7: Two compartment modeling

1. What is compartmental modeling ?
2. How can tracer kinetics be mathematically described ?
3. How do 2-deoxyglucose methods trace glucose metabolism ?

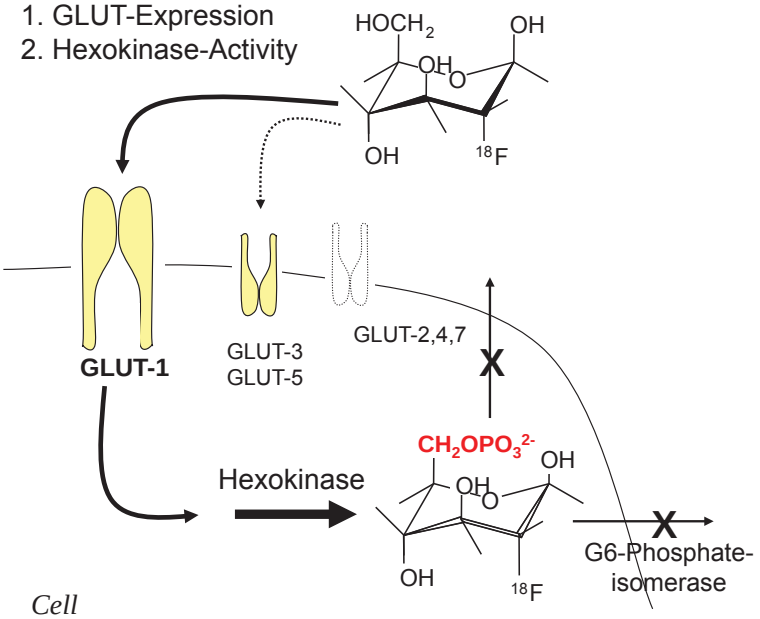
After this course you

1. Understand how mass conservation can be used to model tracer kinetics and estimate metabolic rates
2. Understand the mathematical principle underlying metabolic modeling of imaging data
3. Can apply the principle of modeling tracer uptake to simple kinetic situations
4. Understand the basics of modeling deoxyglucose uptake into tissue to extract metabolic rates

How is intracellular glucose metabolism measured ?

[^{18}F]FDG (2-[^{18}F]Fluoro-2-Deoxy-Glucose)

FDG uptake depends on:
1. GLUT-Expression
2. Hexokinase-Activity



Cell

7-1. What is a compartment model ?

tracers

Definition: Compartment

Concept: Physiological system - decomposed into N interacting subsystems

Subsystem = chemical species in a physical place (**compartment**)

NB. Tracer is considered to be distributed uniformly in compartment

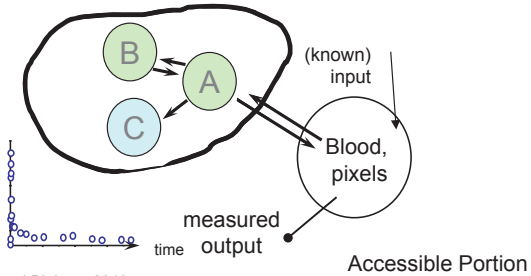
Key elements of compartmental modeling

1. Predict inaccessible features of system
2. Measurement in the accessible portion
3. Estimation of specific *parameters of interest*.

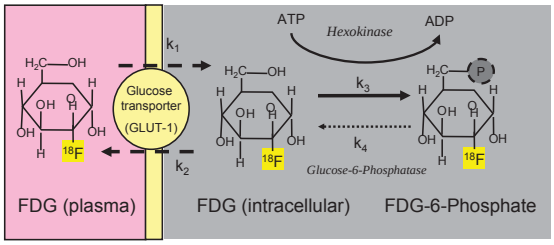
Steady-state assumption:

1. metabolic rate of process is not changing with time
2. concentrations are constant during the evaluation period.

Inaccessible portion



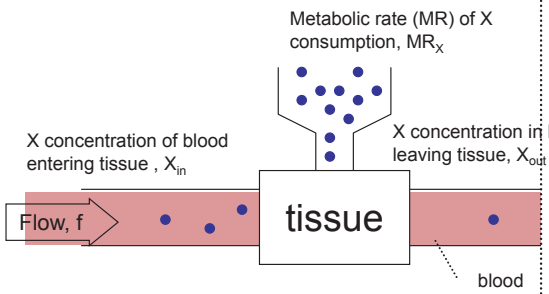
processes can be described with pseudo-first-order rate constants.



How does conservation of mass allow rate determination ?

