Determination of glucose metabolism

The Fluorodeoxyglucose ([^{18}F]FDG) method

Pontus Plavén Sigray

NRU PK-course, March 2022

Metabolism

Organisms capable of aerobic respiration metabolize glucose and oxygen to release energy.

Glucose metabolic pathway

- Glycolysis - the oxidation metabolism of glucose molecules to obtain ATP and pyruvate

Glucose Metabolism in the brain: BBB passage

Passive diffusion

Facilitated diffusion

Active transport

Glucose transport by specialized transporters: e.g., GLUT1, GLUT2

Transport of Glucose across the blood-brain barrier is a saturable process of facilitated diffusion

Why do we want to measure glucose metabolism?

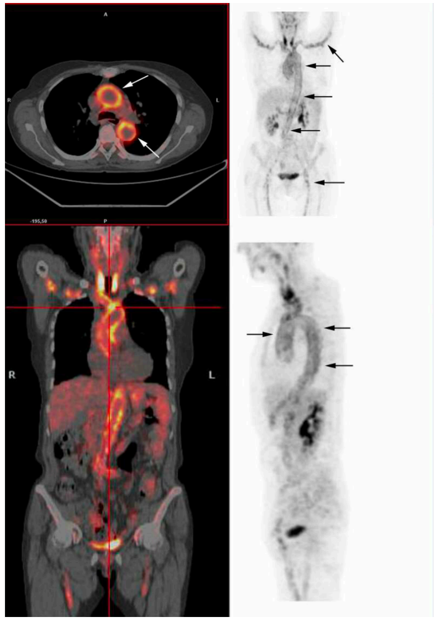
CNS hypometabolism in AD

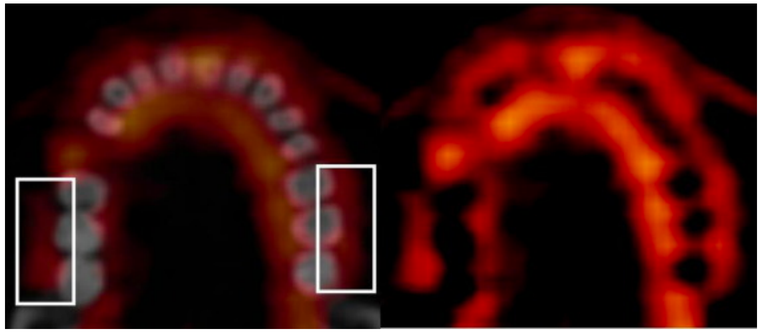
Hypermetabolism in Cancer:
increased glycolysis in tumours
Aka “The Warburg effect”

Why do we want to measure glucose metabolism?

- Tumour assessment/monitoring
- Diagnosis and monitoring of conditions with dysregulated metabolism (e.g., AD)

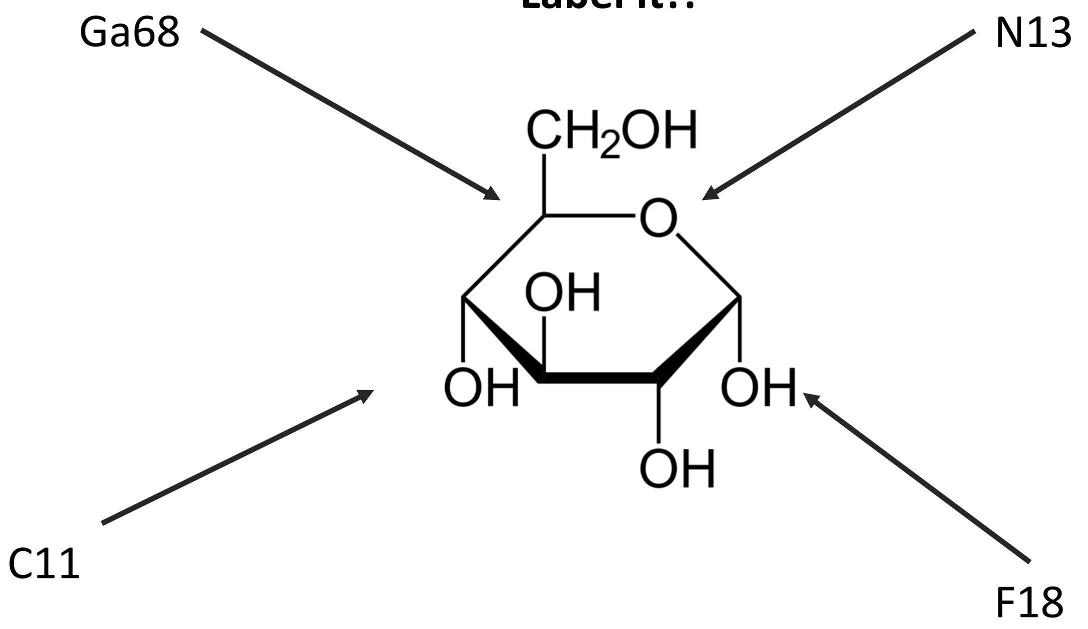
- Inflammation, e.g.
  - Cardiovascular
  - Periodontitis





