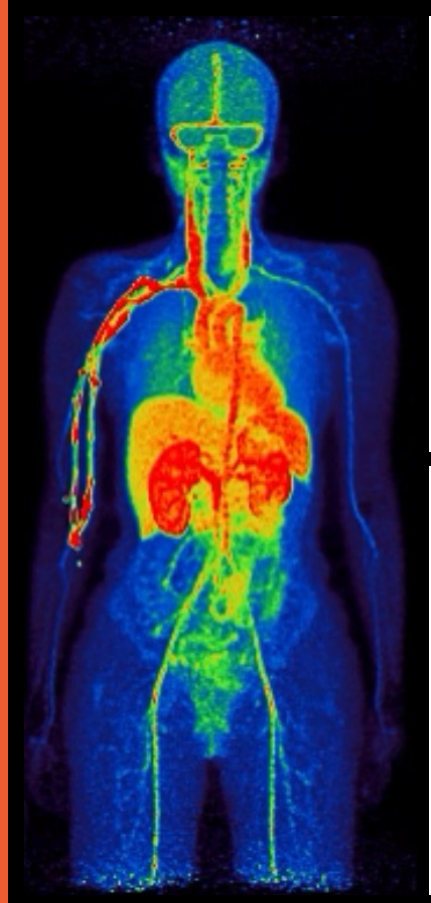
Introduction to Kinetic Modelling

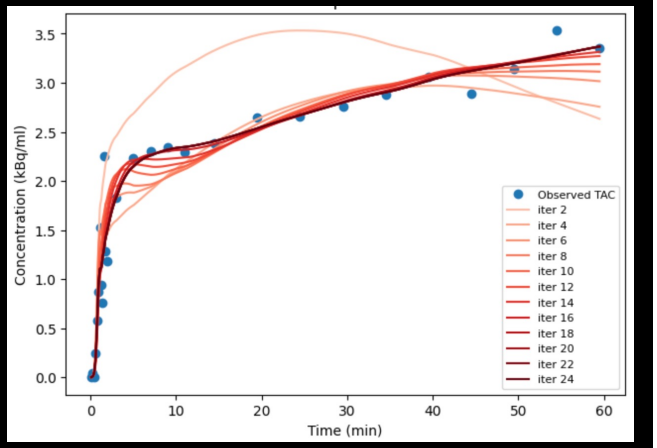
Steven Meikle, Ph.D.
Sydney School of Health Sciences,
Brain and Mind Centre &
Sydney Imaging

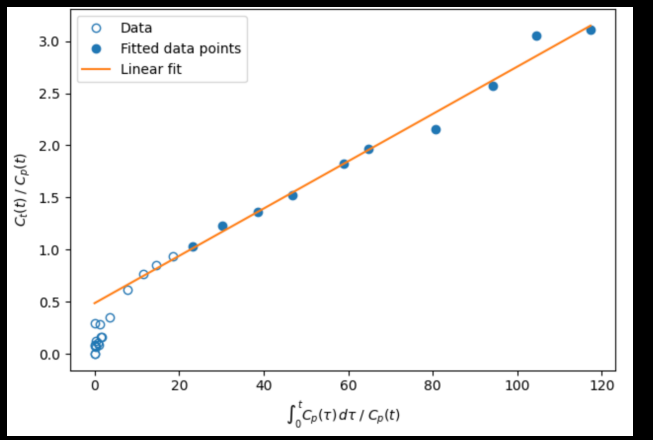
THE UNIVERSITY OF SYDNEY

NATIONAL IMAGING FACILITY

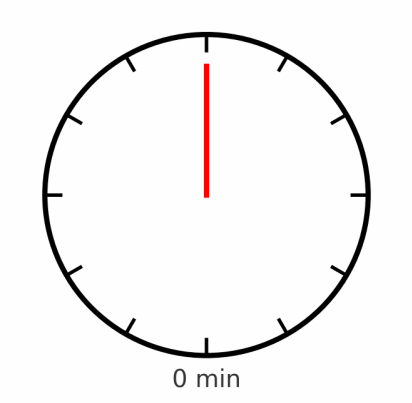
School on Advanced Topics in Medical Imaging - Ho Chi Minh City

