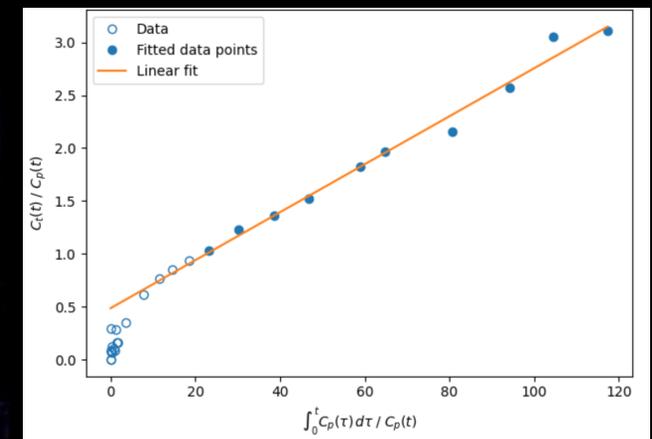
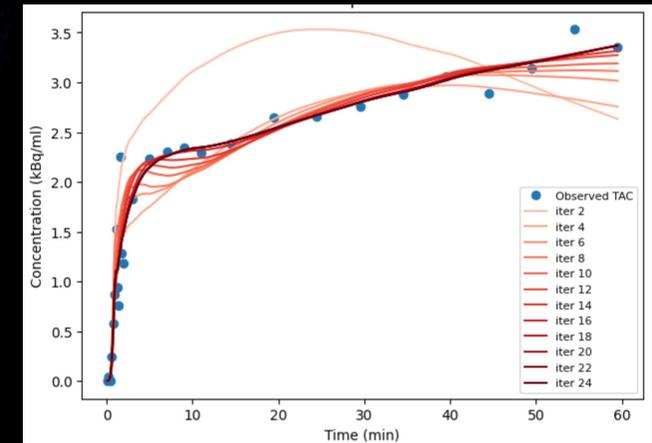


Introduction to Kinetic Modelling

Steven Meikle, Ph.D.
Sydney School of Health Sciences,
Brain and Mind Centre &
Sydney Imaging



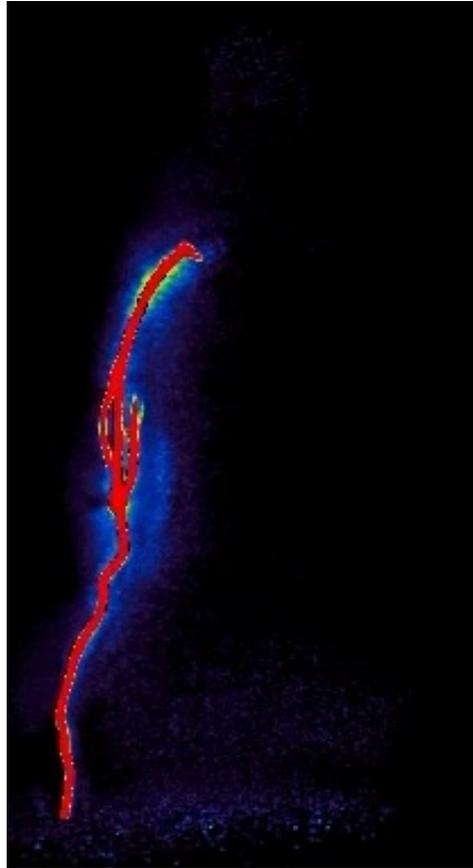
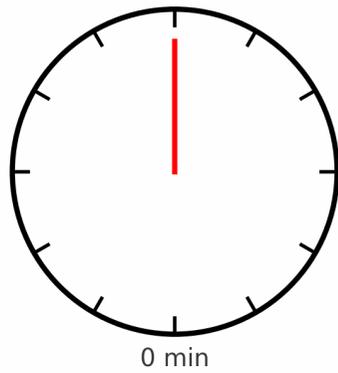
School on Advanced Topics in Medical Imaging - Ho Chi Minh City



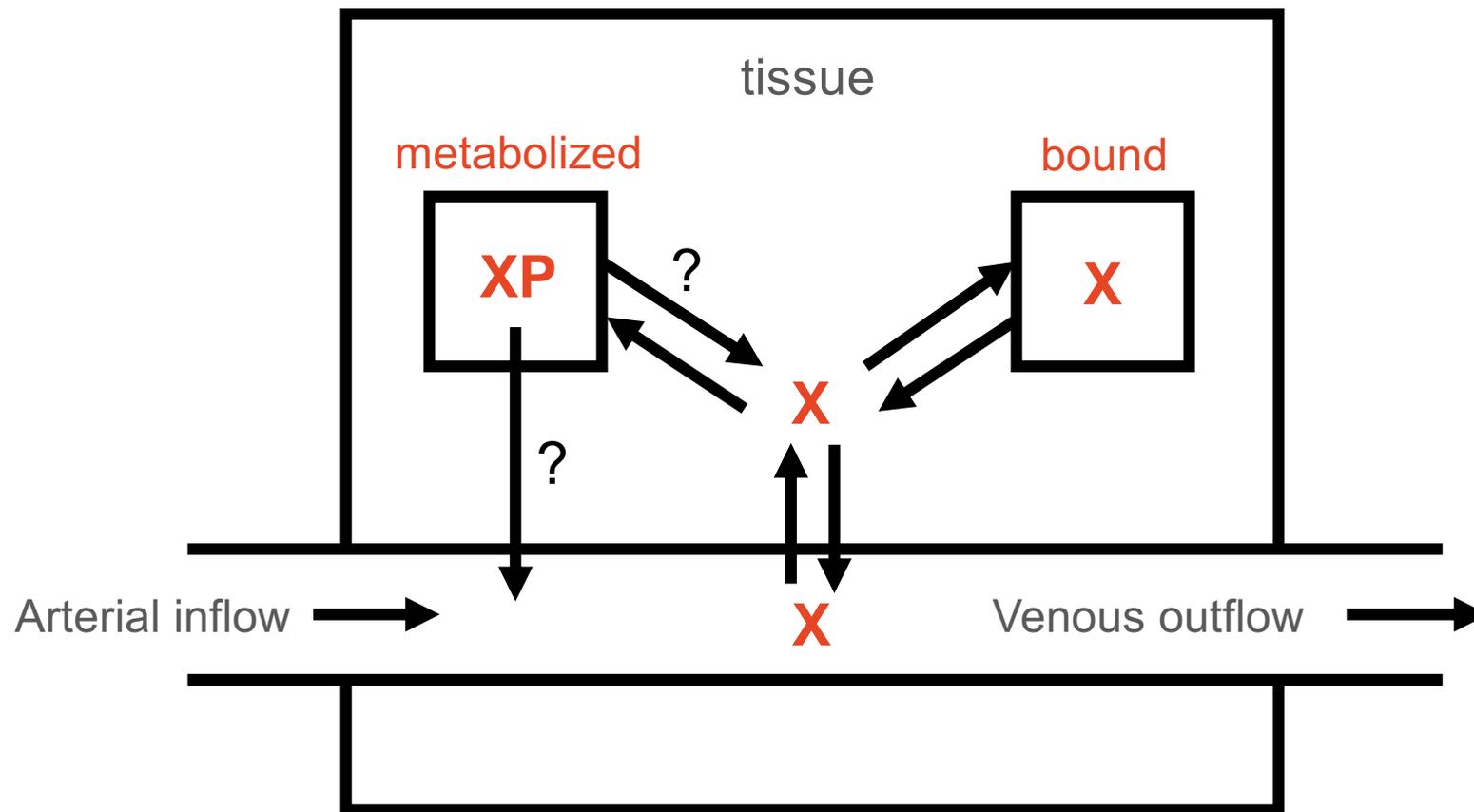
Overview

- Principles of kinetic modelling
 - Tracer principle
 - Compartmental models
 - Impulse response function and convolution
 - Parameter estimation
- Estimating metabolic rate with FDG
 - 2-tissue compartment model and non-linear least squares
 - Patlak plot
- Modelling receptor-binding tracers
 - Reference region methods
 - Logan plot
 - Neurotransmitters

Radiotracer distribution changes with time



A general model of tracer exchange in tissue

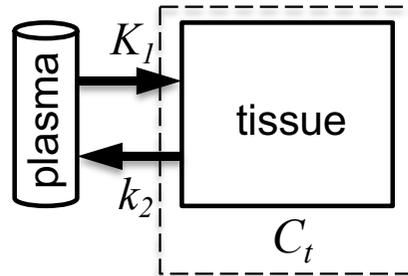


Compartments may represent...

- a **physical** space
 - intravascular, extracellular, or intracellular
- a **pharmacological** state
 - free or bound to protein
- a **metabolic** state
 - parent compound or metabolic product

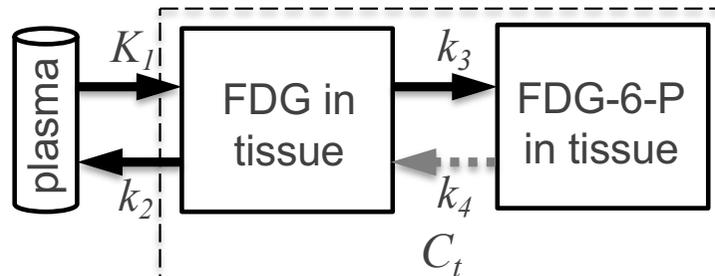
Common compartmental models

Flow model:



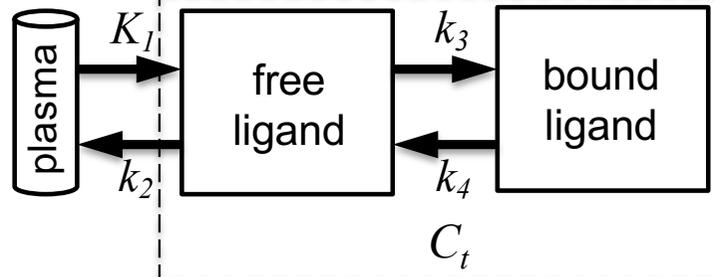
$$K_1 = fE$$

FDG model:



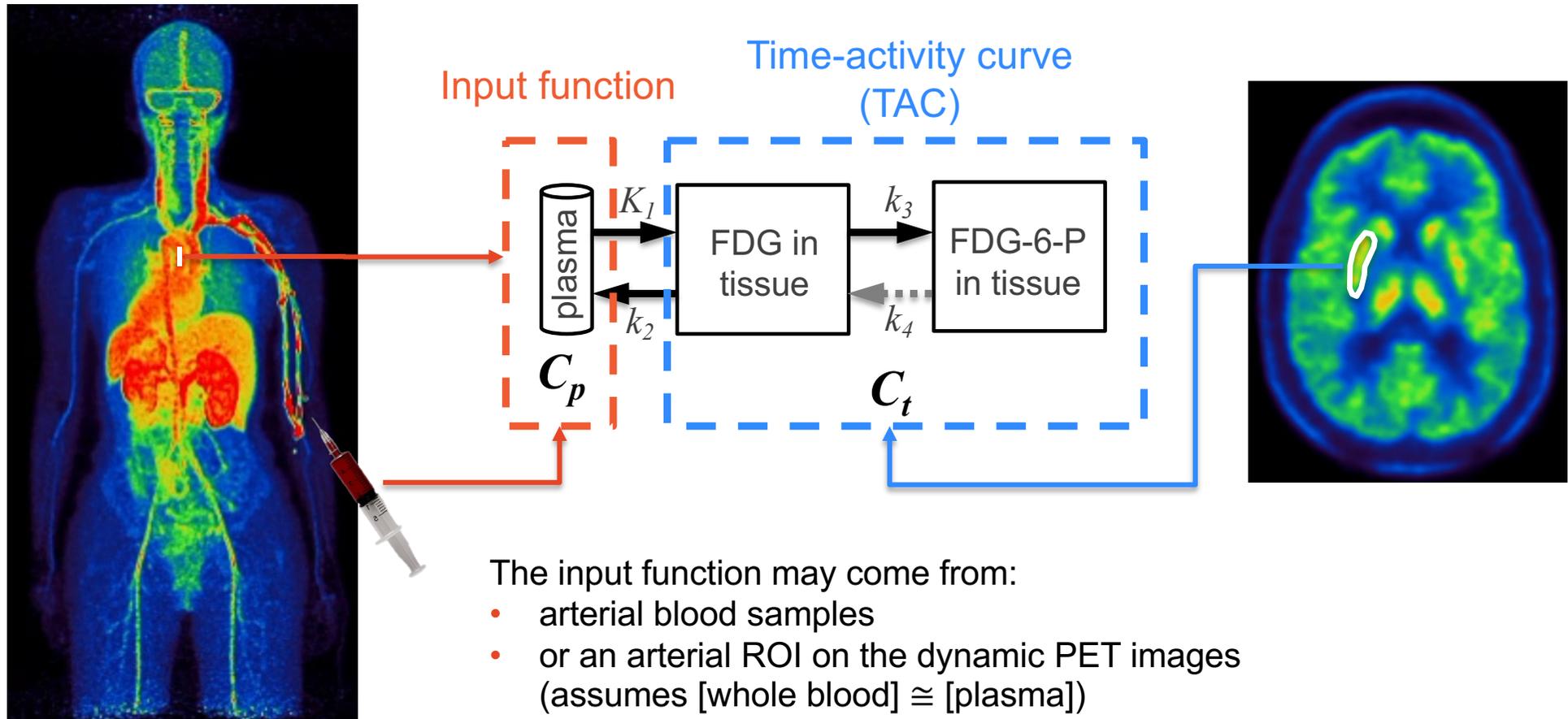
$$K_i = K_1 \left(\frac{k_3}{k_2 + k_3} \right)$$

Receptor binding model:



$$BP_{ND} = \frac{k_3}{k_4}$$

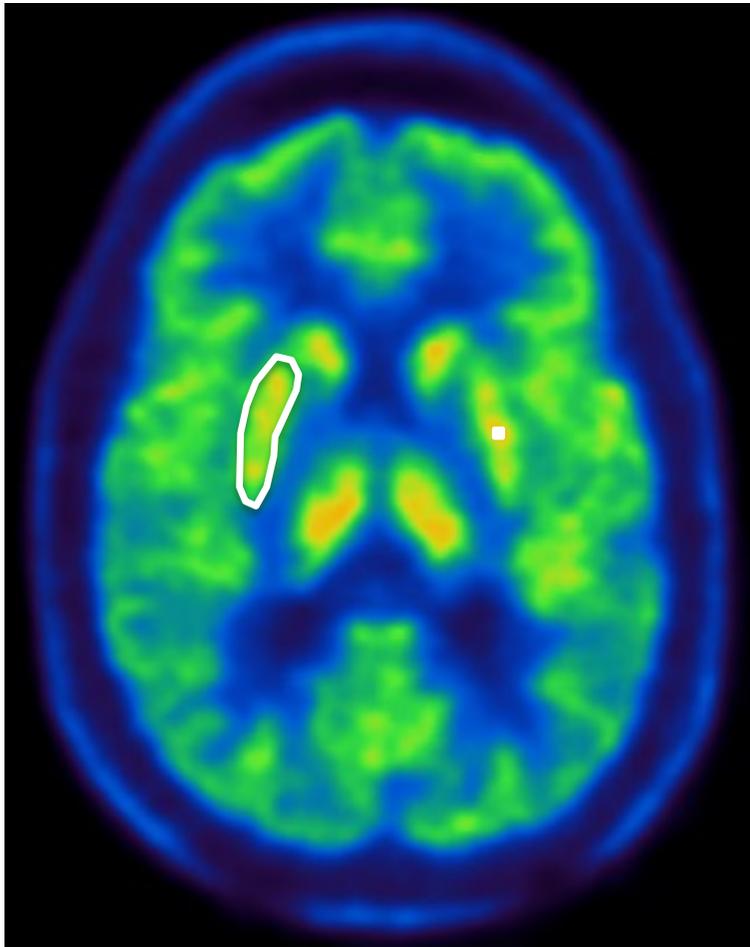
What do these models represent?



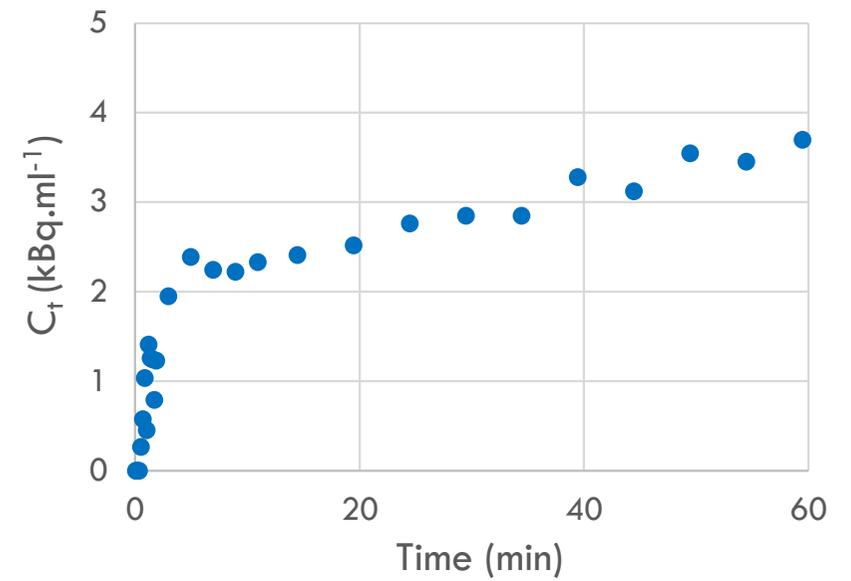
The input function may come from:

- arterial blood samples
- or an arterial ROI on the dynamic PET images (assumes [whole blood] \cong [plasma])
- or a previously measured population average (assumes minimal inter-subject variability)

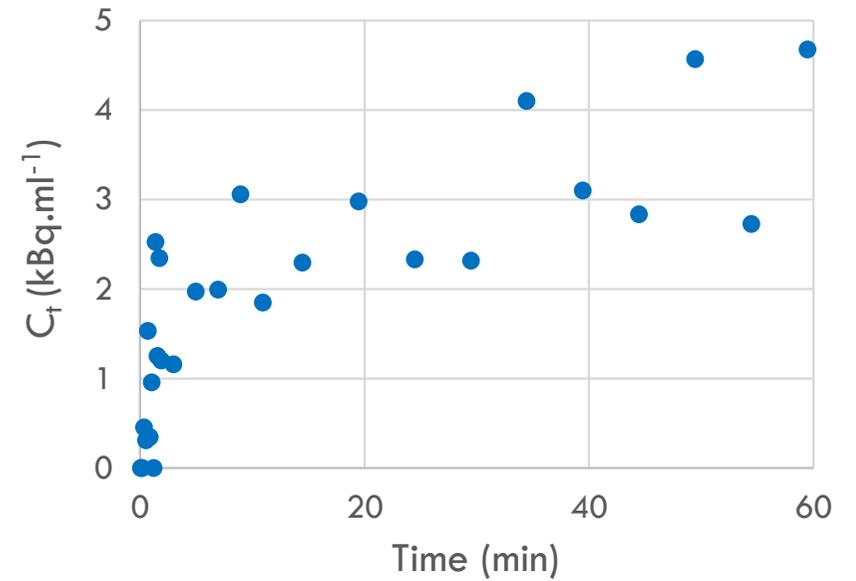
Time-Activity Curves (TAC)



ROI:



voxel:



Typical modelling assumptions

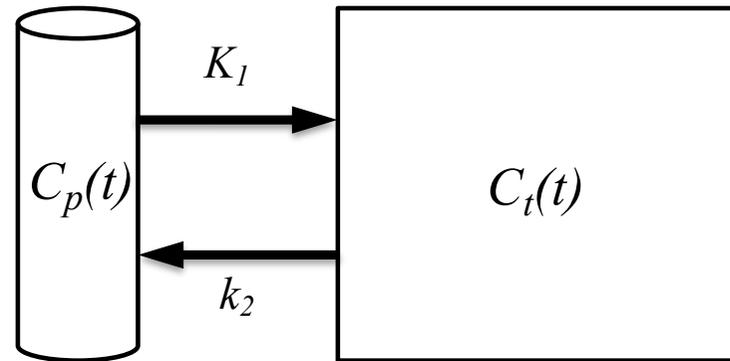
- Radiopharmaceutical is in **tracer** concentrations in the body
- Compartments are **homogeneous** and well-mixed
- The system (body) is in a **steady state**
 - i.e. the rates of exchange between compartments are **constant**
 - that is why we call them **rate constants**
- labelled metabolites (if any) do not enter the tissue

1-Tissue Compartment Model

- $K_1 = \text{Flow } (F) \times \text{Extraction } (E)$

$$E = 1 - \exp(-PS/F) \quad *$$

where P = capillary permeability
S = capillary surface area



- Limiting cases:

- $PS \gg F$: $K_1 \simeq F$ (e.g. $H_2^{15}O$ and other freely diffusible tracers)

- $F \gg PS$: $K_1 \simeq PS$ (most PET tracers)

- Assuming steady-state conditions:

$$\frac{dC_t}{dt} = K_1 C_p - k_2 C_t$$

Solution:

$$C_t(t) = C_p \otimes K_1 \exp(-k_2 t)$$

input function

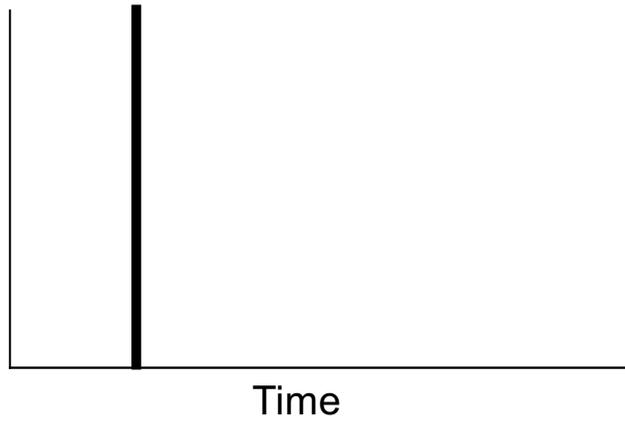
impulse response function

* Renkin, J Am Physiol 197:1205-10 1959, DOI: [10.1152/ajplegacy.1959.197.6.1205](https://doi.org/10.1152/ajplegacy.1959.197.6.1205)