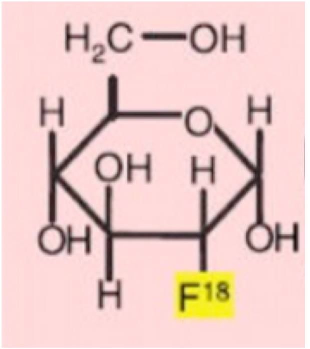
How do we measure glucose metabolism?

Label it!?



How do we measure glucose metabolism?

- Fluorodeoxyglucose (18F) or 2-deoxy-2-[18F]fluoro-D-glucose
- Aka [18F]FDG
- FDG is a glucose analouge

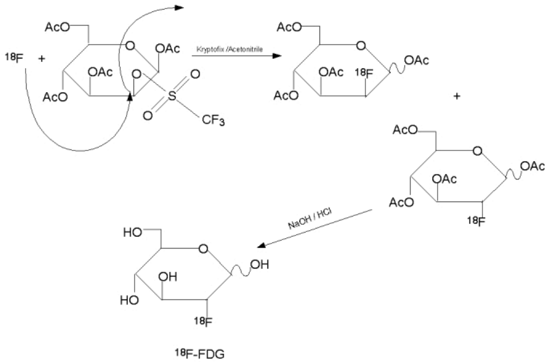


How do we measure glucose metabolism?

