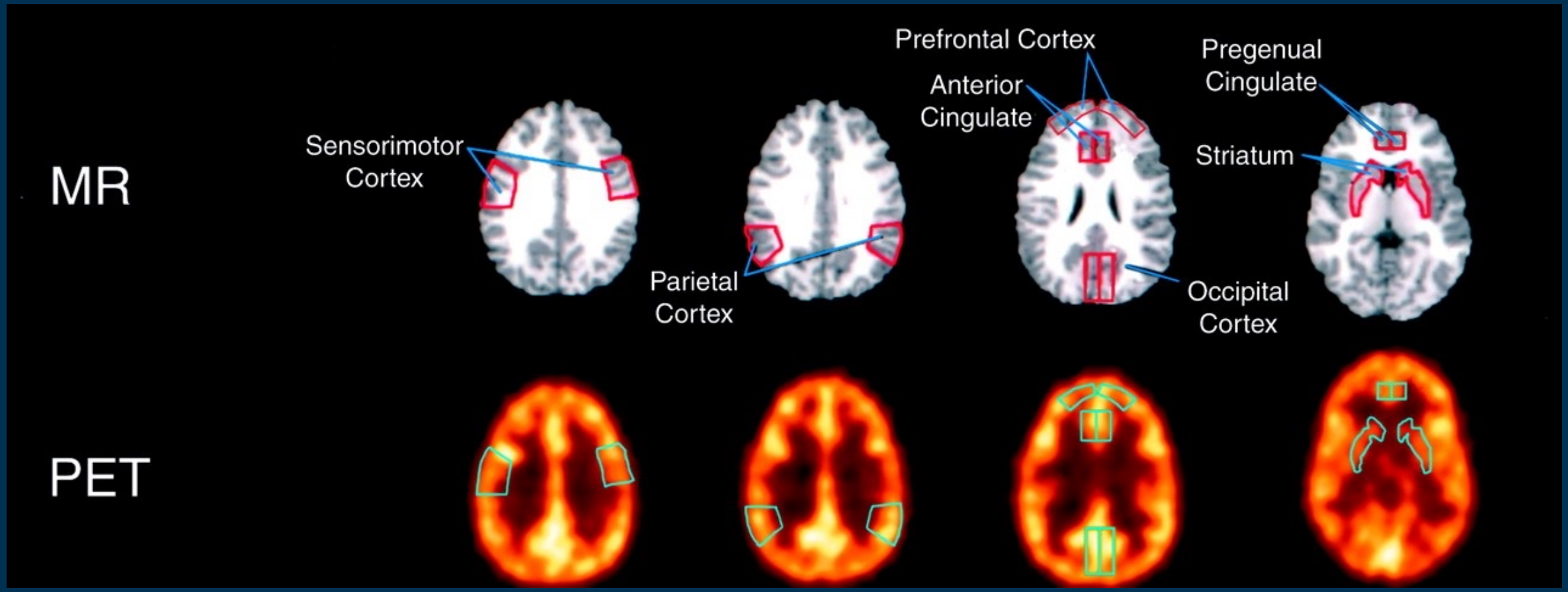
PET-MRI image segmentation in neuroimaging



https://www.fil.ion.ucl.ac.uk/spm/

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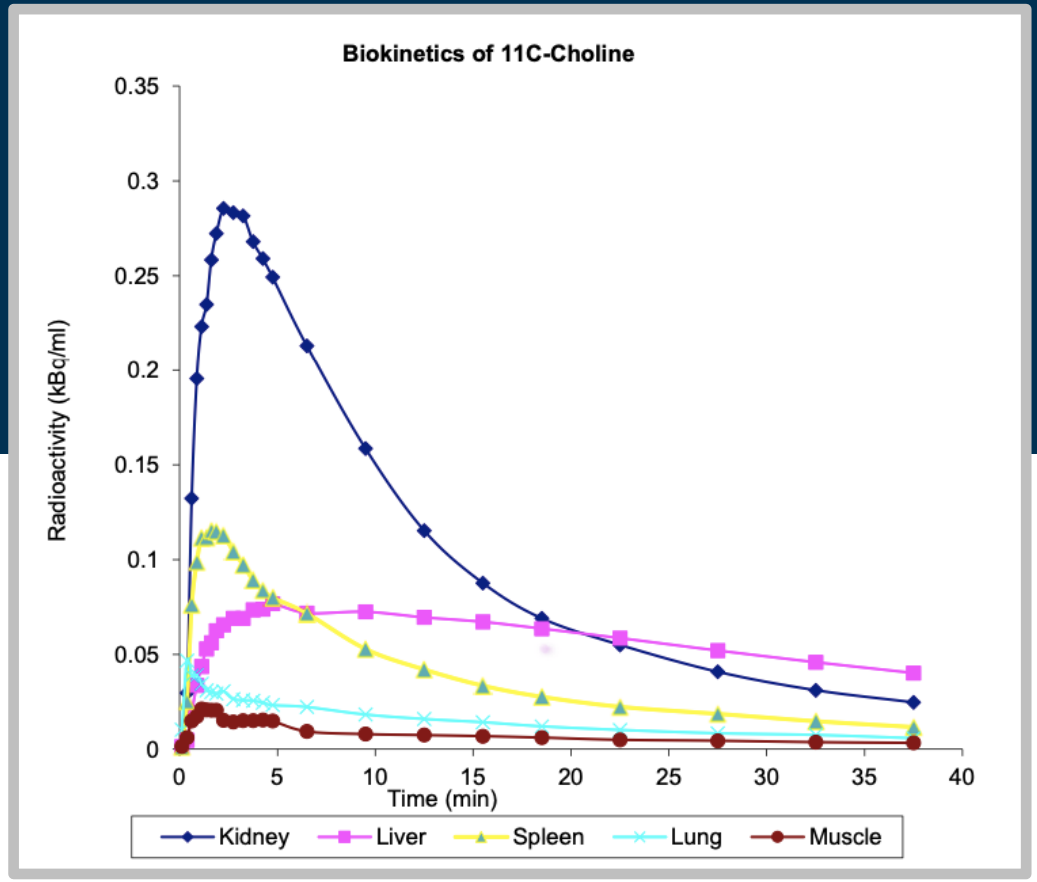
Time Activity Curve (TAC)