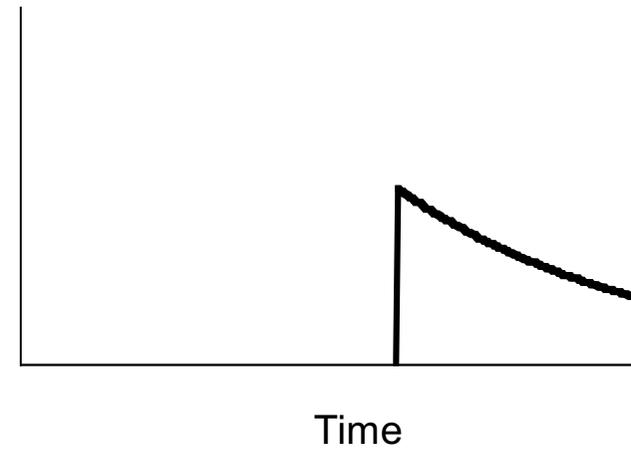
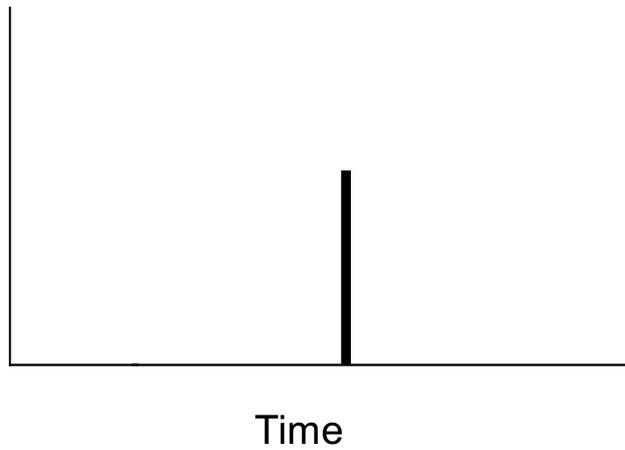
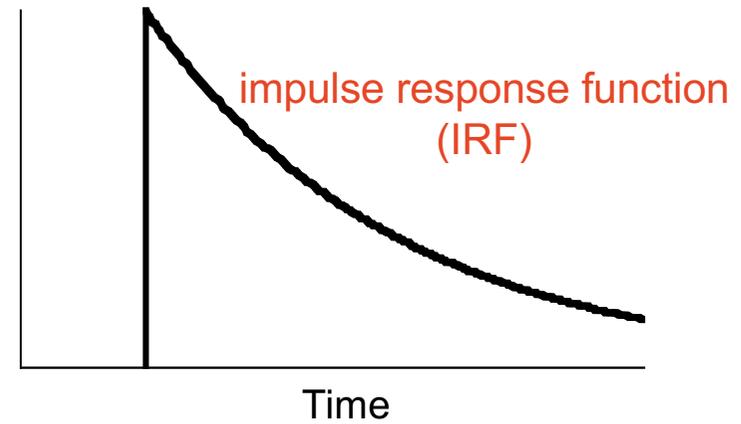
Crone, Acta Physiol Scand 58:292-305 1963, DOI: [10.1111/j.1748-1716.1963.tb02652.x](https://doi.org/10.1111/j.1748-1716.1963.tb02652.x)

Ideal bolus injections

Input function

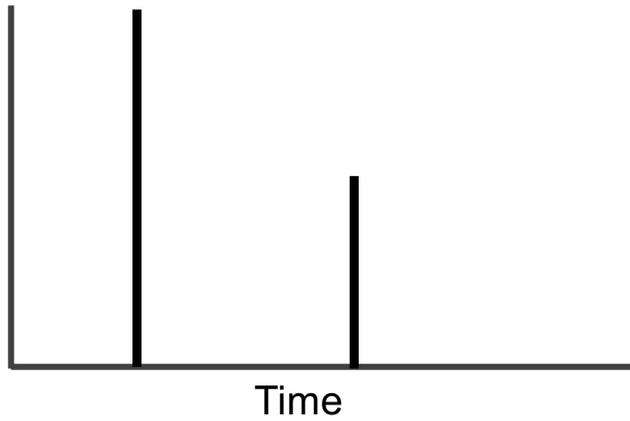


Tissue (impulse) response

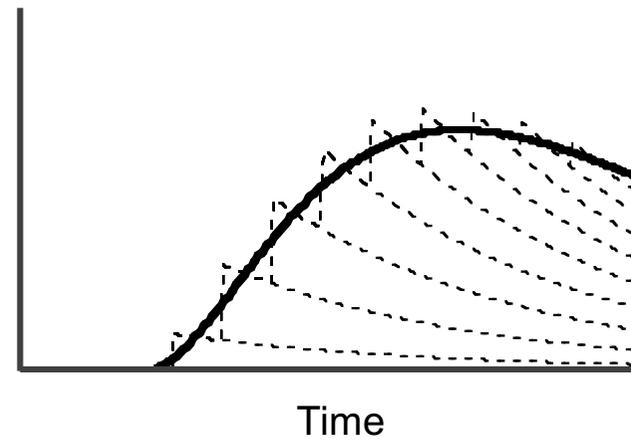
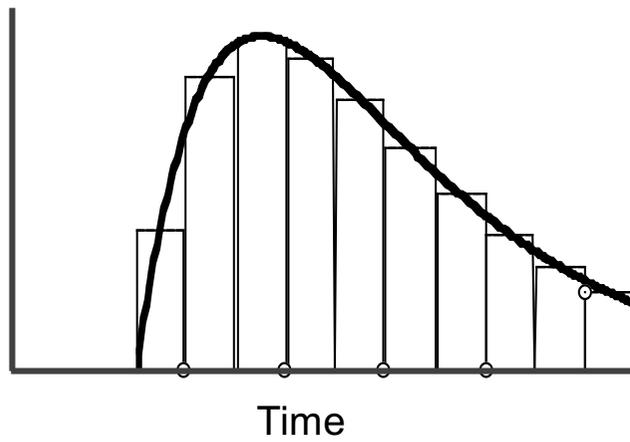
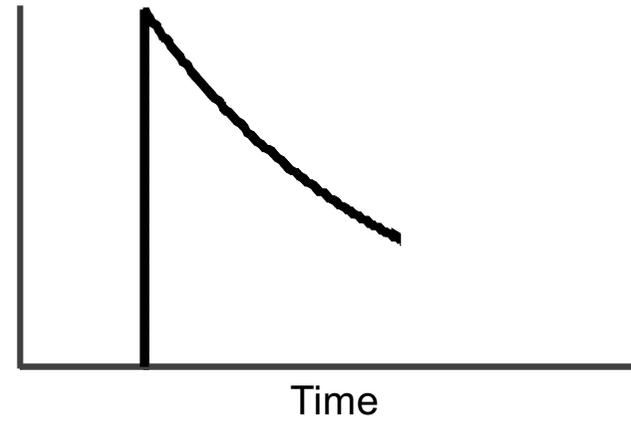


Convolution: Sum of ideal boluses

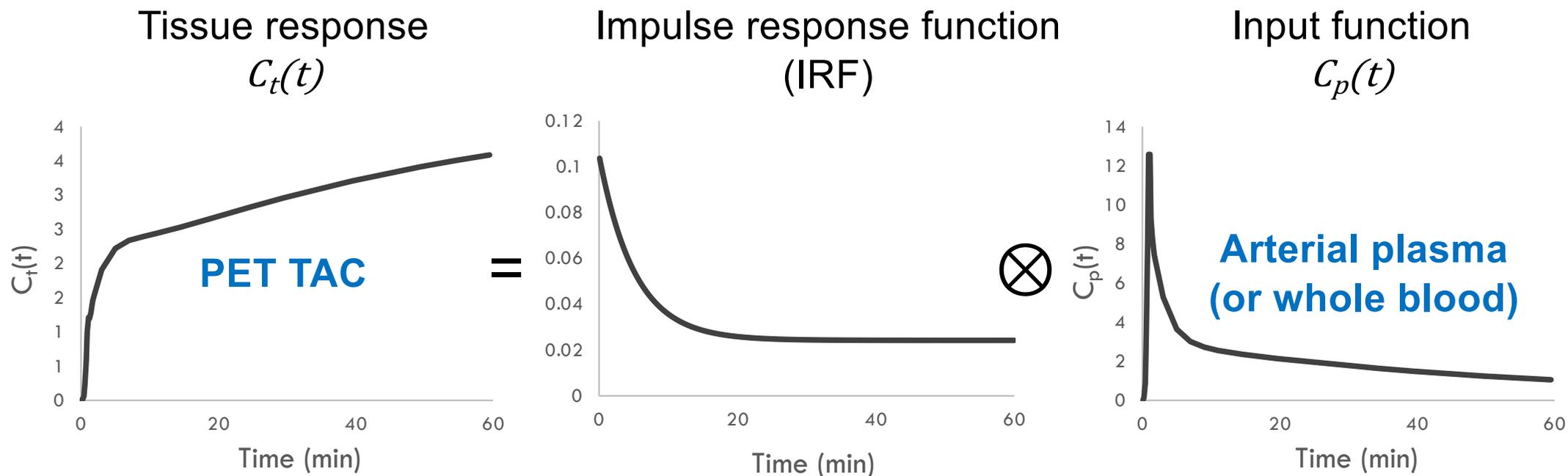
Input function



Tissue response



Relationship between input function, IRF and tissue response



$$C_t = C_p \otimes IRF$$

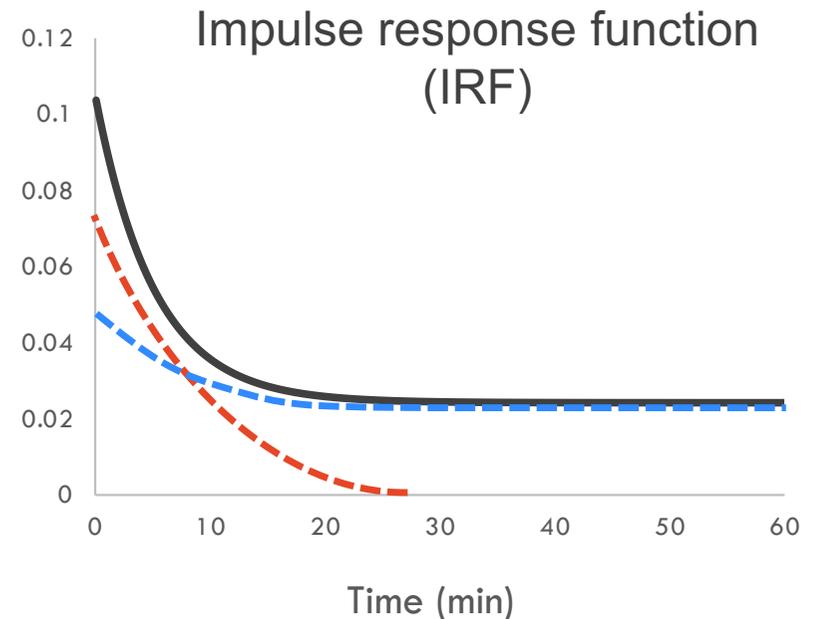
Relationship between Input Function, IRF and Tissue Response