Fick's principle

Fick Principle (steady state conditions)



$MR_X = f \times \{[X]_{in} - [X]_{out}\}$

X = O_2, glucose, ammonia, water

Brain physiology: O_2 consumption increases less than Flow

Q: What is the consequence?

$$[O_2]\text{ entering} - [O_2]\text{ leaving} = \frac{\text{rate of } O_2 \text{ consumption}}{\text{Flow}}$$

Definition Tracer

- radio-activity emitting, labelled molecule
- structurally related to the natural substance (*tracee*) or involved in the dynamic process

See earlier examples, but also O_2 (left)

introduced in a trace amount (=orders of magnitude below tracee); process being measured is not perturbed by it.

few tracer molecules contain radioactive isotope; others contain "cold" isotope

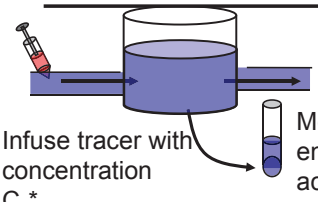
Specific activity (SA) = "hot" / "cold" tracer molecules

SA is always measured; [MBq/µmol or mCi/µmol]

→ convert measured radioactivity concentrations in tissue and blood to mass (correct for physical decay)

7-2. What are first-order tracer kinetics ?

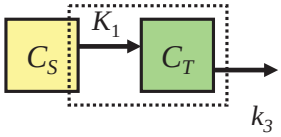
One-tissue compartment model



Infuse tracer with concentration C_s*

Measure tracer enrichment/specific activity C_T*

Unidirectional chemical reaction S → T:



First-order process S->T

Reaction velocity *V* [µmol/g/min] : k≡V/C

$$V = \frac{dC_T(t)}{dt} = K_1 C_S(t) - k_3 C_T(t)$$

K_1, k_3 - (pseudo) first-order rate **constants**;

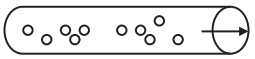
⇒ independent of concentration and time;
unit: [sec^{-1} or min^{-1}]

The rate of labeled molecules entering C_T

dC_T*/dt = Metabolic flux V x probability of precursor C_S labeled

$$\frac{dC_T^*(t)}{dt} = V\frac{C_S^*}{C_S} = K_1 C_S^*(t)$$

How many labeled (red) molecules/per min ? (Assume the rate is V=10/min)



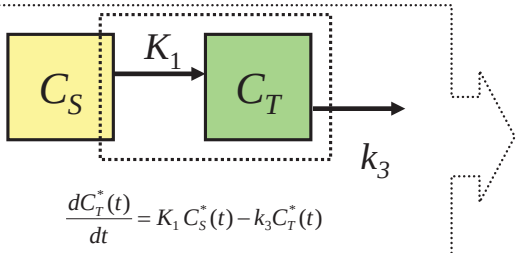
$$\frac{dC_T^*(t)}{dt} = ?$$

Need to add efflux from C_T:

k_3: Metabolic efflux V x probability of molecule C_T being labeled

$$\frac{dC_T^*(t)}{dt} = K_1 C_S^*(t) - k_3 C_T^*(t)$$

What describes the one-tissue compartment model ?



Linear first-order ordinary differential equations (ODEs):

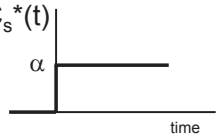
→ Laplace transformation

$$C^*_T(t) = K_1 C^*_S(t) \otimes e^{-k_3 t}$$

$$a(t) \otimes b(t) = \int_0^t a(\tau) b(t-\tau) d\tau$$

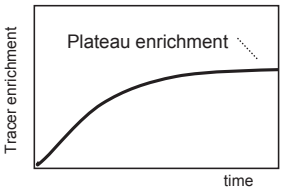
Example:
C_s* increased from 0 to α at t=0

$$\frac{dC_T^*(t)}{dt} = k_1 \alpha - k_3 C_T^*(t)$$

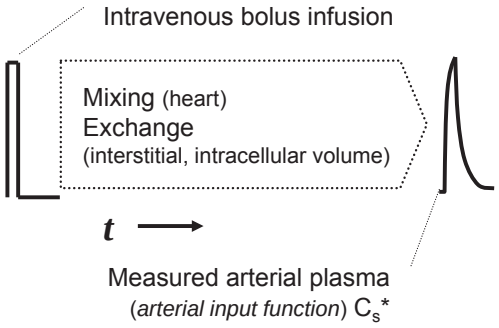


$$C_T^*(t) = \frac{k_1 \alpha}{k_3}\left(1 - e^{-k_3 t}\right)$$

C_T*(0)=0

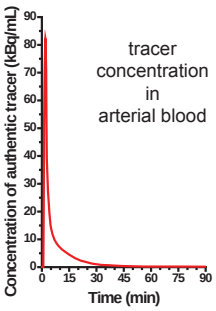


What is the input function ?