- Dynamic PET images form a 3D video over time
- Activity in a PET image for the same region in different time is called Time Activity Curve (TAC)
- The region can be e.g.
  - Segmented tissue or organ
    - A single voxel
- TAC illustrates how the tracer behaves over time
- TACs in different regions have different behaviour



T. Tolvanen: Studies on dosimetry of positron emitting radiopharmaceuticals. Doctoral dissertation, 2023.

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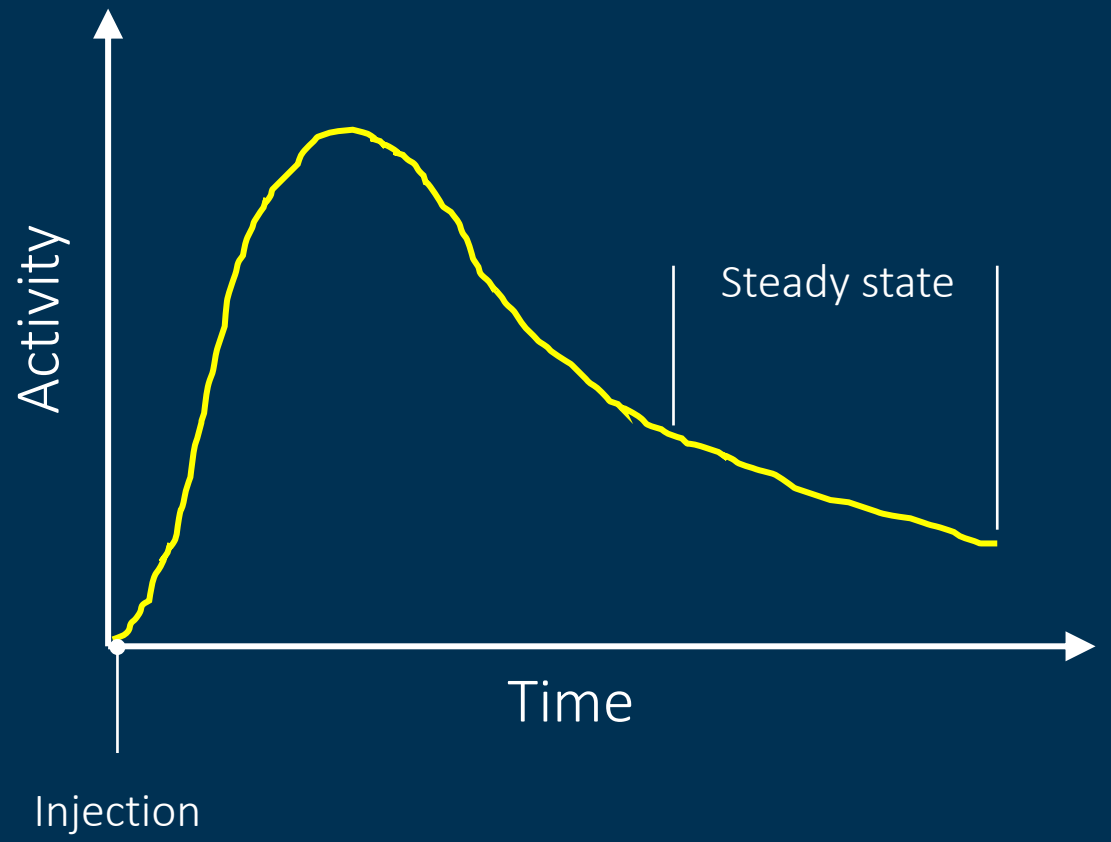
Modelling of tracer kinetics

- Tracer injection and steady state
- Injection time(s) and imaging time
  - Depending on tracer, imaging can be done several minutes after the injection
- Delay: tracer reaches some tissues earlier than others
- Tracer behaviour
  - Reversible uptake
  - Irreversible uptake



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Idea of PET modelling

Tissues are considered as separate compartments assuming

- Uniform concentration in each compartment
- Tracer flow from a compartment is relative to it’s concentration
- Tracer does not change physiology
- Labelling the tracer molecule with a radionuclide does not alter its properties

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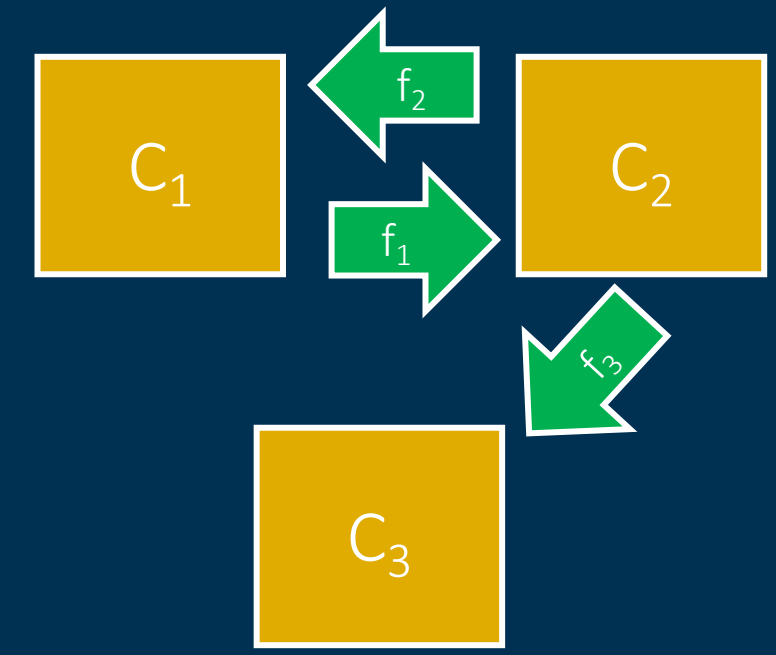
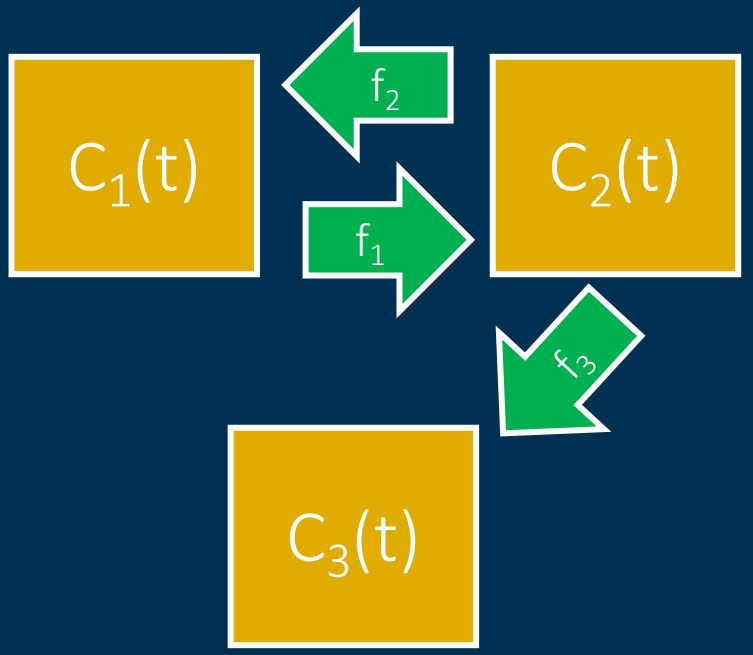
Compartment models