Cyclotron

18F

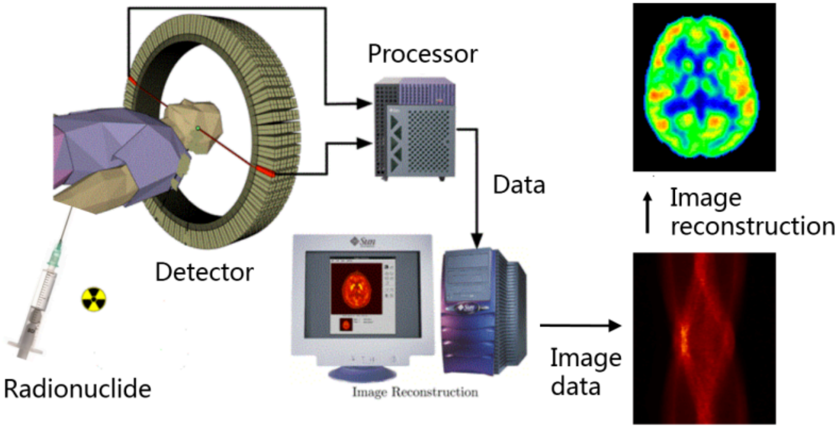
Synthesis



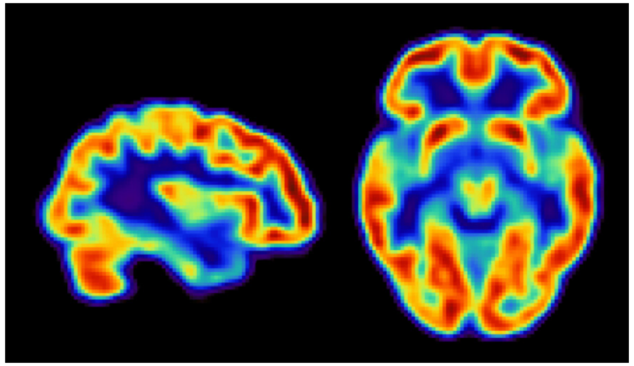
[18F]FDG

PET system

Injection, scanning

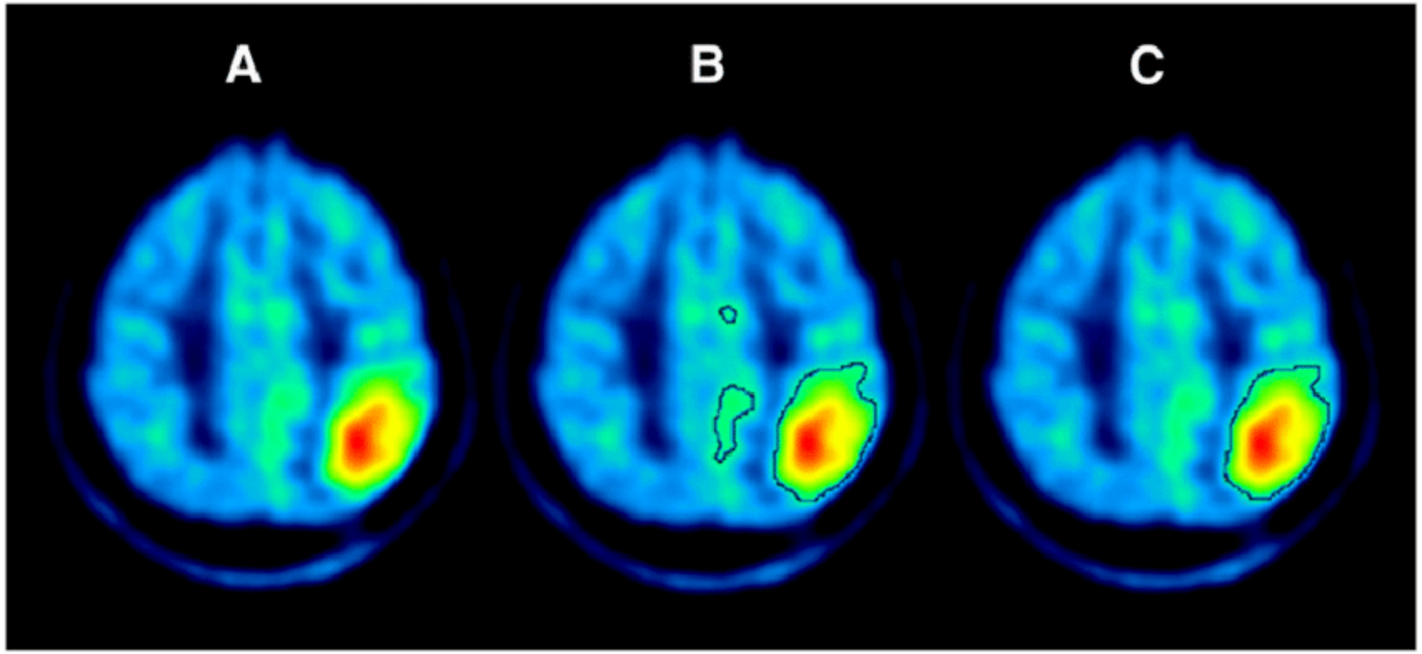


Quantification



How do we measure glucose metabolism?

- Radioactivity in region?



How do we measure glucose metabolism?

- Radioactivity in region?
- Standardized Uptake value?

$$\frac{Radioactivty\ in\ region}{\quad}$$

How do we measure glucose metabolism?

- Radioactivity in region?
- Standardized Uptake value?

$$SUV = \frac{Radioactivty\ in\ region}{injected\ radioactivty/bodyweight}$$

- Full quantification: directly account for how much radioligand is “presented” to the brain

How do we measure glucose metabolism?