- The mathematical form of the IRF is determined by the chosen model
- **The number of exponentials is equal to the number of tissue compartments**
- The area under the IRF is 1
- The amplitudes and decay rates of the exponential components are the model parameters we wish to estimate

$$IRF = A_1 \exp(-\alpha_1 t) + A_2 \exp(-\alpha_2 t)$$

fast component

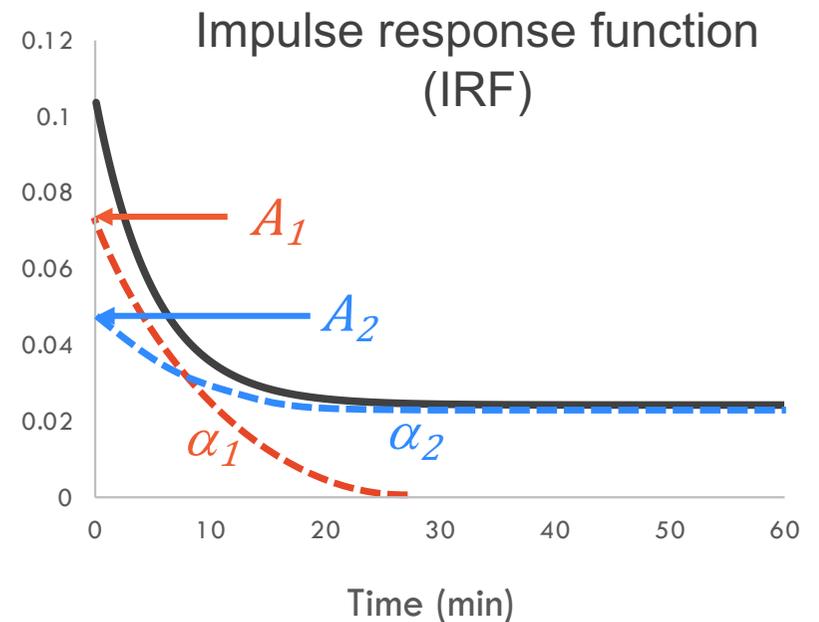
slow component



The PET Kinetic Modelling Problem

- PET kinetic modelling can be framed as the problem of estimating the IRF (the A_i 's and α_i 's) for an n -compartment model that, after convolution with the input function, best fit the **noisy** observed PET time-activity curves
- How do we know what n should be?
- How do we estimate the model parameters?
- How does noise affect our ability to estimate the parameters?

$$IRF = A_1 \exp(-\alpha_1 t) + A_2 \exp(-\alpha_2 t)$$



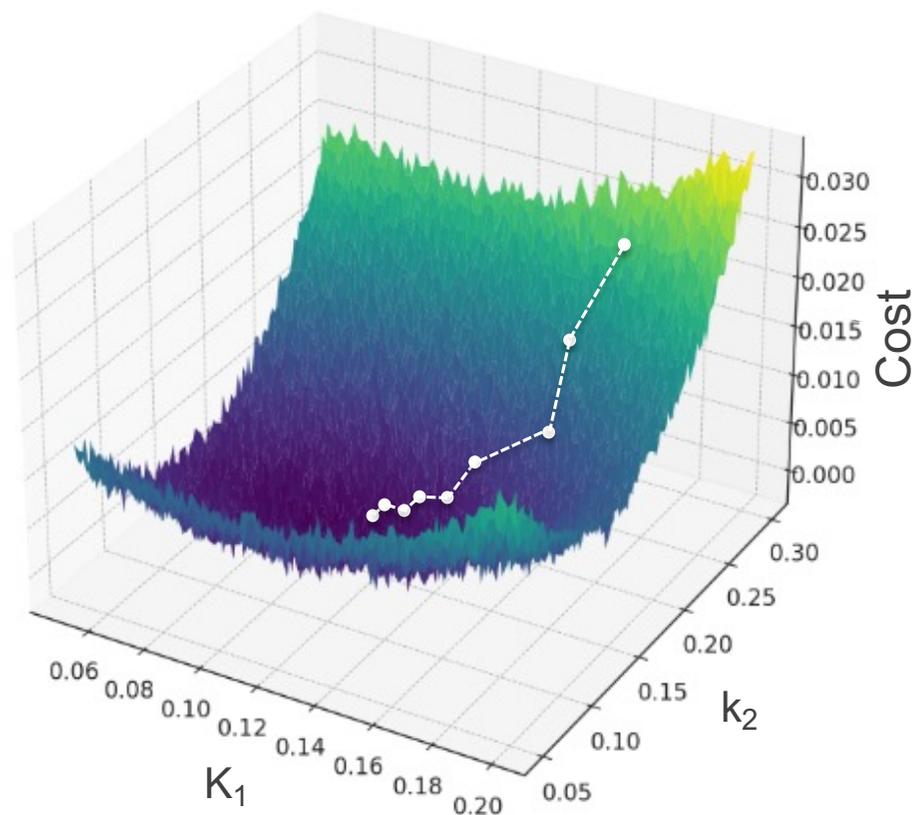
Parameter estimation

- Specify a model that maps the input function, C_p , onto the tissue data, C_t
- Define the relative noise in the data, $var(C_i)$
- Define the relative weights for the data, $w_i \propto 1 / var(C_i)$
- Select a cost function, e.g.:

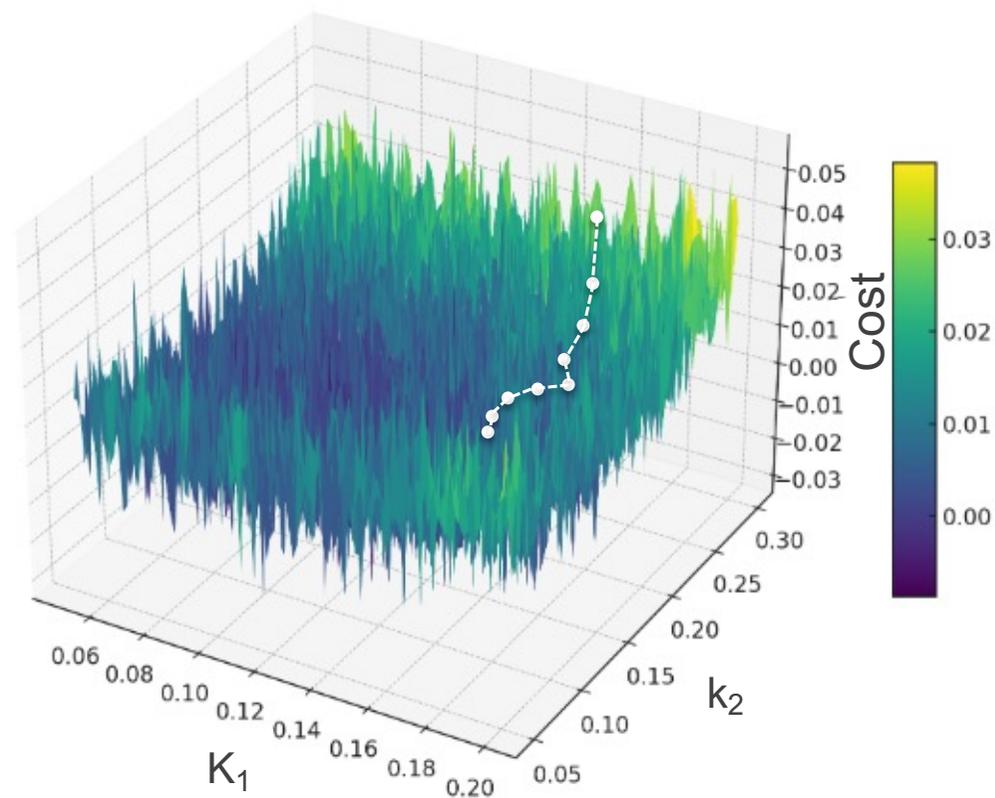
$$\Psi^2 = \sum_{i=1}^N w_i (\hat{C}_i - C_i)^2$$

- Select an optimizer that minimizes the cost function by iteratively improving the model parameter estimates:
 - non-linear least squares (e.g. Levenberg-Marquardt)
 - gradient descent

Optimisation



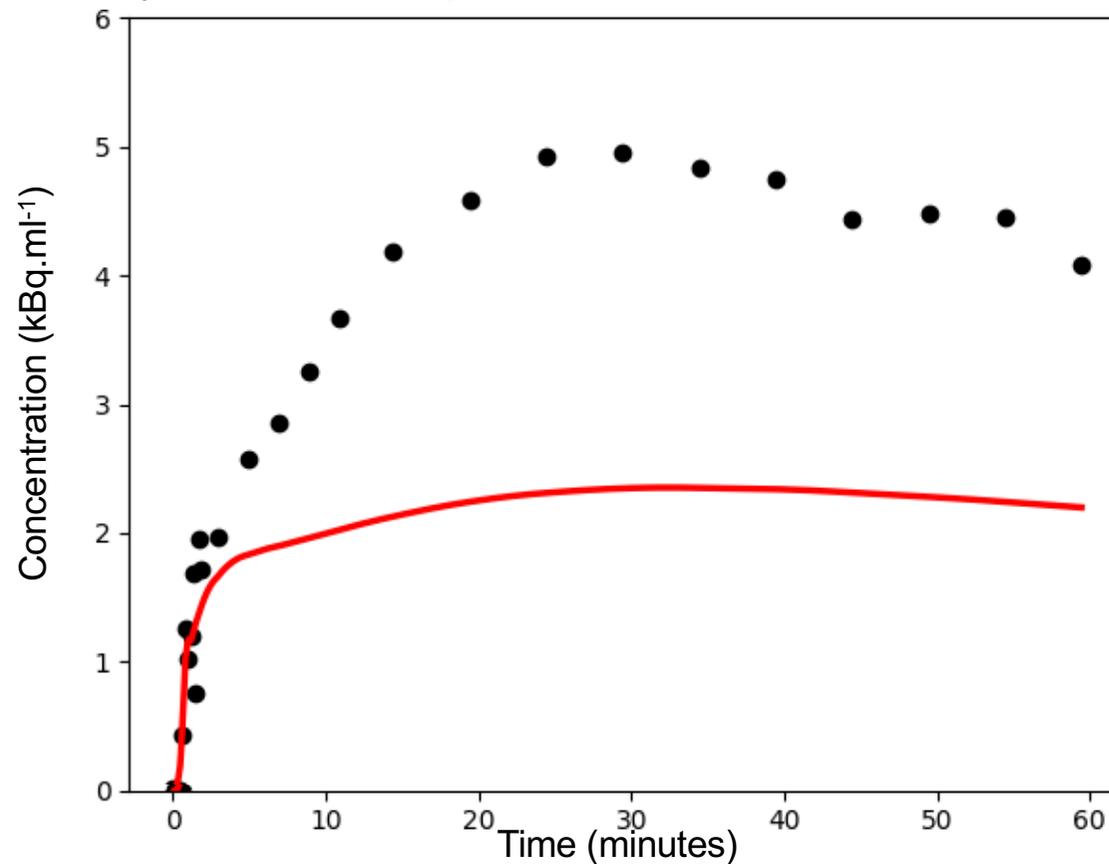
low noise (ROI level)



high noise (voxel level)