- Compartment is a uniform object with measurable matter (=tracer concentration)
  - Marked typically as a box (C_1 , C_2 , C_3)
- Flow is a constant that determines movement of the matter
  - Marked typically as an arrow (f_1 , f_2 , f_3)
- Idea of compartment model is to model the flow of the matter in time in each C_i



Compartment models, dynamic modelling

- Concentration in a compartment is a function of time [denoted C(t)], and flow is constant [f]
- From a PET image we can define values $C_i(t)$ for each measured timepoint
- We are interested in finding the flow constants f_i
- E.g. change of $C_1(t)$ at time t is $C_2(t)\ f_2$-$C_1(t)\ f_1$ and change of $C_3(t)$ is $C_2(t)\ f_3$



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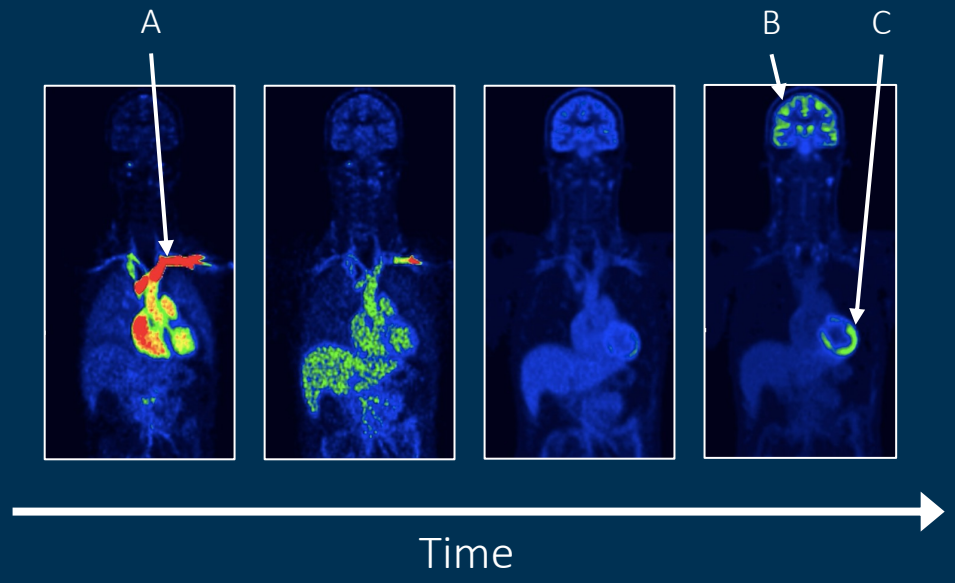
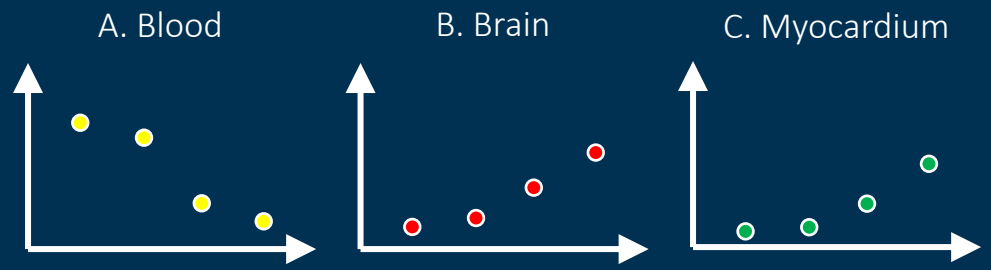
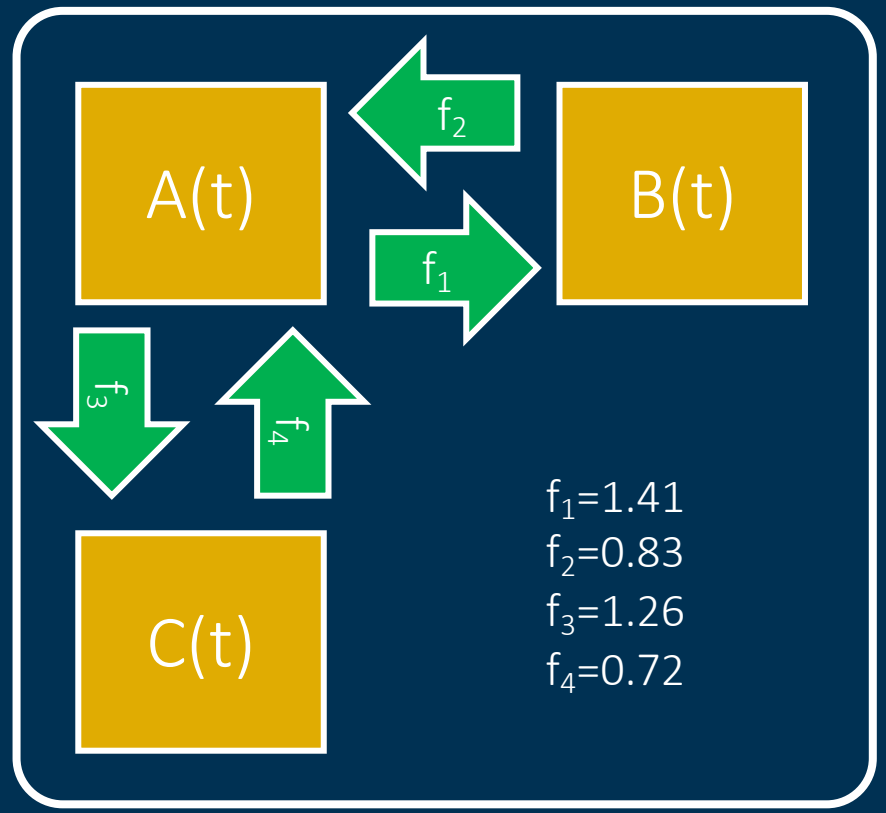
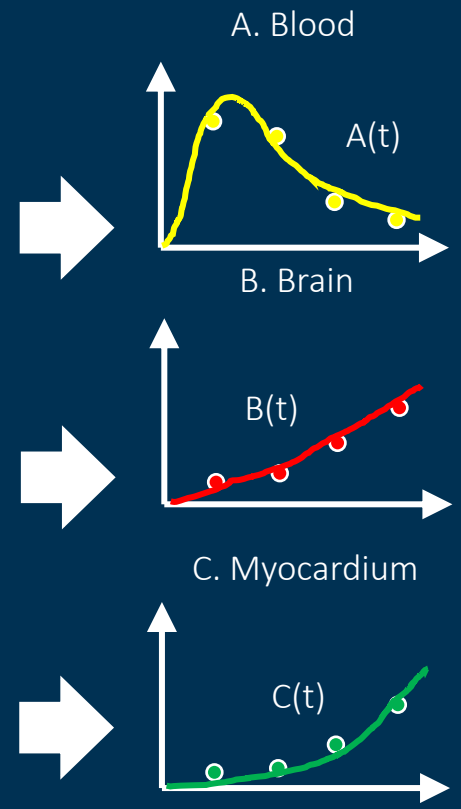
Compartment models, example