- Fluorodeoxyglucose (18F) or 2-deoxy-2-[18F]fluoro-D-glucose
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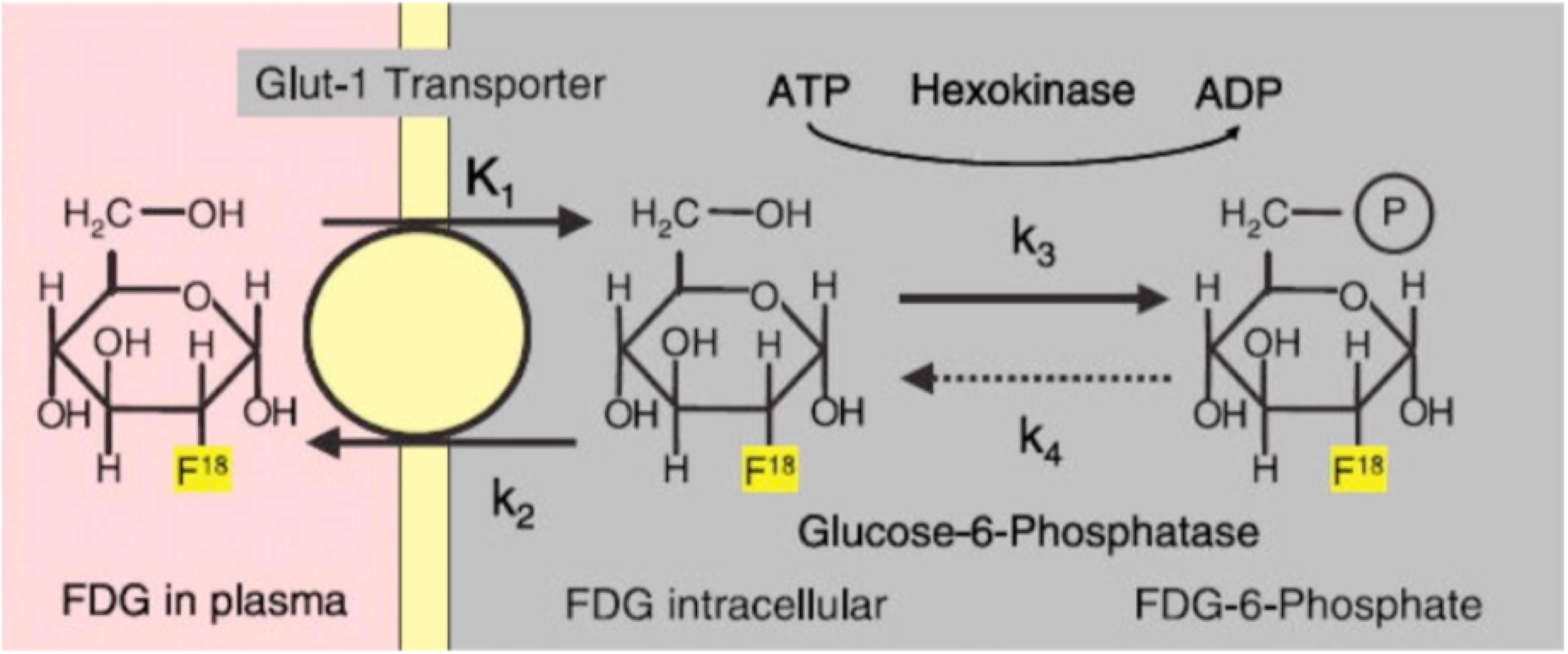
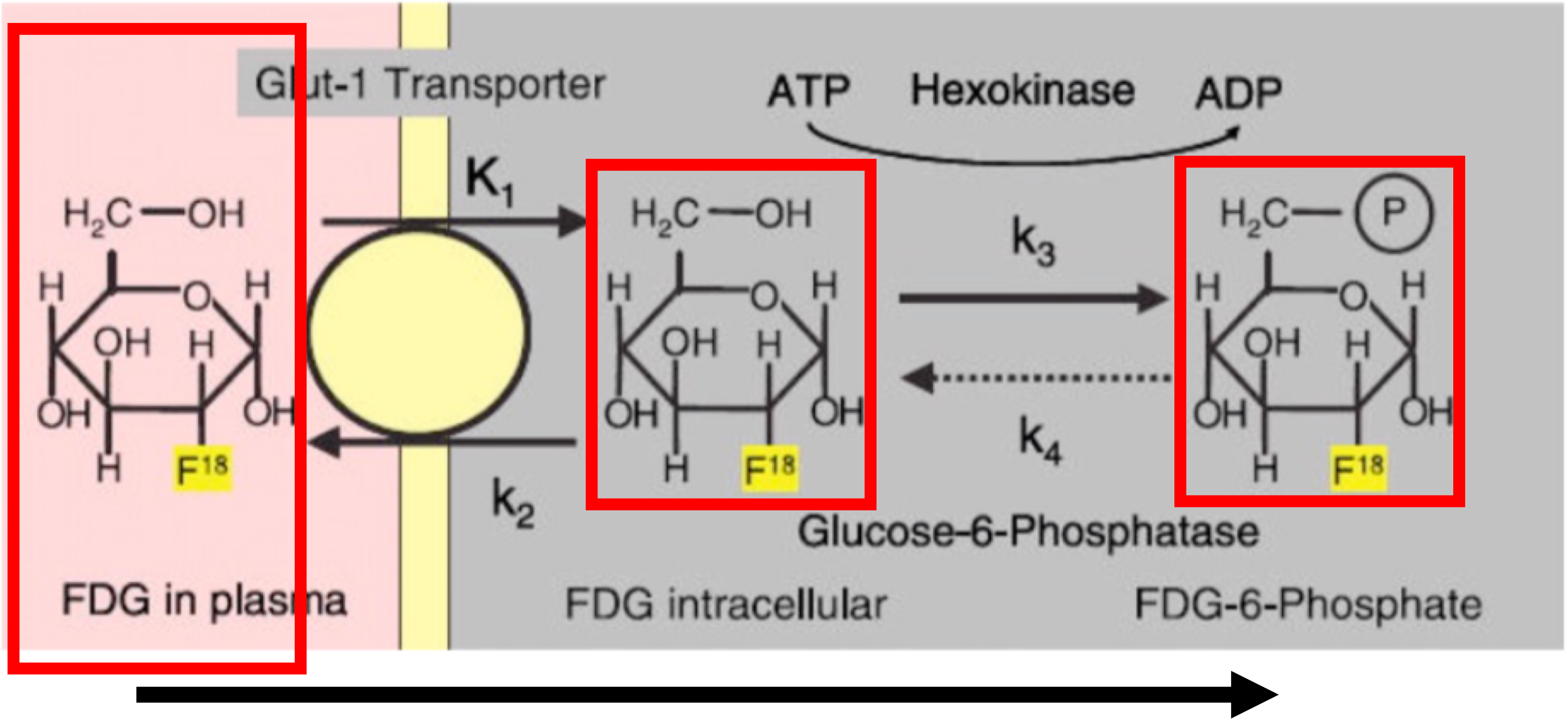
- FDG is a <u>glucose analouge</u>



What does this look similar to?