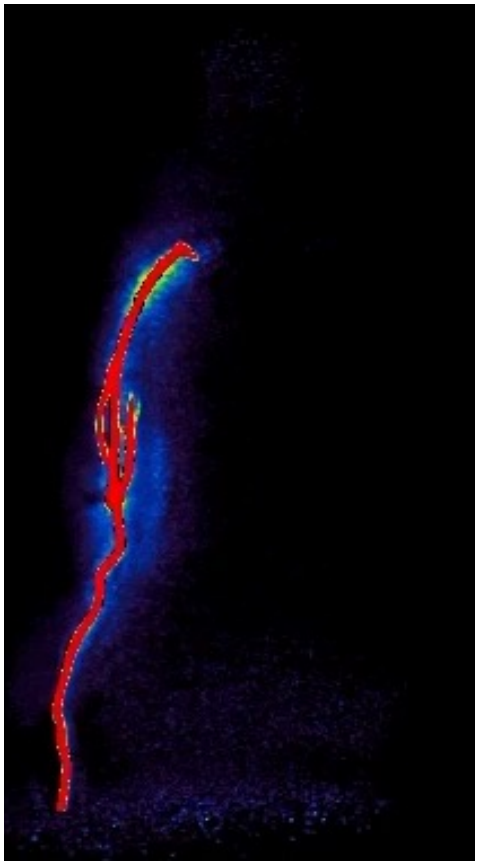




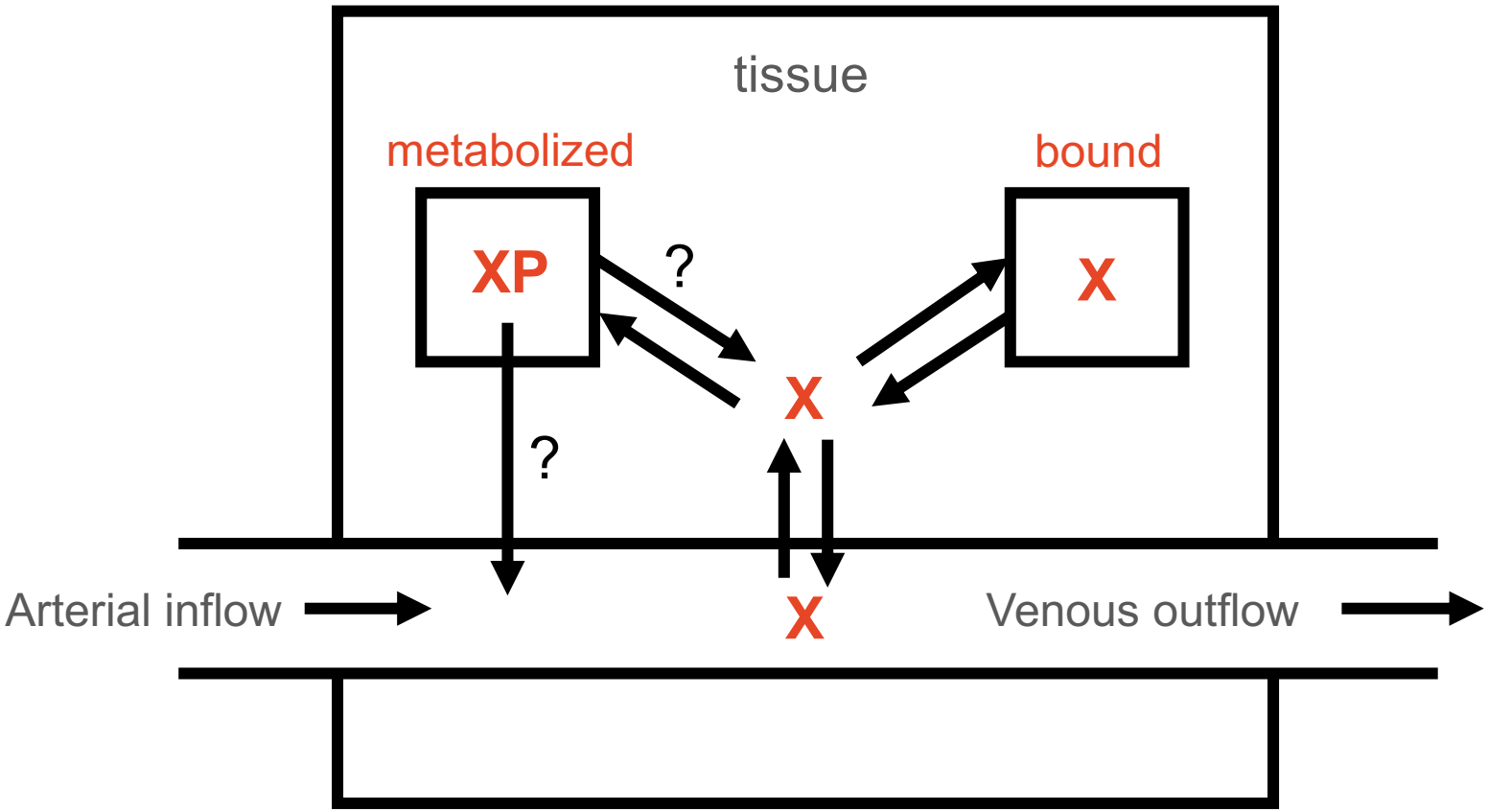


Radiotracer distribution changes with time





A general model of tracer exchange in tissue



Compartments may represent…

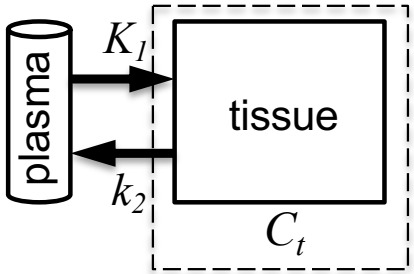
- a **physical** space
  - intravascular, extracellular, or intracellular