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Compartment models, formulas

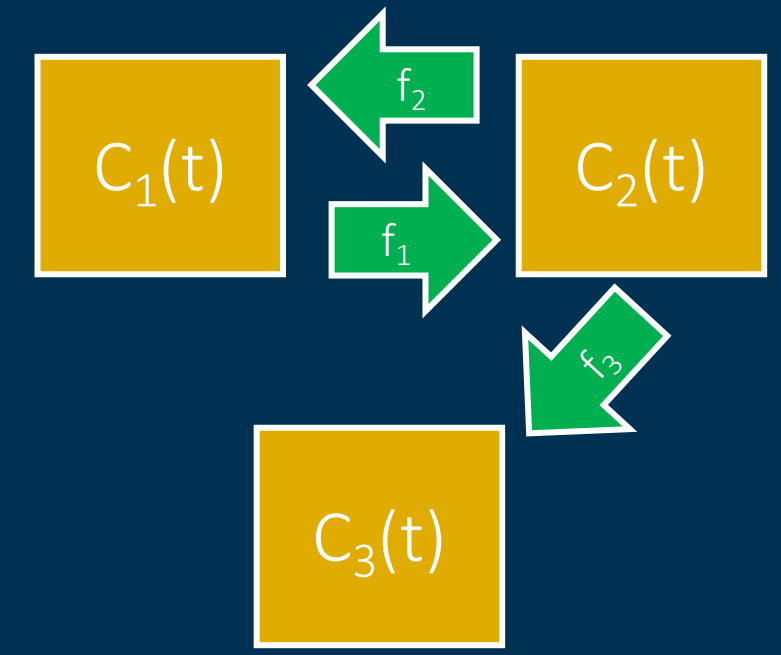
- In mathematical notion the example model becomes a differential equation:

$$\frac{\partial C_1(t)}{\partial t} = C_2(t)f_2 - C_1(t)f_1$$

$$\frac{\partial C_2(t)}{\partial t} = C_1(t)f_1 - C_2\,(t)f_2 - C_2(t)f_3$$

$$\frac{\partial C_3(t)}{\partial t} = C_2(t)f_3$$

- Solving this with the measured $C_i(t)$ values gives the flow constants f_i



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Compartment models in PET imaging

ADD FIG HERE

Typical models in PET have 2 or 3 compartments

- One compartment is blood
- Other compartments for tissues or organs

Thus 1 tissue compartment model

=2 compartment model

and 2 tissue compartment model

=3 compartment model,

Blood in compartment model is called input function.

It can be measured or estimated from image

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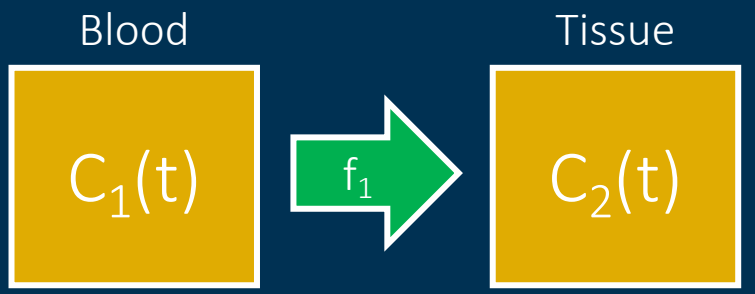
Patlak plot for irreversible uptake

Patlak plot is based on the observation that solution of simple irreversible model satisfies

$$\frac{C_2(t)}{C_1(t)} = A\frac{\int_0^t C_1(s)ds}{C_1(t)} + B$$

In other words, plotting $\frac{C_2(t)}{C_1(t)}$ against $\frac{\int_0^t C_1(s)ds}{C_1(t)}$ gives a line