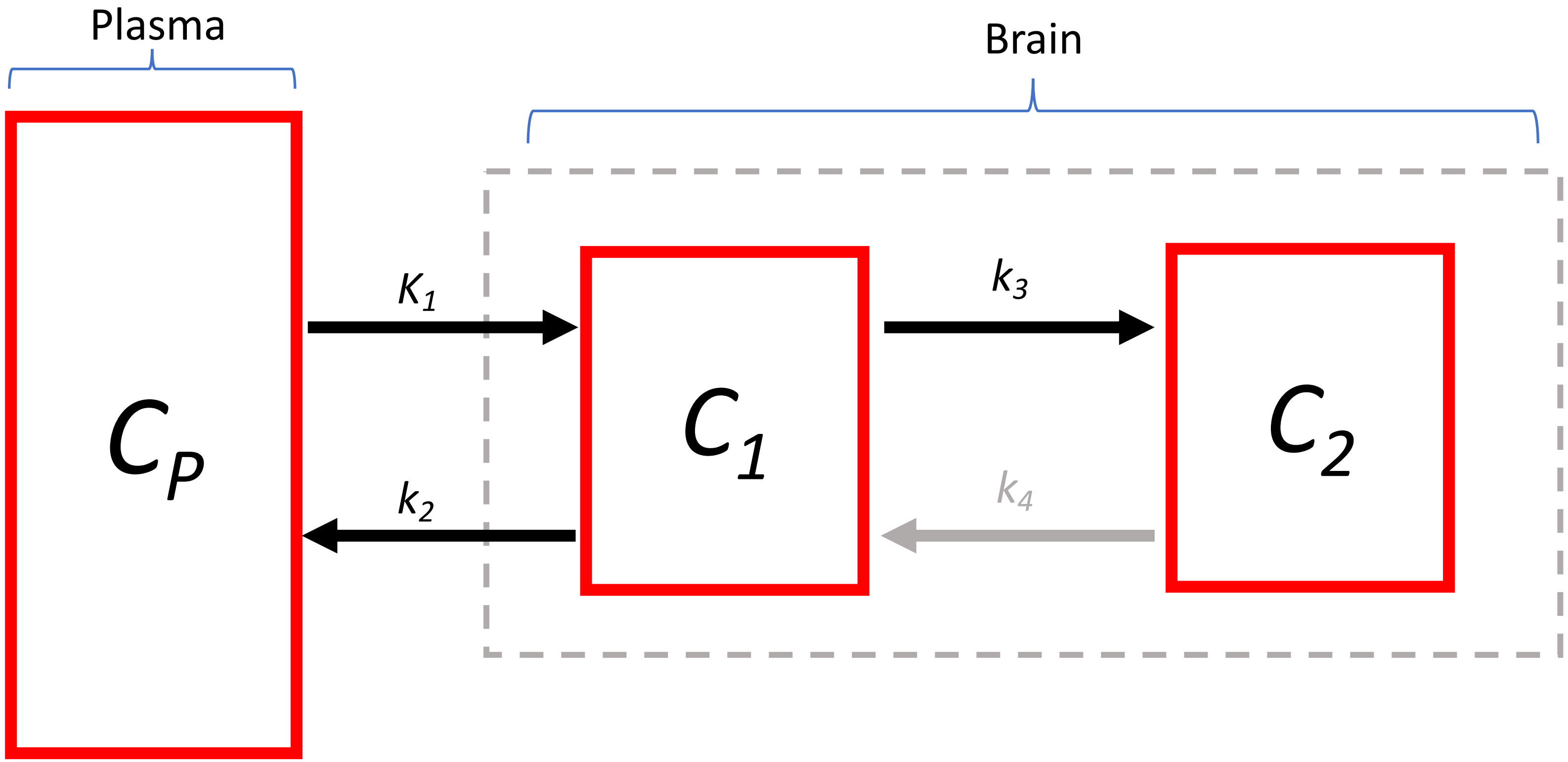
How do we measure glucose metabolism?