Optimisation (Least squares fitting)

- Find values of the parameters that produce the “best fit” (in a least squares sense) to the data points

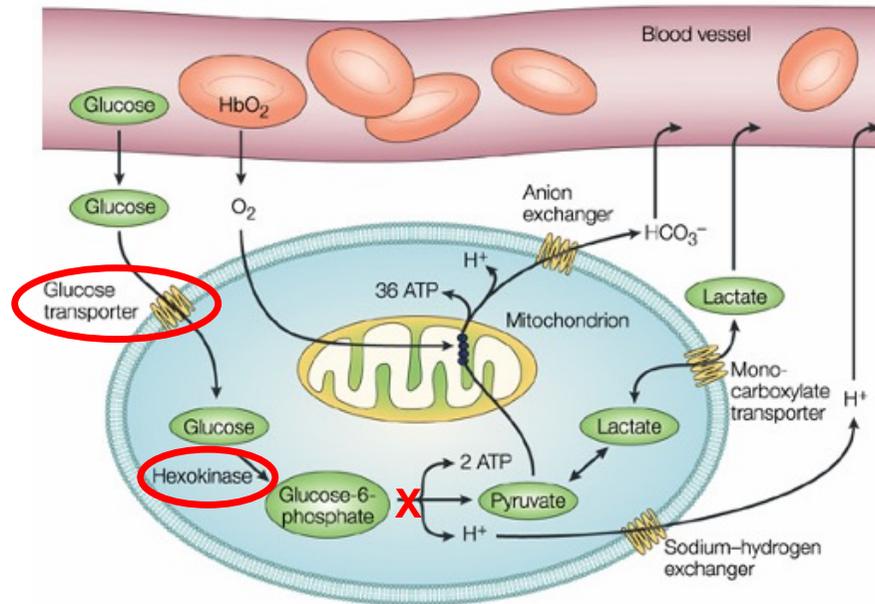


$$\begin{aligned}K_1 &= 0.12 \text{ mL}\cdot\text{min}^{-1}\cdot\text{g}^{-1} \\k_2 &= 0.2 \text{ min}^{-1} \\k_3 &= 0.1 \text{ min}^{-1} \\k_4 &= 0.01 \text{ min}^{-1} \\V_b &= 0.05\end{aligned}$$

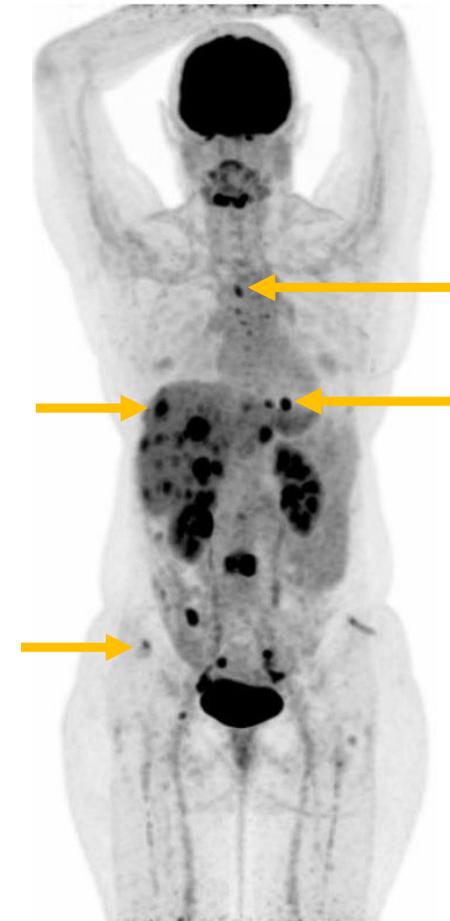
Examples

2-Fluoro-2-deoxy-D-glucose (FDG)

Aerobic Glycolysis is the Conversion of Glucose to Lactate in the Presence of Oxygen

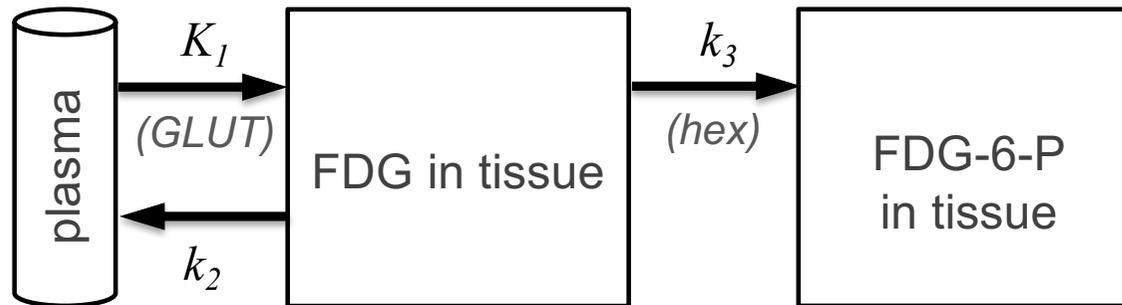


¹⁸F-FDG PET



Robert A. Gatenby & Robert J. Gillies *Nature Reviews Cancer* 4, 891 -899 (2004)

FDG 2-Tissue Compartment Model (2TC)



$$K_i = K_1 \left(\frac{k_3}{k_2 + k_3} \right) = \text{net influx rate (min}^{-1}\text{)}$$

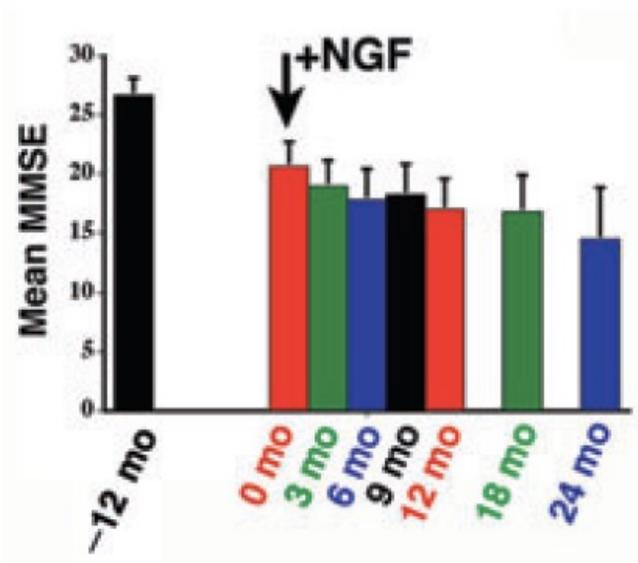
$$MR_{glu} = C_{glu} \frac{K_i}{LC} = \text{glucose metabolic rate}$$

C_{glu} = plasma glucose concentration

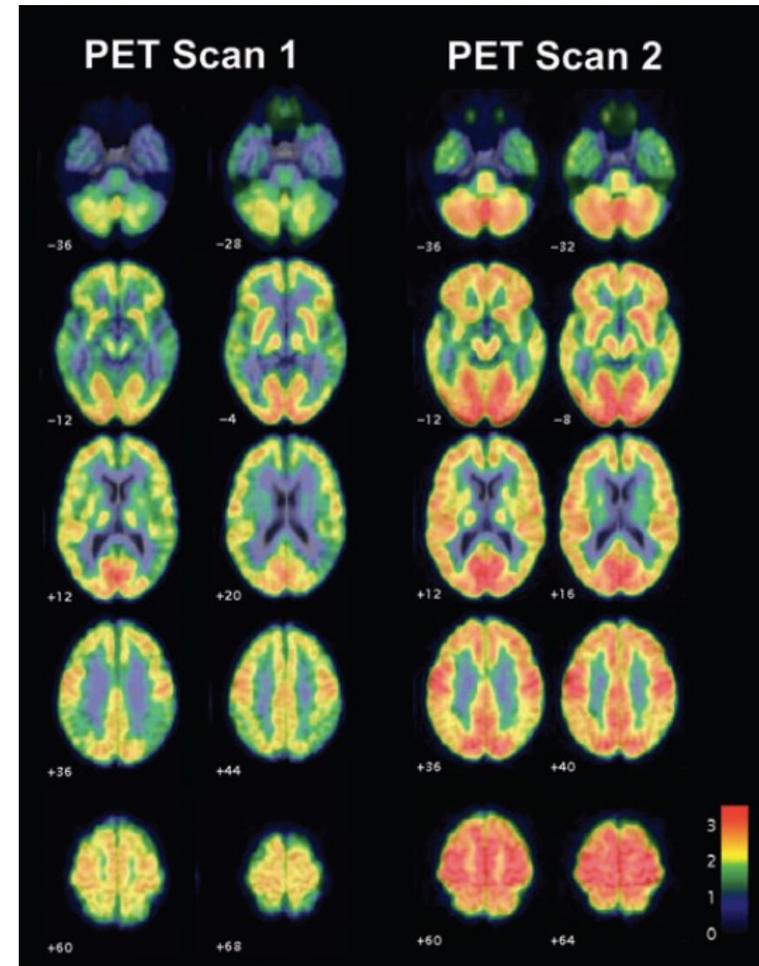
LC = lumped constant (glucose vs FDG)

¹⁸FDG PET in gene Tx treated AD patients

Phase 1 trial of *ex vivo* NGF gene delivery in eight individuals (67.2 ± 2.6 yrs, range 54–76 yrs) with early stage Alzheimer disease



Tuszynski et al, *Nat Med* 2005



Other Methods of Parameter Estimation

- Graphical methods
 - Patlak-Gjedde-Rutland analysis for irreversible systems
Patlak et al., J Cerebr Blood Flow Metab 3: 1-7, 1983
 - Logan analysis for reversible systems
Logan, Nucl Med Biol 27: 661-70, 2000
- Reference tissue methods
 - Simplified reference tissue model (SRTM)
Lammertsma & Hume, Neuroimage, 4:153-158, 1996
 - Multilinear reference tissue method (MRTM)
Ichise et al., J Cerebr Blood Flow Metab 23:1096-1112, 2003
- Basis function methods
 - *Gunn et al., J Cerebr Blood Flow Metab 22: 1425-39, 2002*
- Spectral analysis
 - *Cunningham et al., J Cerebr Blood Flow Metab 13: 15-23, 1993*
- Ratio methods
 - Distribution volume ratio (DVR)
Logan et al., J Cerebr Blood Flow Metab 16: 834-40, 1996

TOPICAL REVIEW

Quantitative imaging of protein targets in the human brain with PET

Roger N Gunn, Mark Slifstein, Graham E Searle and Julie C Price

Published 29 October 2015 • © 2015 Institute of Physics and Engineering in Medicine

[Physics in Medicine & Biology](#), [Volume 60](#), [Number 22](#)

Citation Roger N Gunn *et al* 2015 *Phys. Med. Biol.* **60** R363

DOI 10.1088/0031-9155/60/22/R363



PMOD Kinetic Modeling (PKIN) (Version 4.4)

Navigation: »No topics above this level«

PKIN Reference

- PMOD Kinetic Modeling Tool (PKIN)
- Introduction to Modeling in PET
- PKIN Configuration
- PKIN Data Processing
- PKIN for Regional Parametric Mapping (option)
- PKIN Reference**
 - Compartment Models
 - Compartment Models for Cardiac PET
 - Compartment Models for Cardiac SPECT
 - Reference Tissue Models
 - Non-Compartmental Models
 - Interpolation Functions for Whole-Blood and Plasma Activity
 - Interpolation Functions for Plasma/Whole-Blood Fraction
 - Interpolation Functions for Parent/Plasma Fraction
- References
- PMOD Disclaimer
- PMOD Copyright Notice

PKIN implements different types of models with somewhat different properties.