- a **pharmacological** state
  - free or bound to protein
- a **metabolic** state
  - parent compound or metabolic product

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

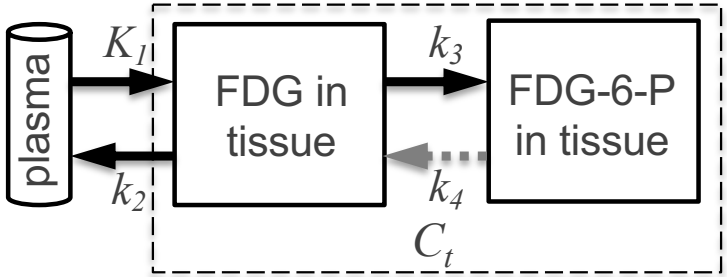
Common compartmental models

Flow model:



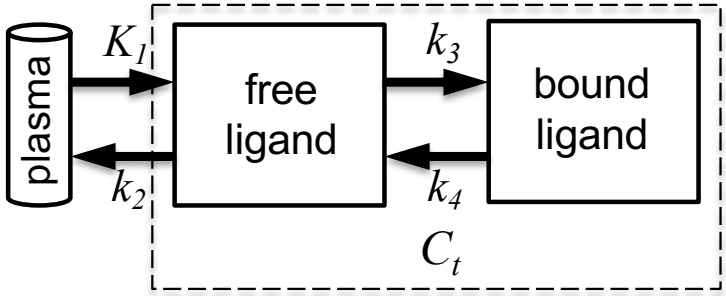
$$K_1 = fE$$

FDG model:



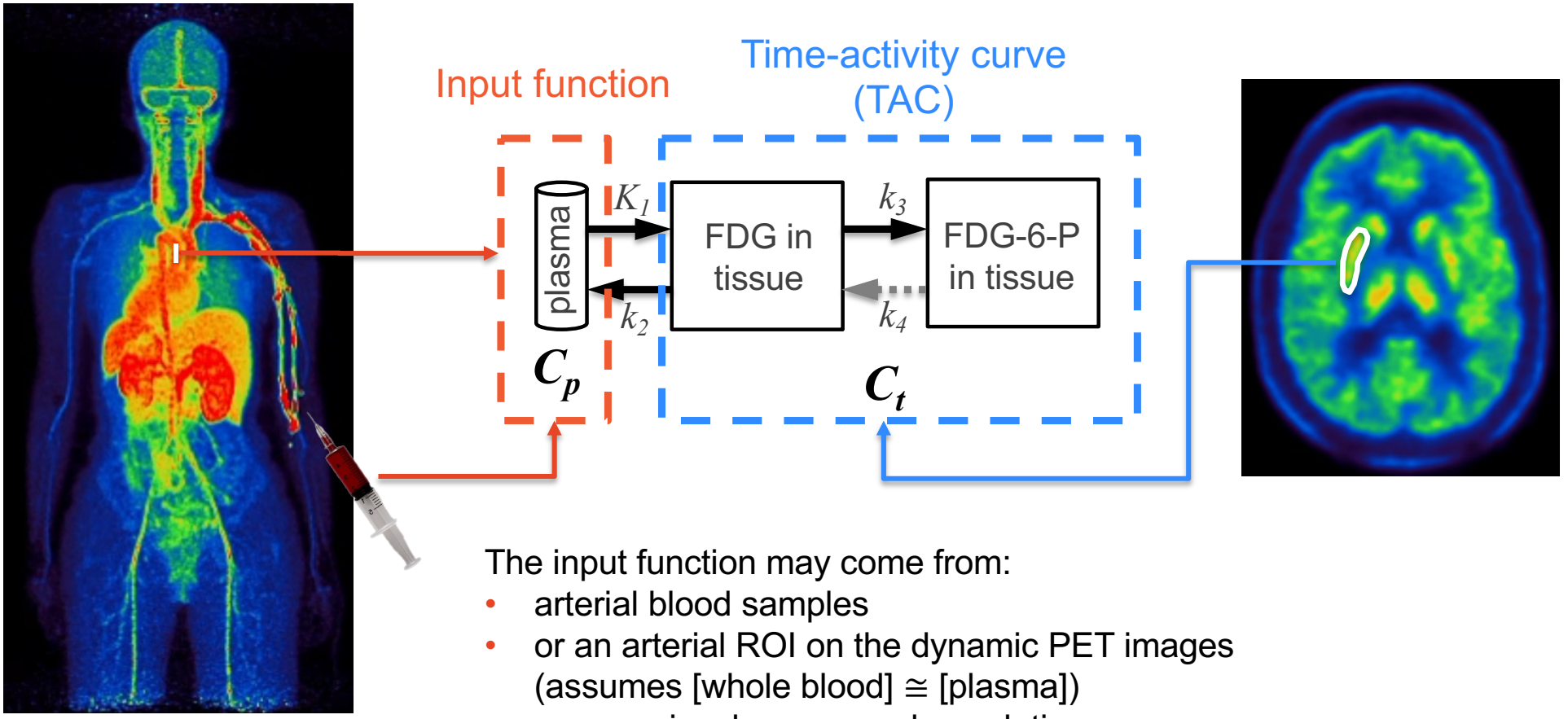
$$K_i = K_1\left(\frac{k_3}{k_2 + k_3}\right)$$

Receptor binding model:



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

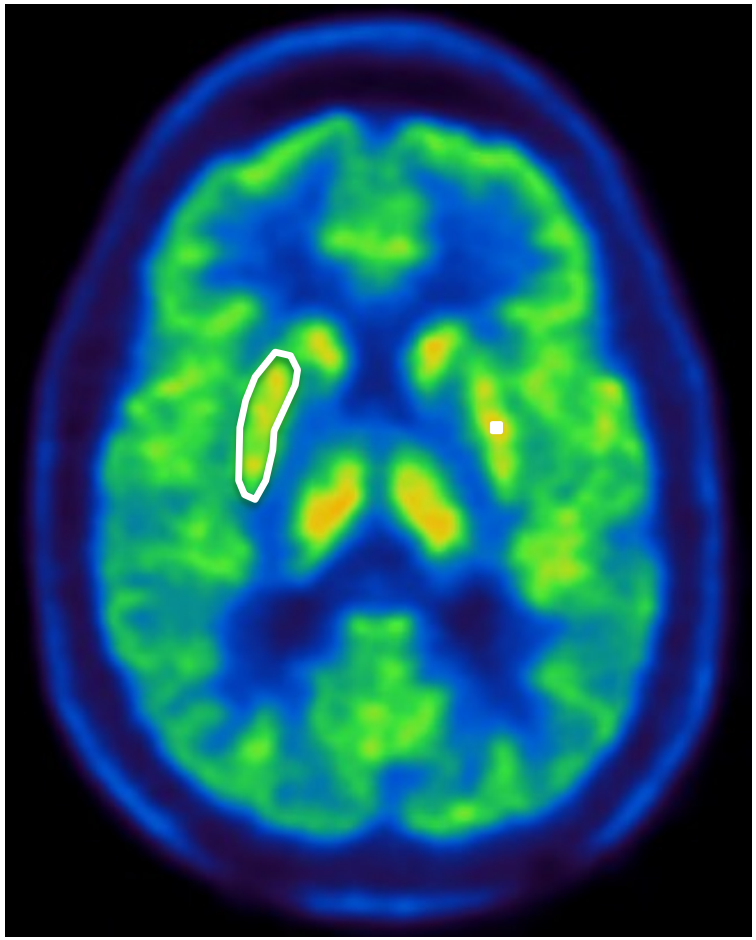
What do these models represent?