- Works also for 2 tissue compartment model



1 tissue compartment model

$$\frac{\partial C_2(t)}{\partial t} = C_1(t)f_1$$

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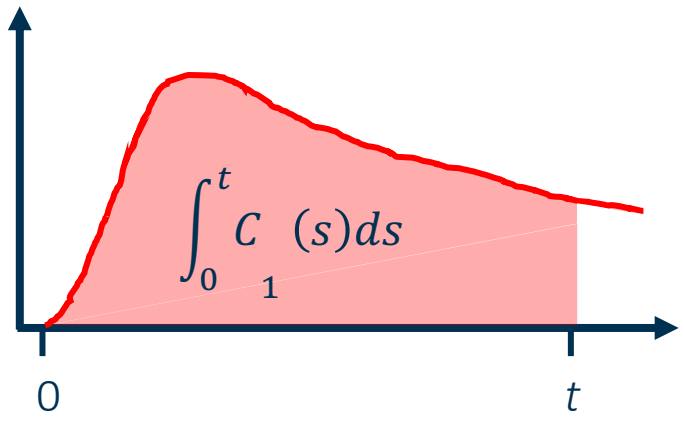
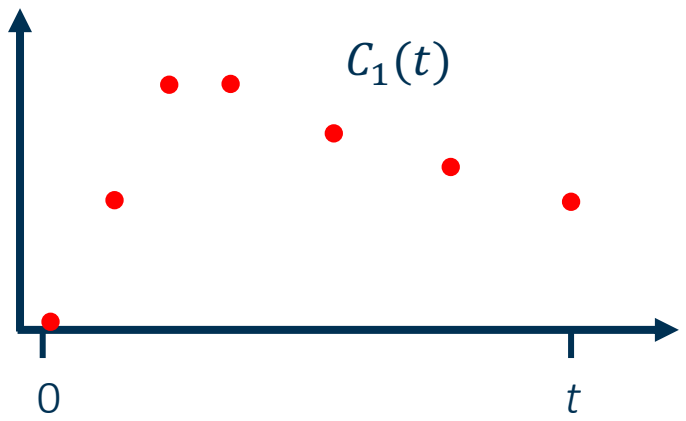
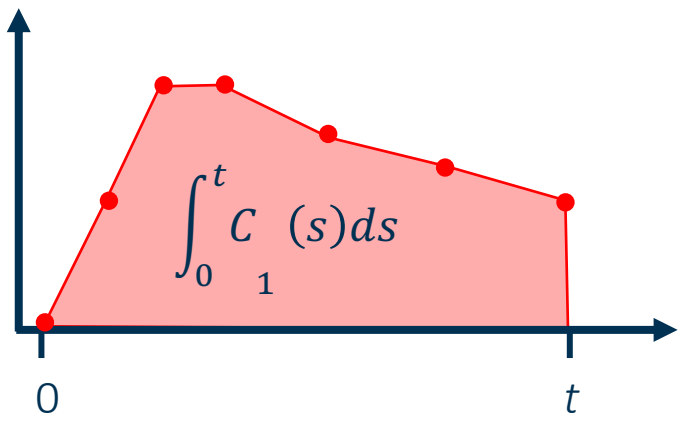
What is $\int_0^t C_1(s)ds$?

- $\int_0^t C_1$ is integral from 0 to t, which means area under the curve
- In practice simple area
  - Only rectangulars and triangles







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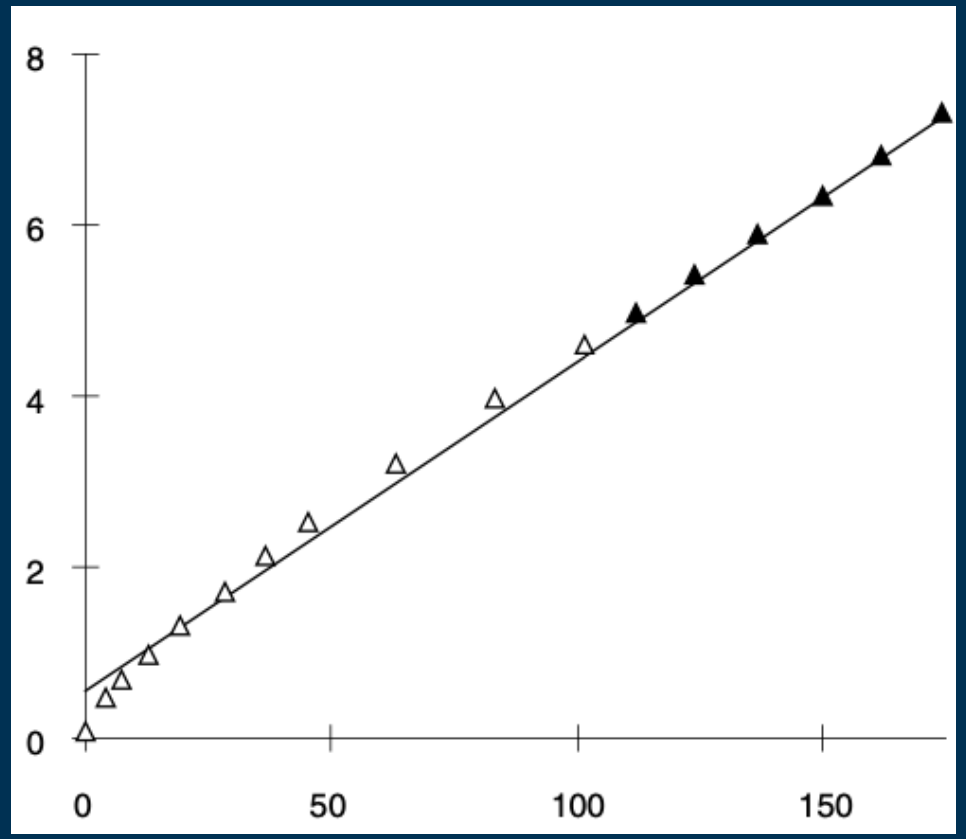
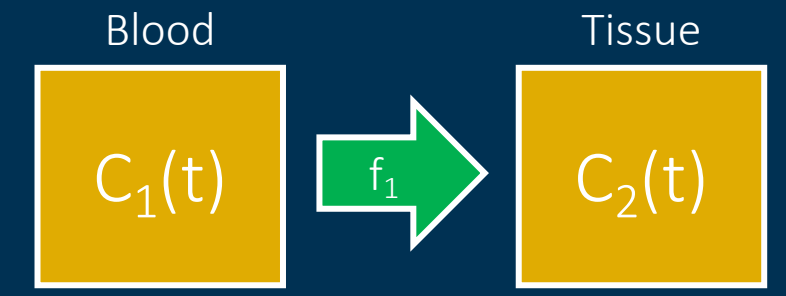
Patlak plot for irreversible uptake

$$\frac{C_2(t)}{C_1(t)}$$



$$\frac{\int_0^t C_1(s)ds}{C_1(t)}$$

K.C. Schmidt, F.E. Turkheimer: Kinetic modeling in positron emission tomography. Q J Nucl Med. 2002 Mar;46(1):70-85.