1. Compartment Models require an input curve for the calculation of the expected concentrations in the different compartments. Most of them also support a blood spillover correction term.
2. Reference models do not use explicit blood information. Rather, a reference TAC is specified which must satisfy specific criteria. The reference TAC is used to calculate the response in the tissue of interest.
3. Non-compartment models perform different types of analyses which are not based on a compartment structure of the model. Most of them use the input curve.

Note: It is assumed that all data used has been **decay corrected** to the same time point.

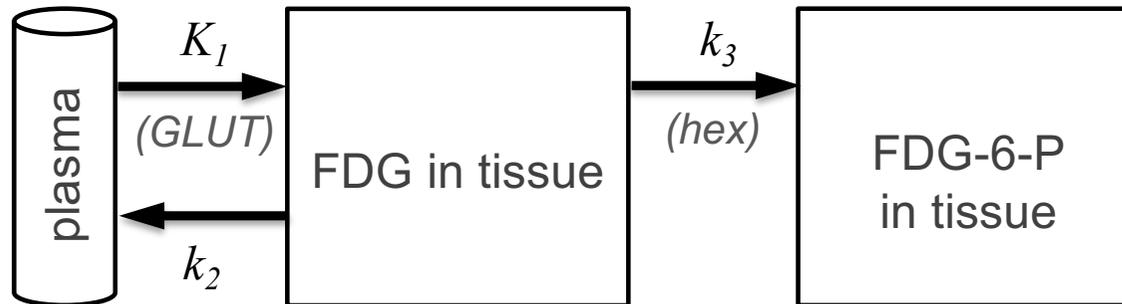
Graphical Methods

- Operational equations are nonlinear in the unknown parameters
- This requires iterative optimisation which is too slow for voxel level parameter estimation
- Can we linearise the OE to make it a $Y = mX + b$ problem?
- Then we could use non-iterative linear regression and fit for m and b
- Much more efficient, much faster!

Examples:

- Patlak plot for irreversible tracers
- Logan plot for reversible tracers

Patlak-Gjedde-Rutland Plot



- If we assume FDG becomes irreversibly trapped in the 2nd tissue compartment ($k_4 = 0$):

$$C_t(t) = K_i \int_0^t C_p(\tau) d\tau + V_0 C_p(t)$$

K_i = net influx rate

C_p = plasma input function

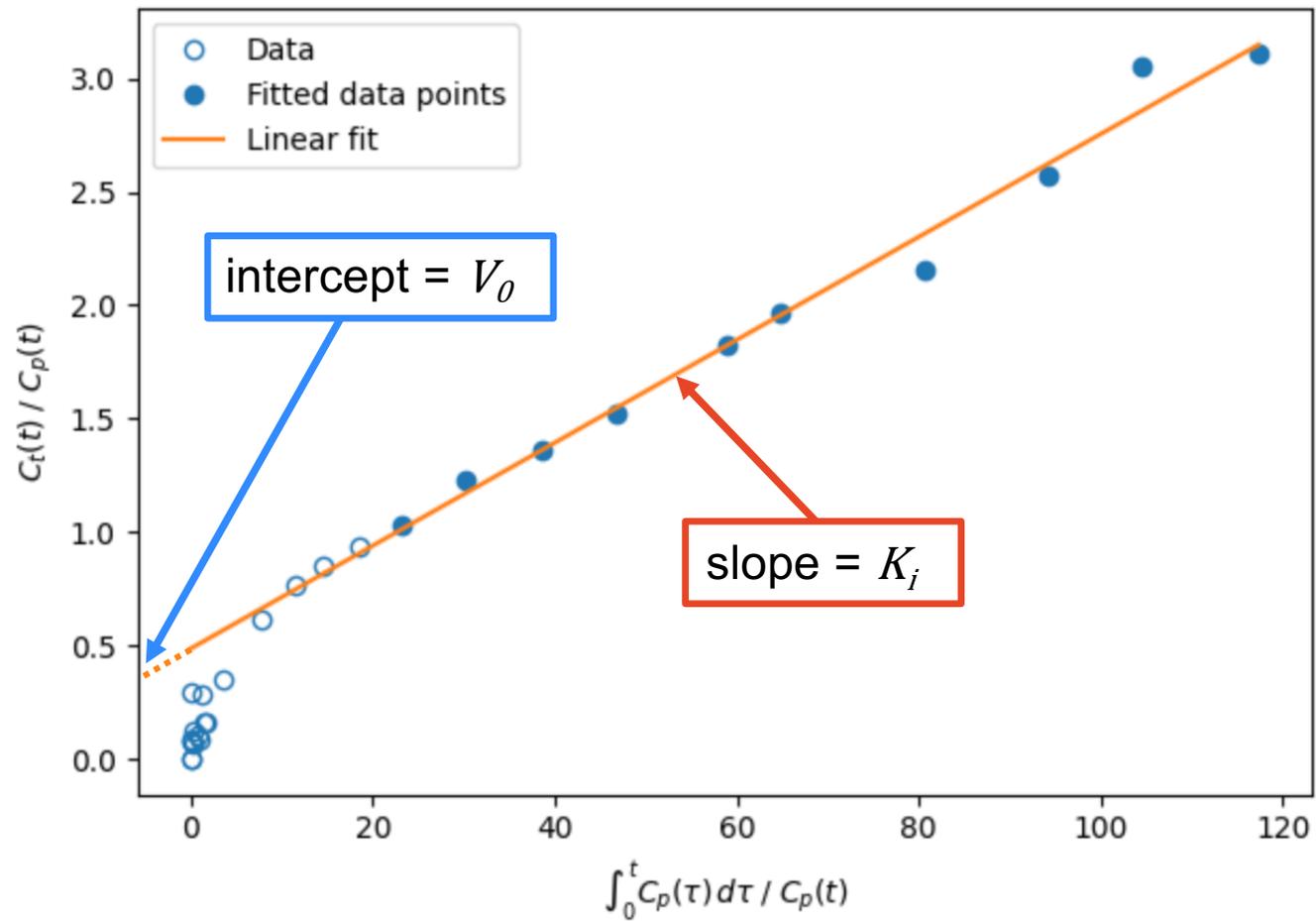
V_0 = volume of distribution of 1st comp

- Now, divide throughout by C_p and we get:

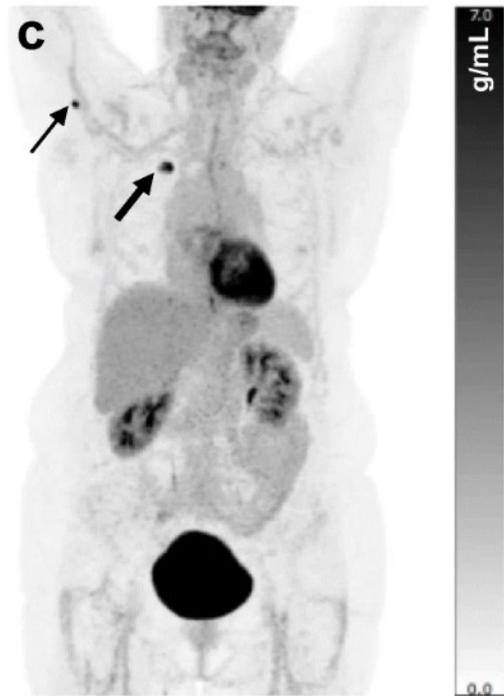
$$\frac{C_t(t)}{C_p(t)} = K_i \frac{\int_0^t C_p(\tau) d\tau}{C_p(t)} + V_0$$

which is now in the form $Y = mX + b$

Patlak Plot for [¹⁸F]FDG



Clinical Application of Patlak Method



SUV

K_i

V_0

Dias et al, *Eur J Nucl Med Mol Imaging*, 2021

DOI: <https://doi.org/10.1007/s00259-020-05007-2>

Standardised Uptake Value (SUV)