Tracer: injected intravenously (as a bolus, i.e. Short time period)

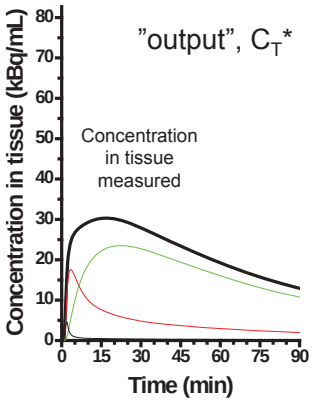
1. well mixed with blood (heart)
2. distributed to capillary bed→ exchange with tissue
3. Tracer concentration in tissue increases by extraction of tracer from plasma
4. Concentration in tissue is reduced by backward transfer



tracer concentration in arterial blood

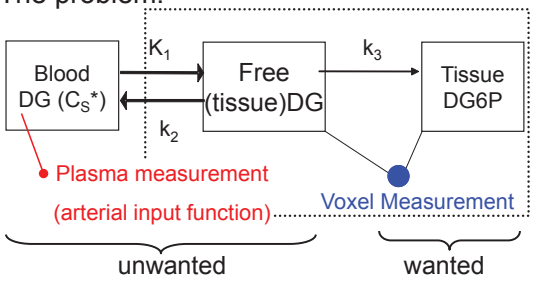
Uptake into tissue, e.g.
Perfusion
Endothelial permeability
Vascular volume fraction
Transport across cell membranes

Specific binding to receptors
Non-specific binding
Enzyme activity



7-3. How does Deoxyglucose (DG) measure glucose metabolism ?
(autoradiography, FDG PET)

The problem:

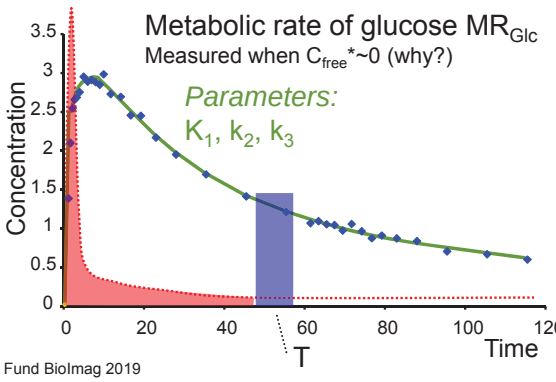


$$\frac{dC^*_{free}(t)}{dt} = K_1 C^*_S(t) - (k_2 + k_3) C^*_{free}(t)$$

$$\frac{dC^*_T(t)}{dt} = k_3 C^*_{free}(t) \qquad C^*_T(T) = k_3 \int_0^T C^*_{free}(t)dt$$

Rapid glucose transport : C_S*(t)≅C_{free}*(t)

$MR_{Glc} \propto k_3$ $\quad k_3 = \dfrac{C^*_T(T)}{\int_0^T C^*_S(t)dt}$



Metabolic rate of glucose MR_{Glc}
Measured when C_{free}*~0 (why?)

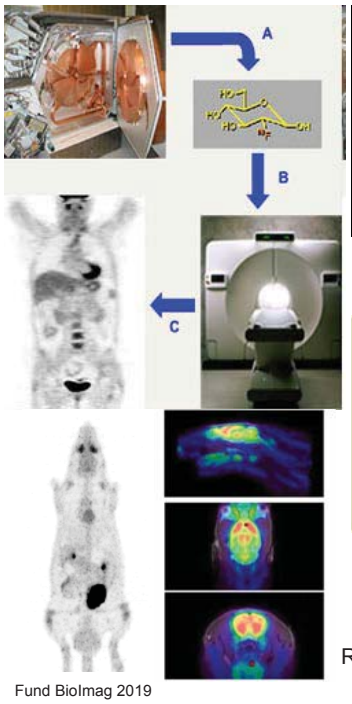
Parameters:
K_1, k_2, k_3

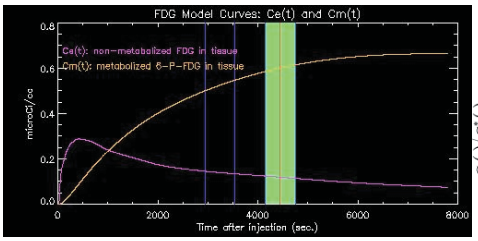
$$MR_{Glc} = \frac{C_S}{LC} \frac{C^*_T(T)}{\int_0^T C^*_S(t)dt}$$

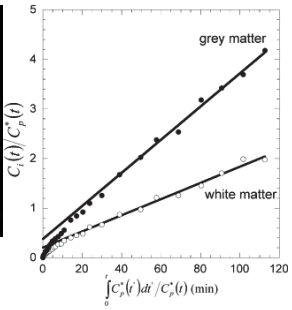
Lumped constant (LC): differences between glucose and DG
(affinities for transporters and hexokinase)
C_S: blood glucose concentration

Unit of MR_{glc}: $\quad [MR_{glc}] = \dfrac{\mu mol\ Glc}{mL\ tissue \times \min}$

Ex. Typical FDG PET scan







45 min uptake phase (minimal tissue FDG)
then scan FDG-6P

Rodent FDG PET