1 tissue compartment model

$$\frac{\partial C_2(t)}{\partial t} = C_1(t) f_1$$

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Logan plot for reversible uptake

Patlak plot is based on the observation that solution of simple irreversible model satisfies

$$\frac{\int_0^t C_2(s)ds}{C_2(t)} = A\frac{\int_0^t C_1(s)ds}{C_2(t)} + B$$

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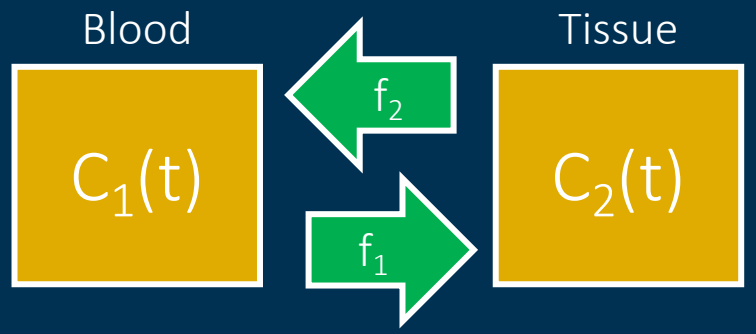

1 tissue compartment model

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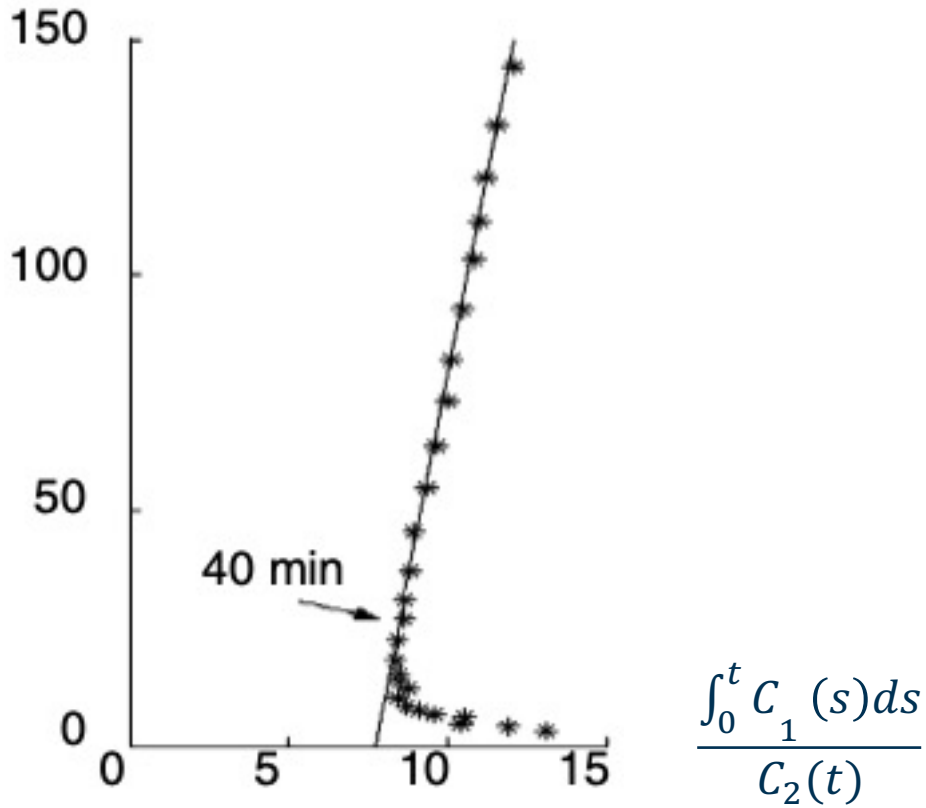
$$\frac{\partial C_2(t)}{\partial t} = C_1(t)f_1 - C_2(t)f_2$$

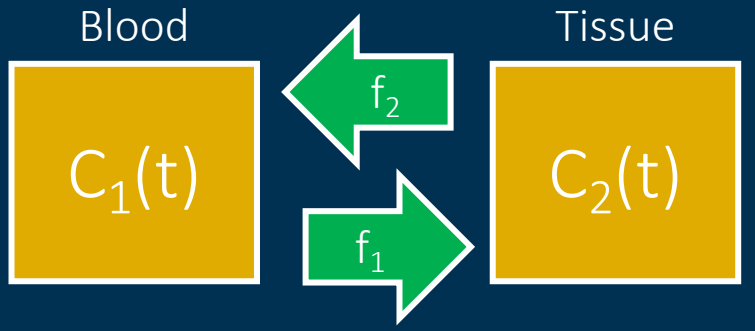
Logan plot for reversible uptake

$$\frac{\int_0^t C_2(s)ds}{C_2(t)}$$



$$\frac{\int_0^t C_1(s)ds}{C_2(t)}$$

K.C. Schmidt, F.E. Turkheimer: Kinetic modeling in positron emission tomography. Q J Nucl Med. 2002 Mar;46(1):70-85.