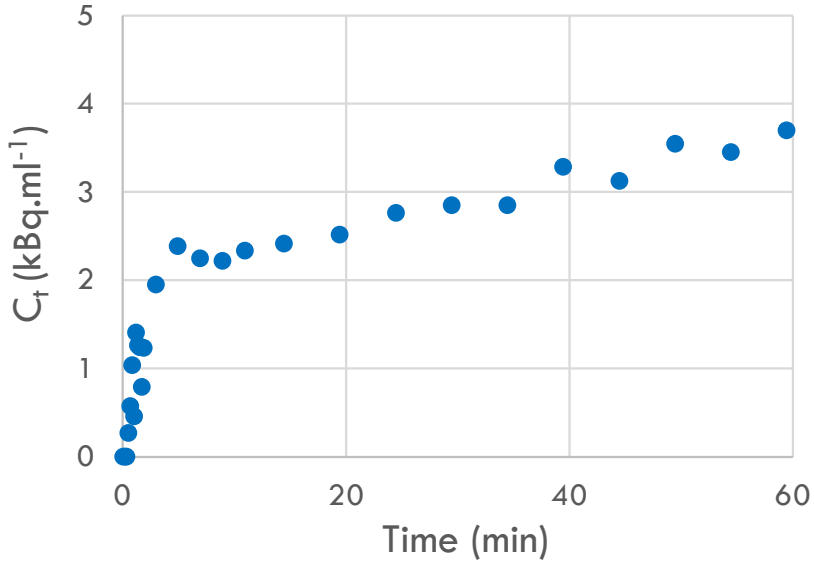
The input function may come from:

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

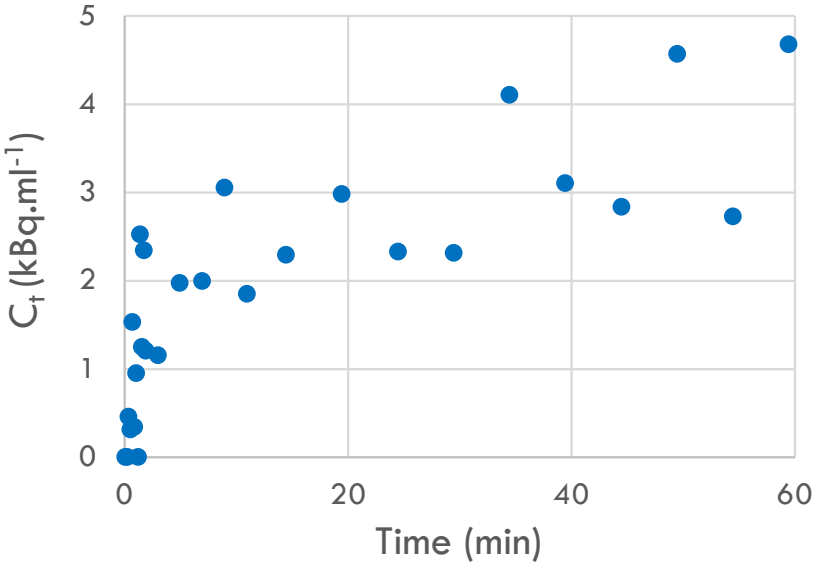
Time-Activity Curves (TAC)



ROI:



voxel:

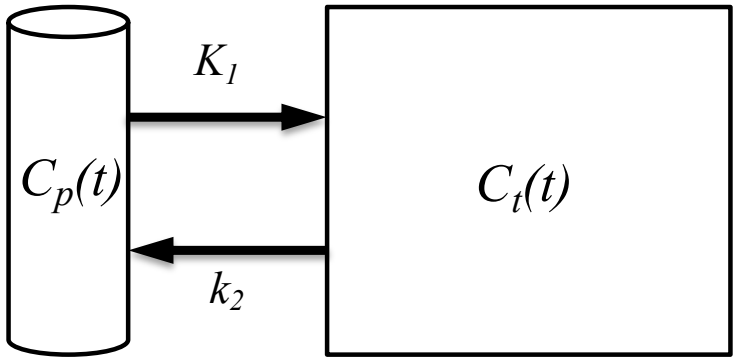


1-Tissue Compartment Model

- K_1 = Flow (F) x Extraction (E)

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

where P = capillary permeability
S = capillary surface area



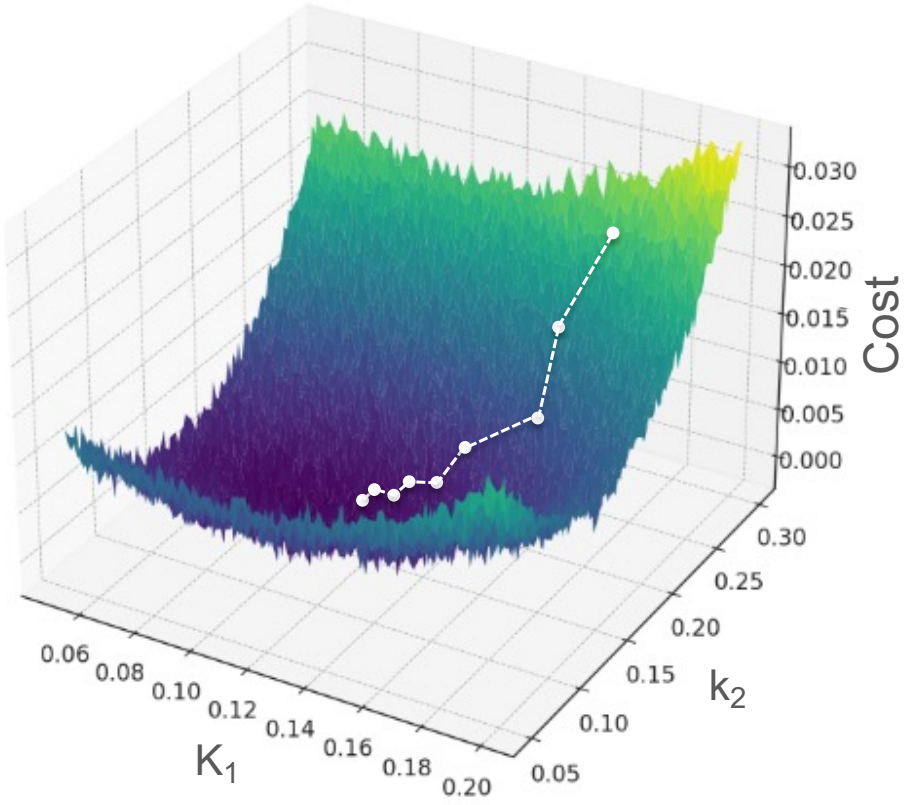
- Limiting cases:
  - $PS >> F$: $K_1 \simeq F$ (e.g. $H_2{}^{15}O$ and other freely diffusible tracers)
  - $F >> PS$: $K_1 \simeq PS$ (most PET tracers)
- Assuming steady-state conditions: $\frac{dC_t}{dt} = K_1 C_p - k_2 C_t$

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
Crone, Acta Physiol Scand 58:292-305 1963, DOI: 10.1111/j.1748-1716.1963.tb02652.x