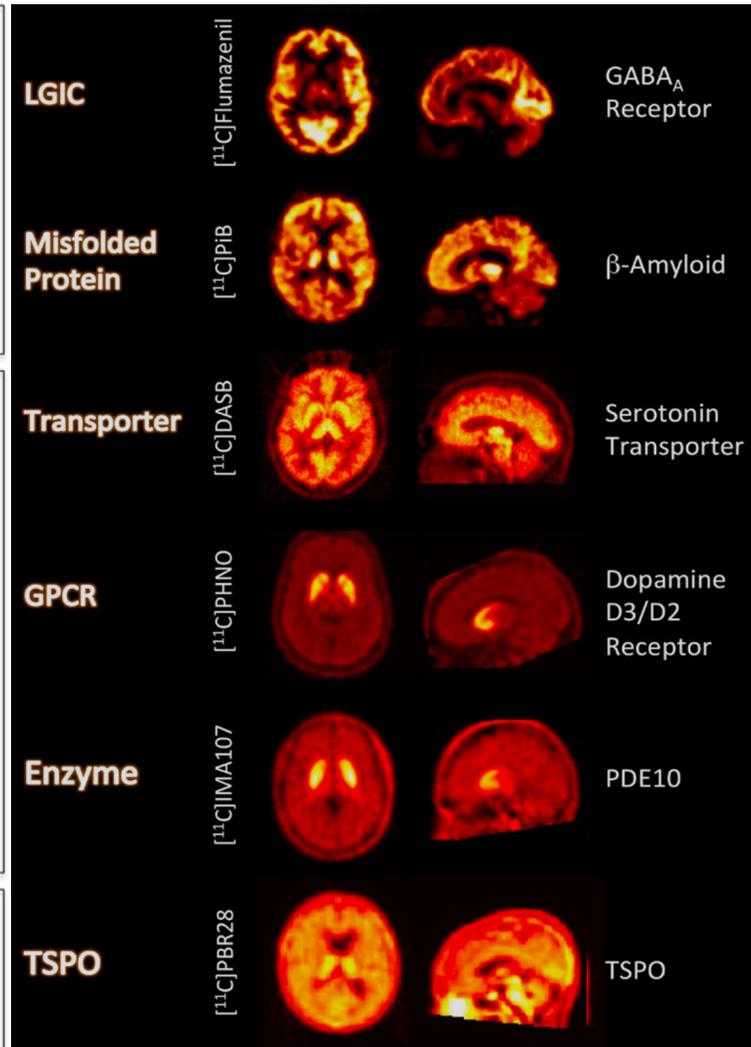
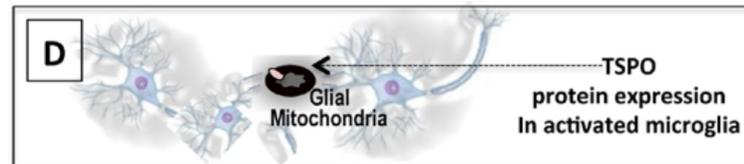
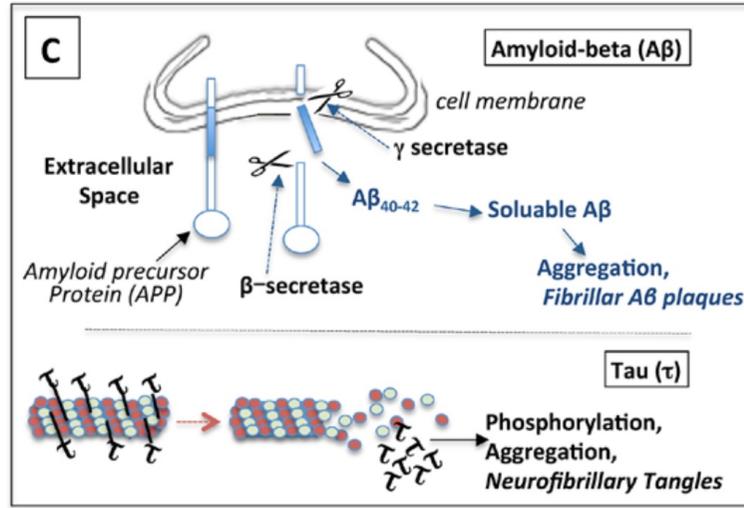
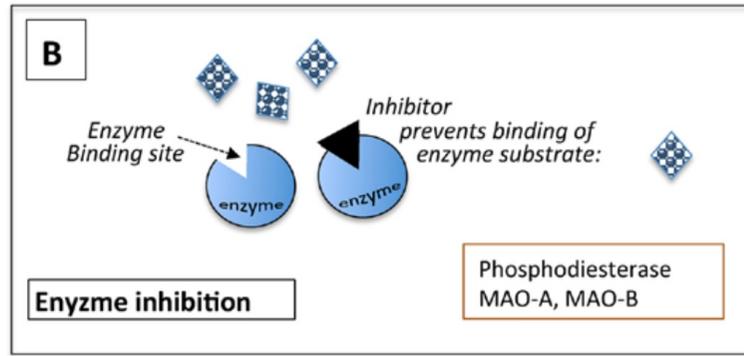
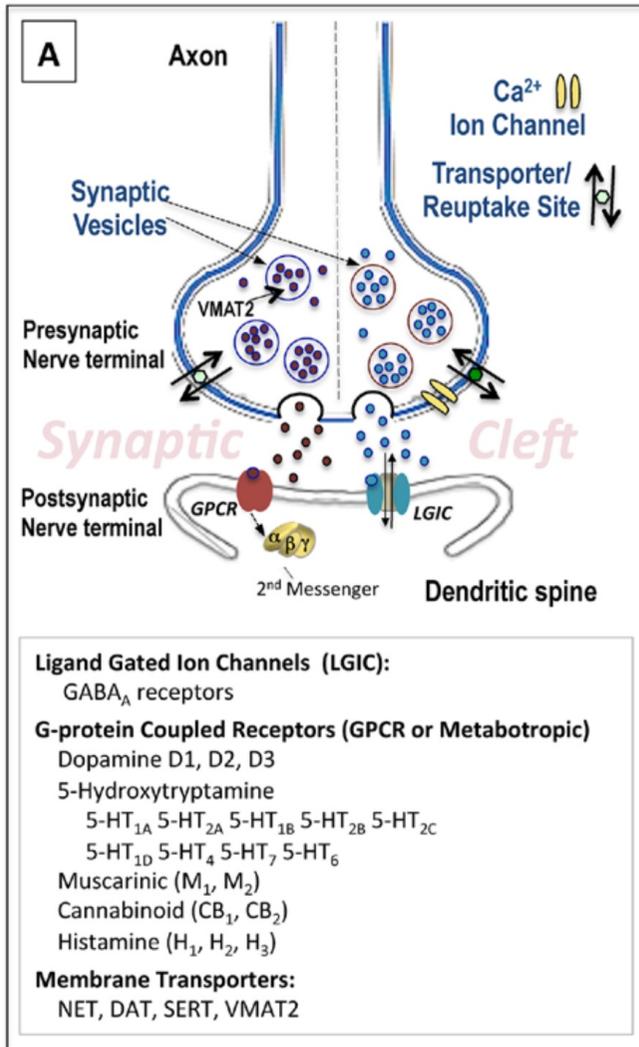
Operational equation for an irreversible tracer: $C_t(t) = K_i \int_0^t C_p(\tau) d\tau + V_0 C_p(t)$

Assume V_0 is negligible at late scan times: $C_t(t) \cong K_i \int_0^t C_p(\tau) d\tau$

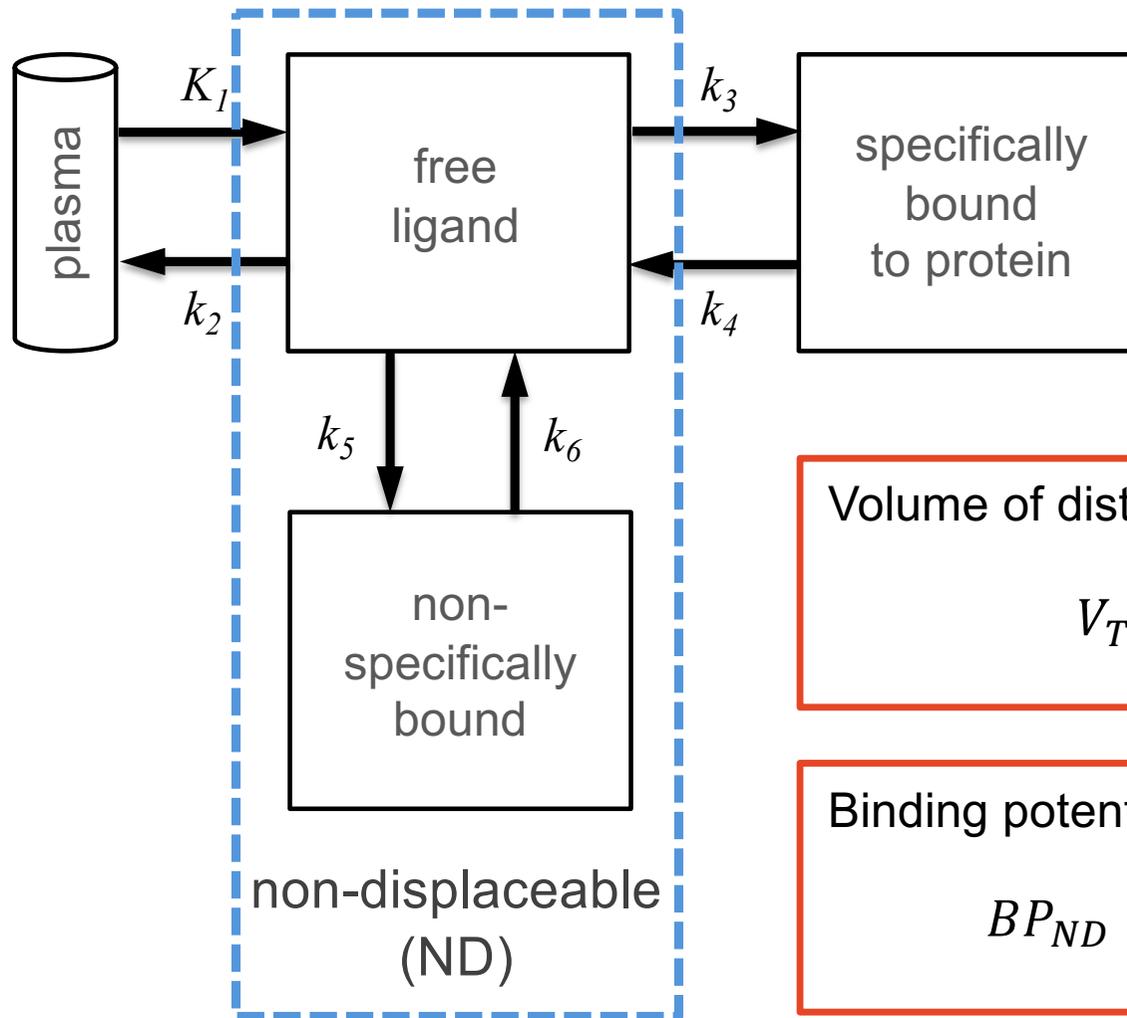
Rearrange: $K_i = \frac{C_t(t)}{\int_0^t C_p(\tau) d\tau}$ and approximate $\int_0^t C_p(\tau) d\tau$ by injected dose / body wt:

$$SUV = \frac{C_t(t)}{\text{dose}/(\text{body weight})} \approx K_i$$

Protein-binding PET tracers



Receptor-Ligand Model



Volume of distribution:

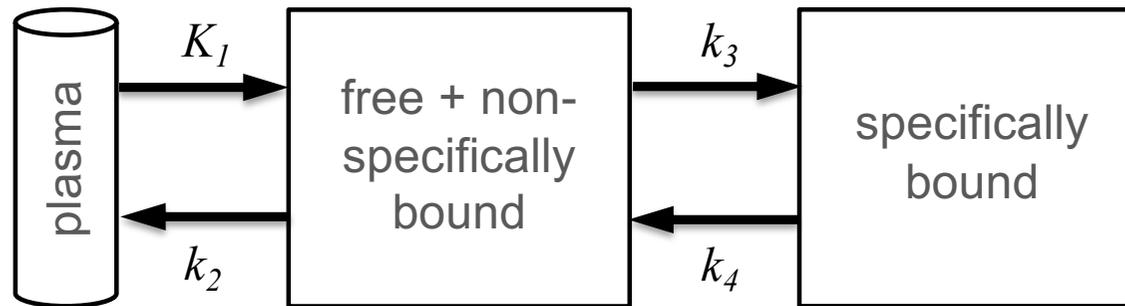
$$V_T = \frac{K_1}{k_2} \left(1 + \frac{k_3}{k_4} \right)$$

Binding potential:

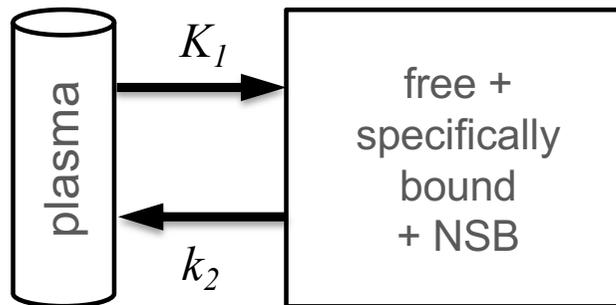
$$BP_{ND} = \frac{k_3}{k_4} = \frac{(V_T - V_{ND})}{V_{ND}}$$

Simplified Ligand Models

Simpler:

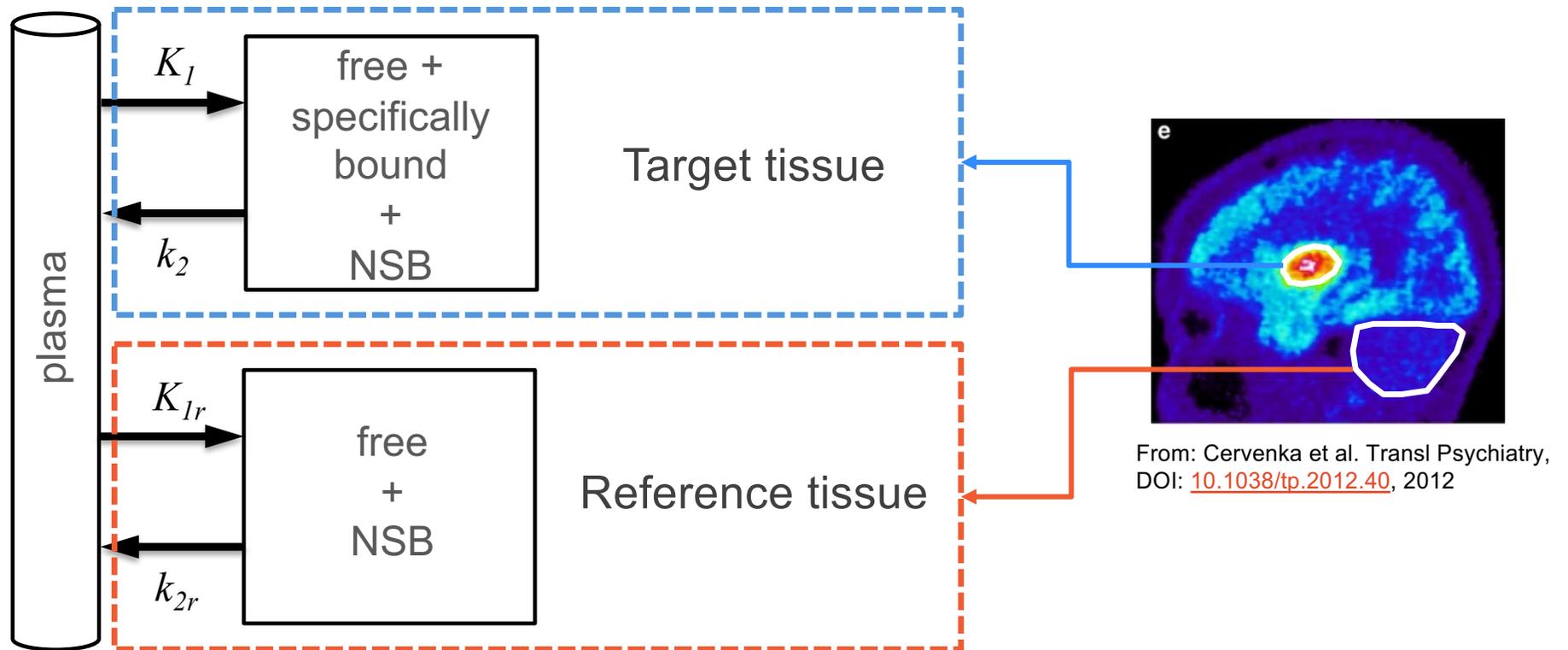


Simplest:



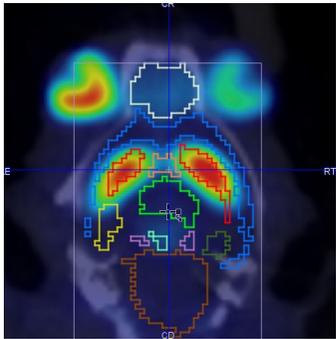
assumes there is a rapid equilibrium between free and bound states, i.e. k_3 and k_4 are relatively fast

Simplified Reference Tissue Model

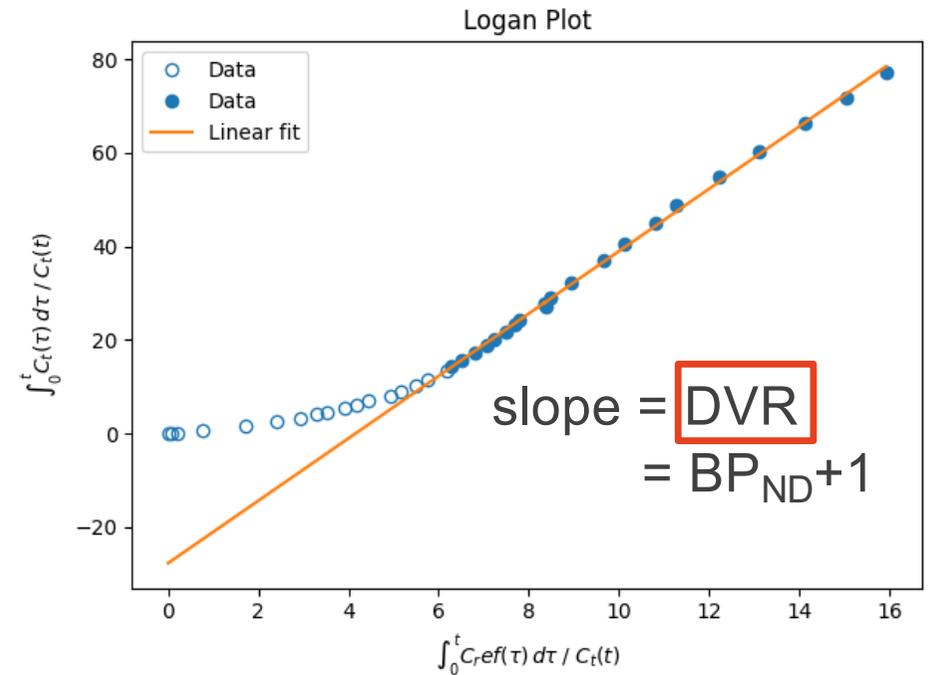
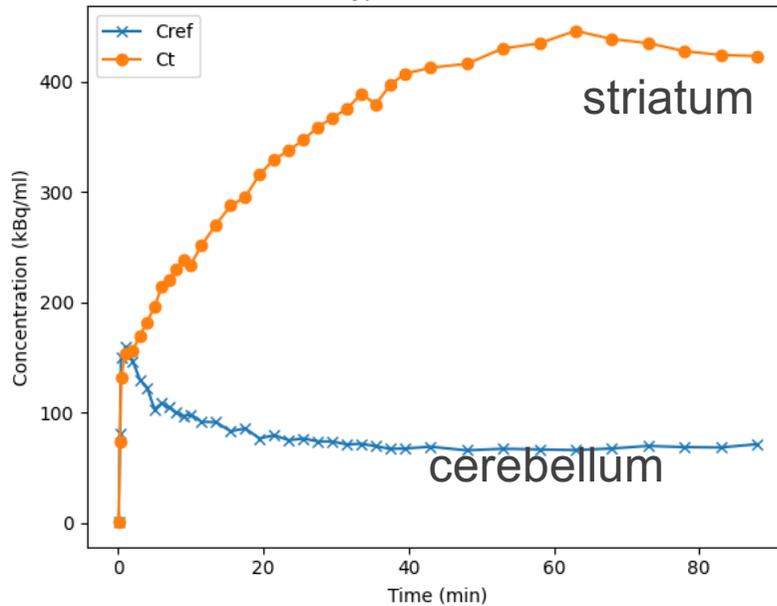


$$C_T(t) = R_1 C_R(t) + \left\{ k_2 - \frac{R_1 k_2}{(1 + BP_{ND})} \right\} C_r(t) \otimes \exp\{-k_2 t / (1 + BP_{ND})\}, \quad R_1 = \frac{K_1}{K_{1r}}$$

Logan Plot



[¹⁸F]Fallypride



$$Y = mX + b$$

$$\frac{\int_0^t C_t(\tau) d\tau}{C_t(t)} = \frac{V_T}{V_{ND}} \frac{\int_0^t C_{ref}(\tau) d\tau}{C_t(t)} + \text{intercept}$$

Advanced Topics in Kinetic Modelling

- Receptor-drug occupancy studies
- Non-steady state studies
 - Drug challenge studies
 - Neurotransmitter stimulus studies
- Kinetic modelling in Total Body PET
 - heterogeneous kinetics
 - multiple input functions, delays
 - metabolites
- Bayesian parameter estimation methods
- Deep learned parameter estimation methods

Kinetic Modelling Resources

- Turku PET Centre:
http://www.turkupetcentre.net/petanalysis/model_compartmental.html
- PMod Technologies:
<https://doc.pmod.com/pkin/pkin.html?compartmentmodels2260.html>
- Gunn, Slifstein, Searle and Price, “Quantitative imaging of protein targets in the human brain with PET”, Phys Med Biol 60: R363–R411, 2015
<http://doi.org/doi:10.1088/0031-9155/60/22/R363>
- Lois, Sari & Price. “Kinetic modelling and parametric imaging” in Quantitative PET in the 2020s: a roadmap, Phys Med Biol 66 06RM01, 2021
<http://doi.org/10.1088/1361-6560/abd4f7>
- Morris, Emvalomenos, Hoyer & Meikle. “Modeling PET data acquired during nonsteady conditions: What if brain conditions change during the scan?”, J Nucl Med 0:1-14, 2024
<http://doi.org/doi:10.2967/jnumed.124.267494>
- Wang, Li, Cherry and Wang. “Total-body PET kinetic modeling and potential opportunities using deep learning”, PET Clin 16:613–625, 2021
<http://doi.org/10.1016/j.cpet.2021.06.009>

Exercise: Introduction to Kinetic Modelling in PET



Vietnam-KineticModellingTutorial-Shared.ipynb ☆ ☁

File Edit View Insert Runtime Tools Help

Q Commands | + Code + Text | ▶ Run all ▼

We will perform the following tasks to illustrate some of the key concepts:

1. Read and plot simulated [^{18}F]FDG PET time-activity curves (TACs) representing the blood input function, C_p , and tissue curve, C_t .
2. Perform nonlinear least-squares fitting of a 1-tissue compartment model to the $[C_p, C_t]$ data.
3. Repeat using a 2-tissue compartment model.
4. Compare the model fits by analysing residuals and the Akaike Information Criterion (AIC).
5. Perform Patlak graphical model fitting to the same data and compare estimates of the net influx rate constant, K_i , by Patlak and least squares.
6. Analyse mouse brain TACs for the reversible D2 receptor-binding ligand, [^{18}F]Fallypride.
7. Analyse the [^{18}F]Fallypride data using the Logan plot.