- Two-tissue compartment model!
- Aka the “2TCM”

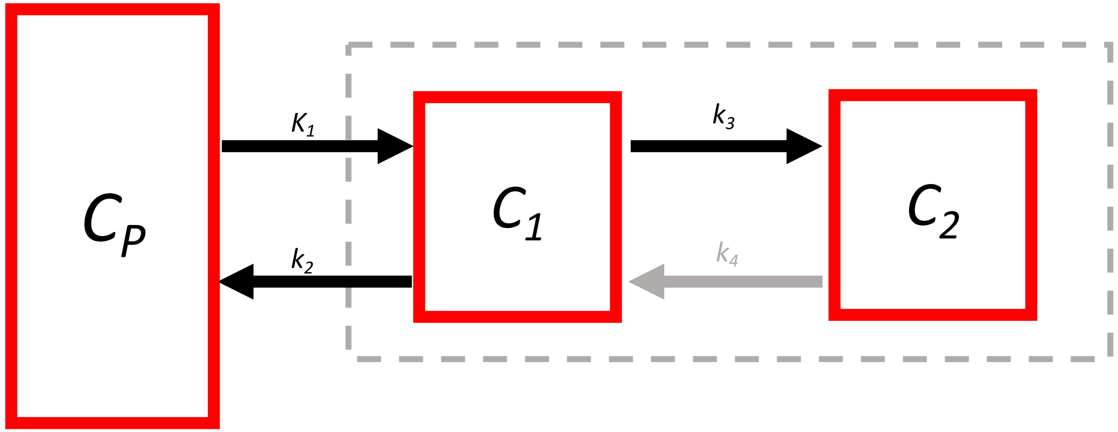


Metabolic rate for FDG (Plasma glucose * rate-constant)

Two-tissue compartment model



Two-tissue compartment model



$$PET(t) = C_1(t) + C_2(t)$$

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

Oxidative phosphorylation-> “trapping” -> irreversible tracer

Reversible v.s. Irreversible radioligands

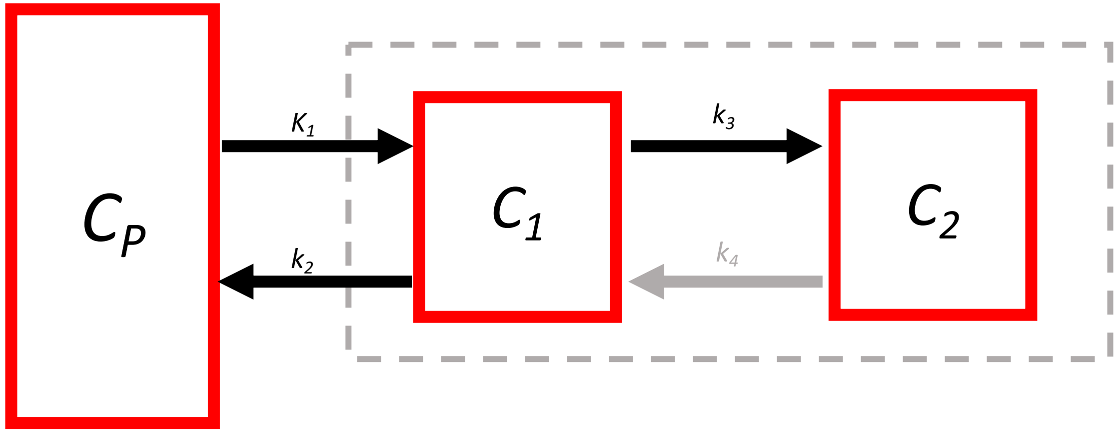
Reversible (e.g. [11C]raclopride):

- Equilibrate rapidly - enables relatively short scan durations
- Often better for suited [11C] labeled radiotracers
- May often be used with single tissue compartment models
- Linearization (Logan), equilibrium, or reference tissue methods all often easily used

Irreversible (e.g. [18F]FDG):

- Dissociate very slowly ($k4 \rightarrow 0$): may require long scan durations
- Often better suited for [18F] labeled radiotracers
- Must be used with 2-tissue compartment models
- Sometimes linearization (Patlak) or reference tissue methods possible