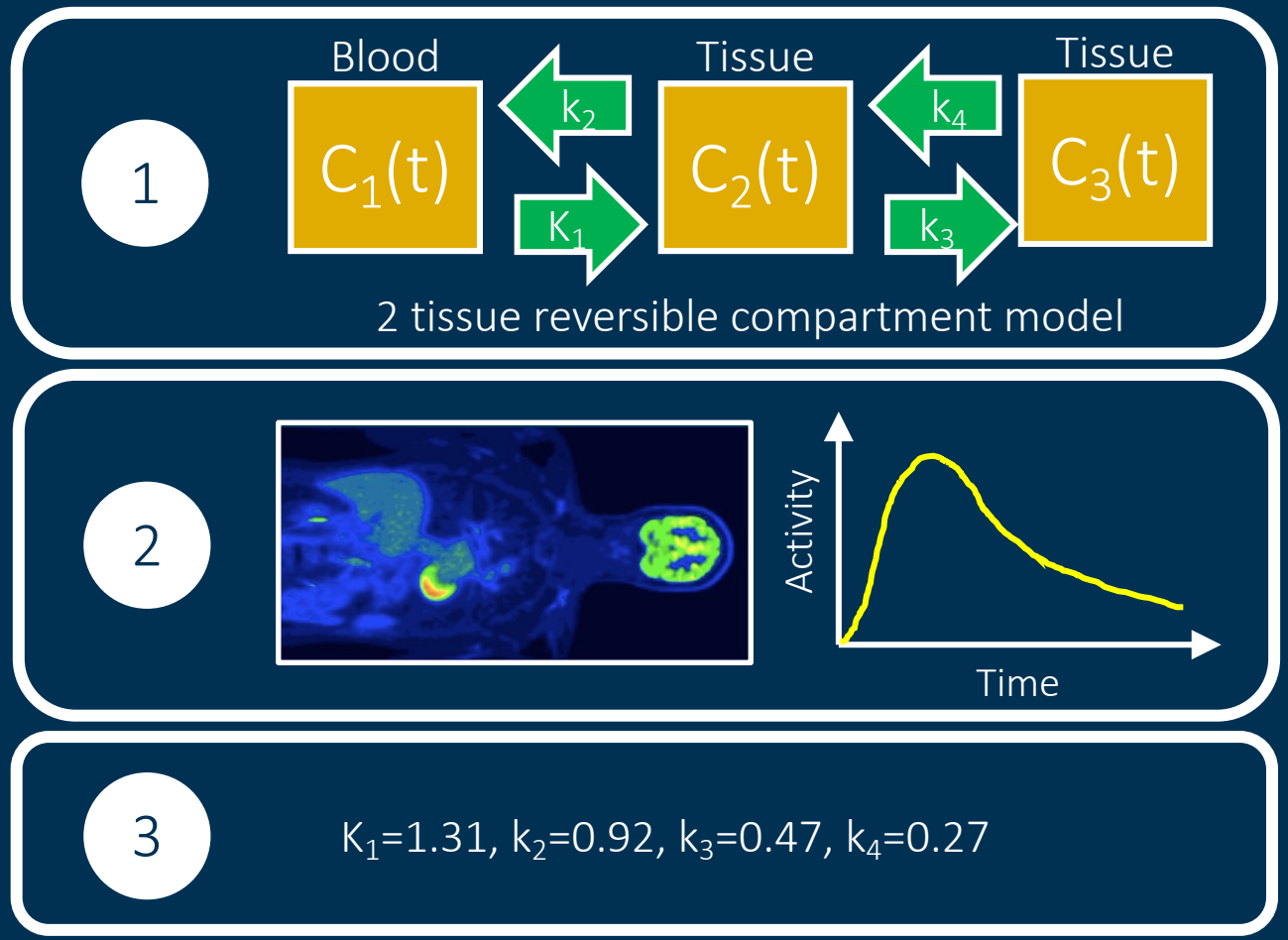
1 tissue compartment model

$$\frac{\partial C_1(t)}{\partial t} = C_2(t)f_2 - C_1(t)f_1$$

$$\frac{\partial C_2(t)}{\partial t} = C_1(t)f_1 - C_2(t)f_2$$

Compartment models in PET

- Step one: define your model
  - Based on literature or experiments
- Step two: obtain data
  - PET scan and image analysis
- Step three: modelling
  - Use software to find coefficients



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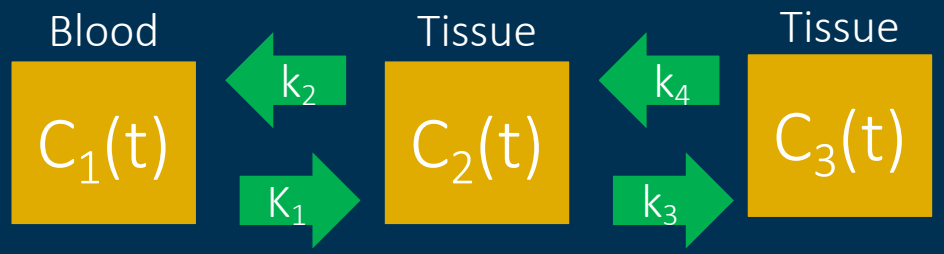
How to interpret modelling results?

- Interpretation depends on the tracer
  - Different tracers are used to image different functions
- For example, FDG accumulates in myocardia and is used to image glucose uptake
  - FDG can be used to measure metabolism
  - Cancer tissue can be located with FDG
- In many applications the most interesting parameter is K_1
  - It represents the transport of the tracer blood compartment to the first tissue compartment
  - Bigger value means faster transport



2 tissue reversible compartment model

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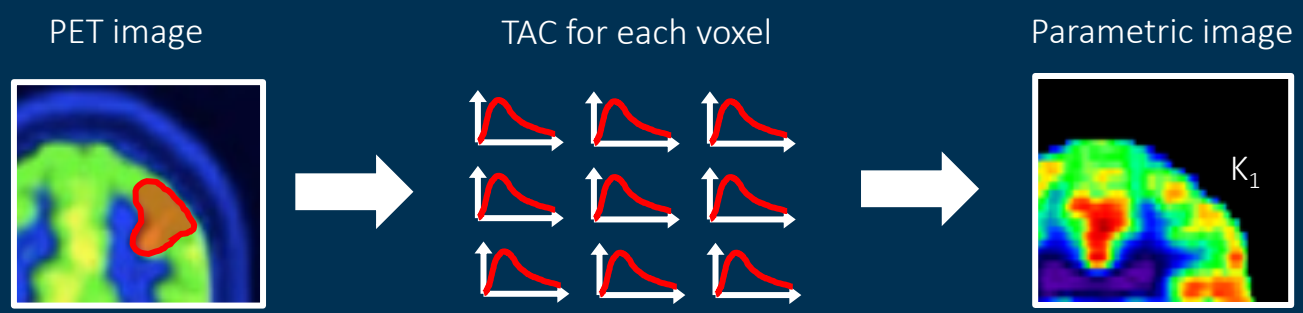
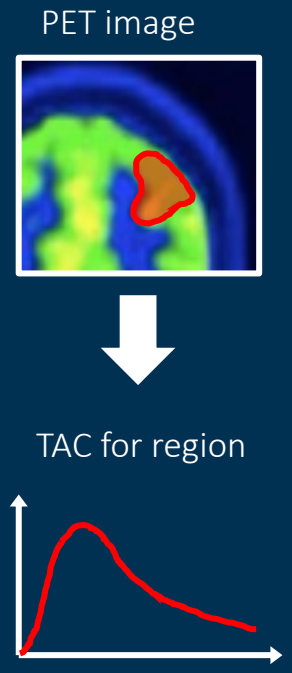
Parametric imaging

- For modelling regions, only one activity value per time point is considered
- Parametric imaging refers to modelling of individual voxels
  - Compartment modelling computationally demanding
  - Typically Logan or Patlak methods are used