Two-tissue compartment model



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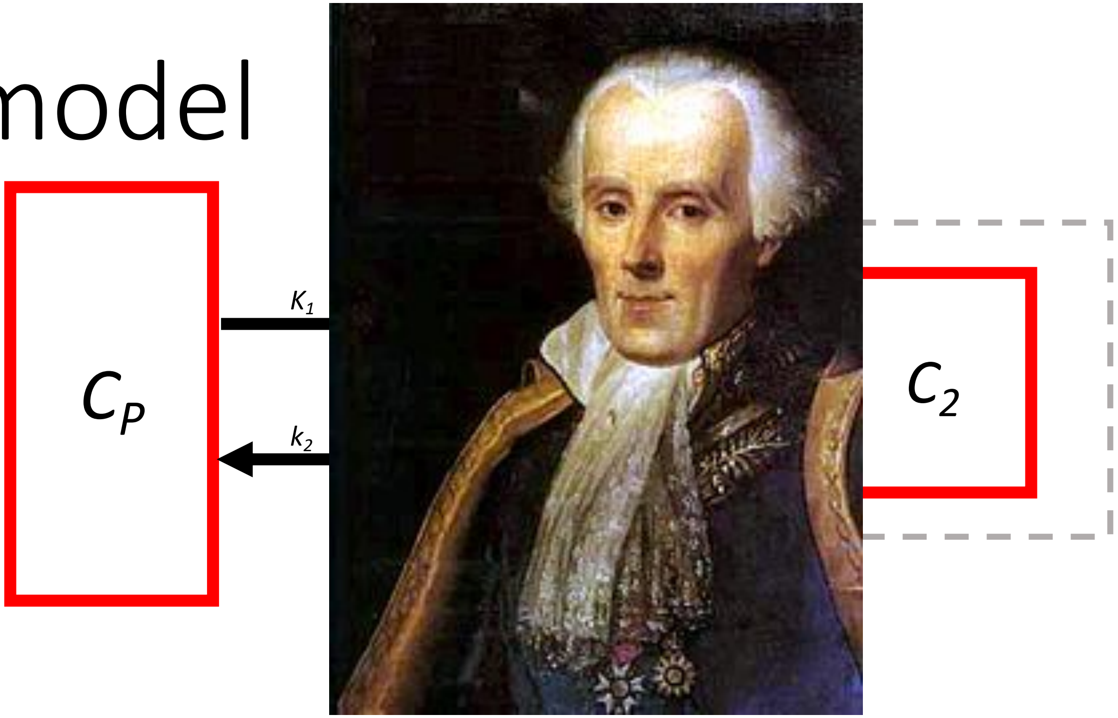
????

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

Two-tissue compartment model



$$PET(t) = C_1(t) + C_2(t)$$

????

$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

Impulse Response Function ***Input function***

$$PET(t) = \left(\frac{K_1 k_2}{k_2 + k_3} e^{-(k_2 + k_3)t} + \frac{K_1 k_3}{k_2 + k_3} \right) \otimes C_P(t)$$

Fitting FDG time-activity curves

- Try out different values for K1, k2 and k3 until a good fit has been obtained

$$PET(t) = \left(\frac{K_1 k_2}{k_2 + k_3} e^{-(k_2+k_3)t} + \frac{K_1 k_3}{k_2 + k_3} \right) \otimes C_P(t)$$

Parameter of interest!

K_I

What is K_I?

- Try out different values for K1, k2 and k3 until a good fit has been obtained

$$PET(t) = \left(\frac{K_1 k_2}{k_2 + k_3} e^{-(k_2 + k_3)t} + \frac{K_1 k_3}{k_2 + k_3} \right) \otimes C_P(t)$$

Parameter of interest!