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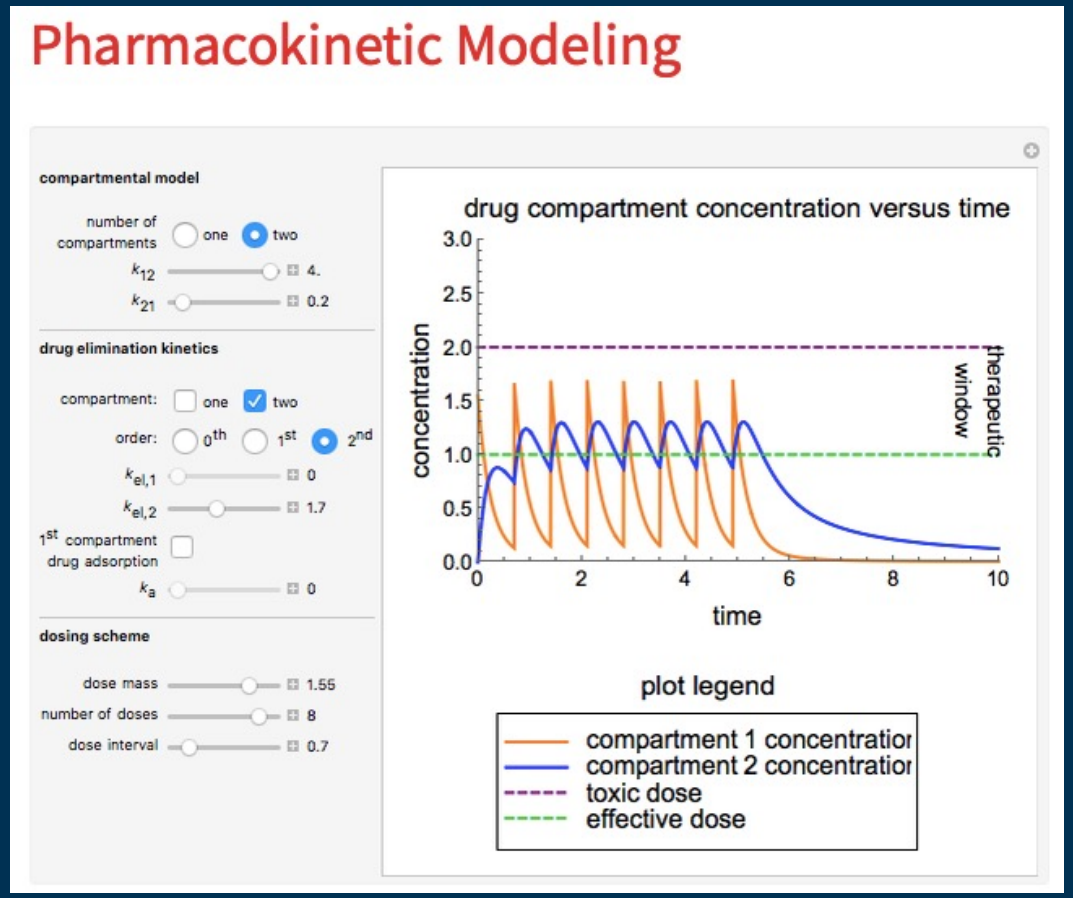
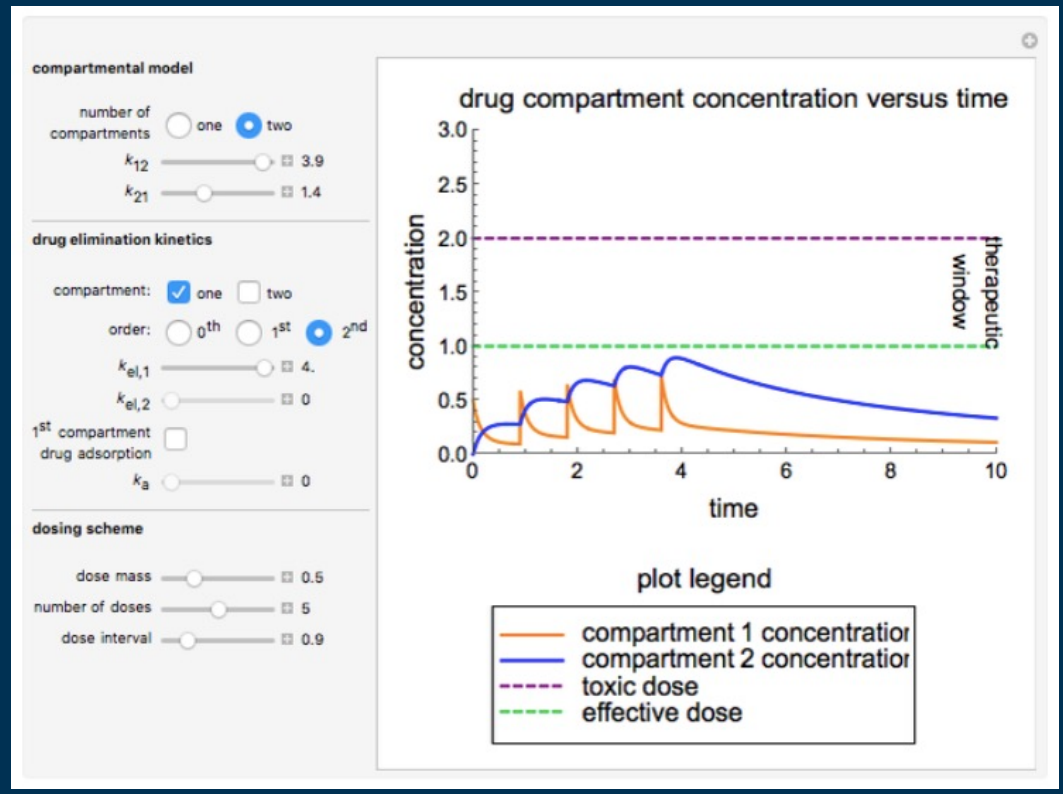
Example MATLAB project compartment models





https://demonstrations.wolfram.com/PharmacokineticModeling/

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What you should have learn

Contents of the talk

- PET imaging
- Image segmentation
- PET modelling
- Interpretation

Key terminology

- Dynamic PET
- TAC
- Compartment model
- Patlak plot
- Logan plot
- Parametric imaging