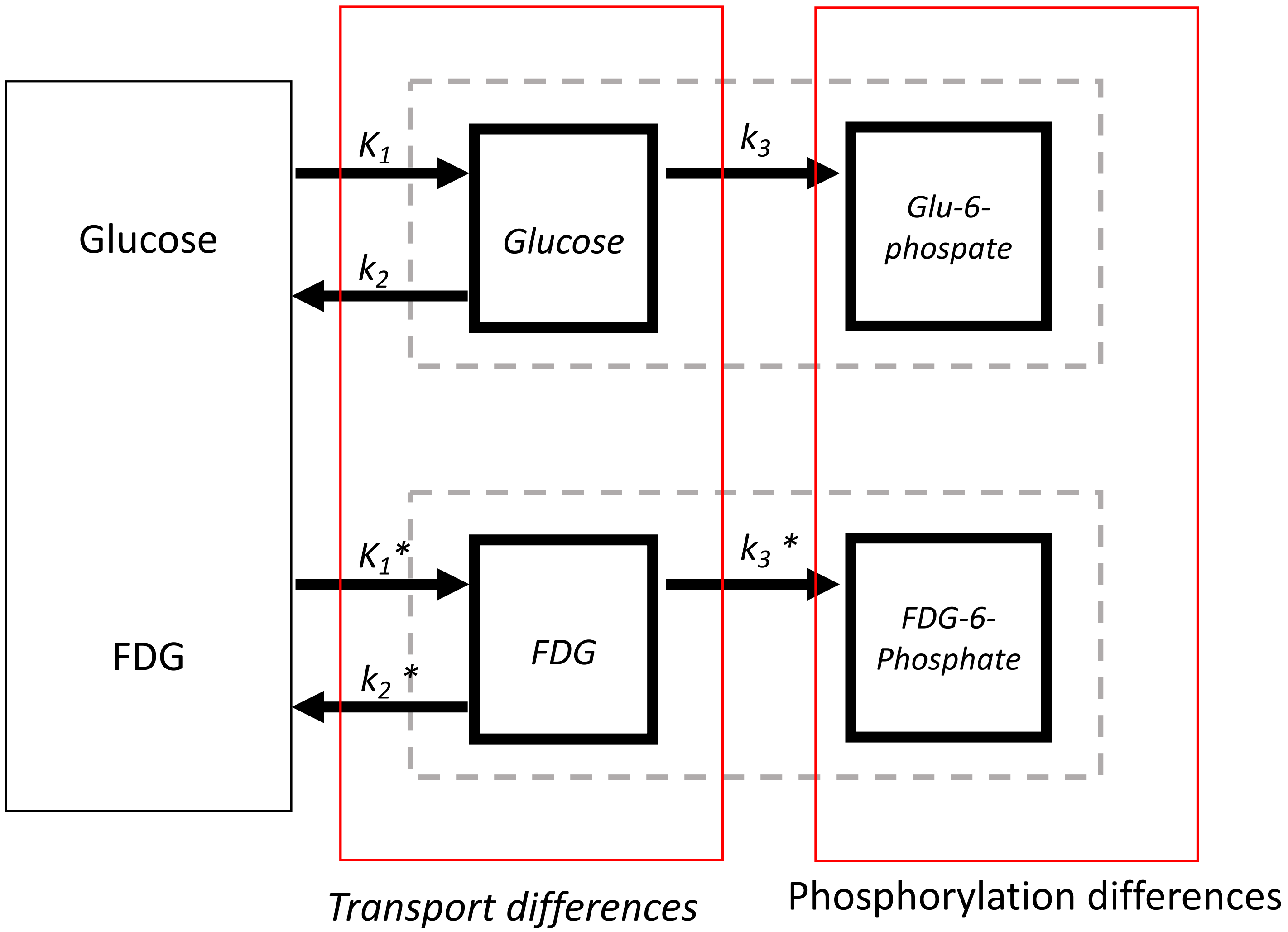
K_I **Metabolic rate constant** or “Influx rate” of FDG

$$Met\ FDG = \boxed{C_P^{GLU}} * K_I$$

Glucose metabolism?

- We have estimated the metabolic rate of FDG
- This is not the same as the metabolic rate of glucose
- We need to make a few corrections…

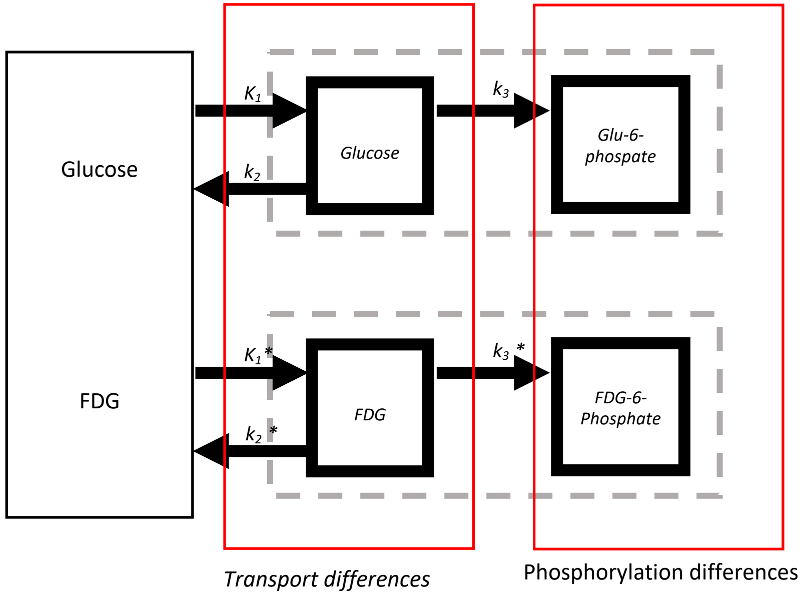
Lumping the corrections together



Glucose Metabolism

$$MR_{Glu} = \frac{C_P^{Glu}}{LC} \quad K_I^{FDG}$$

Lumping the corrections together



$$MR_{Glu} = \frac{C_P^{Glu}}{LC} K_I^{FDG}$$

LC ≈ 0.6

In summary

- Glucose metab is a fundamental biological process in breathing organisms
- Facilitated transportation into the brain is a saturable process
- Critical for diagnosing and monitoring medical conditions
- Radiolabel and inject an glucose analogue: FDG
- Measure uptake in the organ via the PET system
- SUV or full quantification?
  - Two-tissue-compartment model: K_I
  - Met Glucose = $K_I * C_P^{GLU}$ / LC