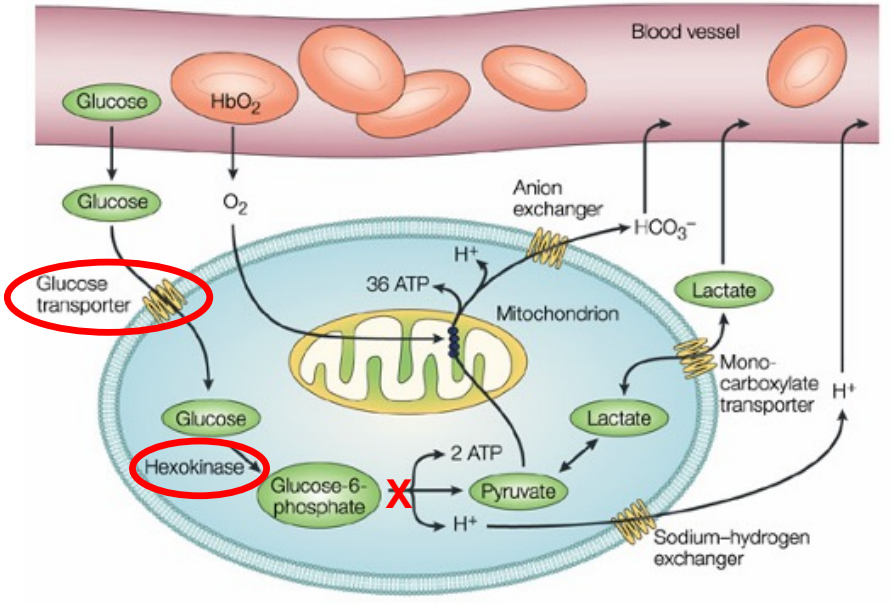
Optimisation



- For a given set of model parameters (K_1, k_2), calculate **cost** as L2 (or L1) distance b/w model-predicted and observed TACs
- Iteratively update parameter estimates using e.g. gradient descent or NLLS
- Continue until **cost** reaches a pre-defined threshold or parameter estimates are not significantly changing

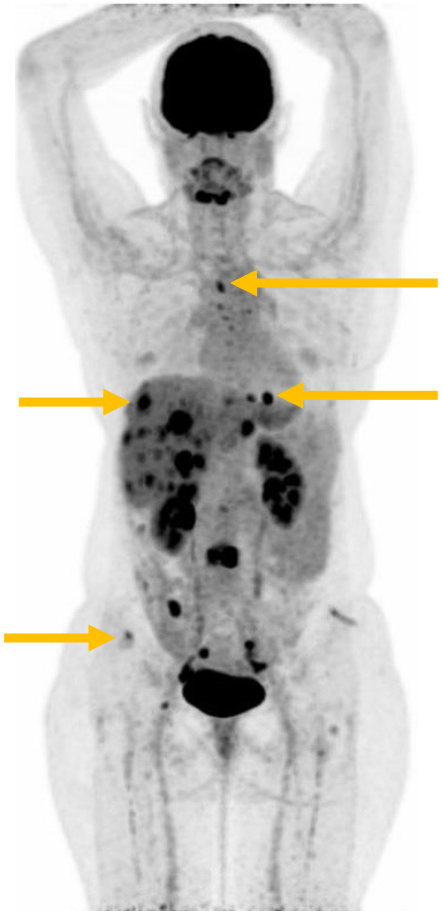
2-Fluoro-2-deoxy-D-glucose (FDG)

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

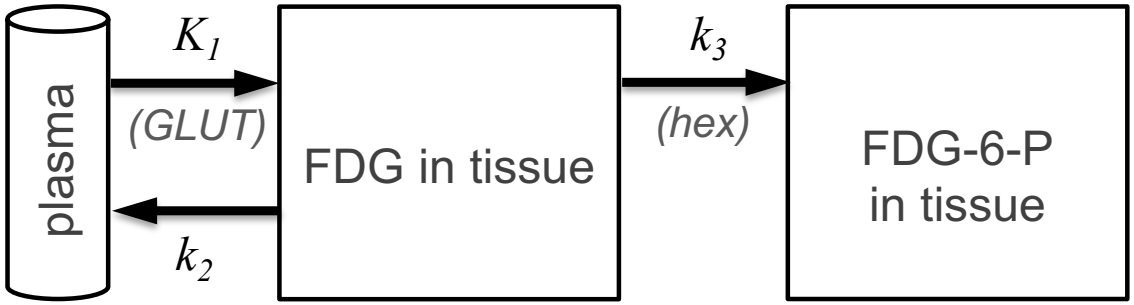


Robert A. Gatenby & Robert J. Gillies *Nature Reviews Cancer* 4, 891 -899 (2004)

^{18}F-FDG PET



FDG 2-Tissue Compartment Model (2TC)

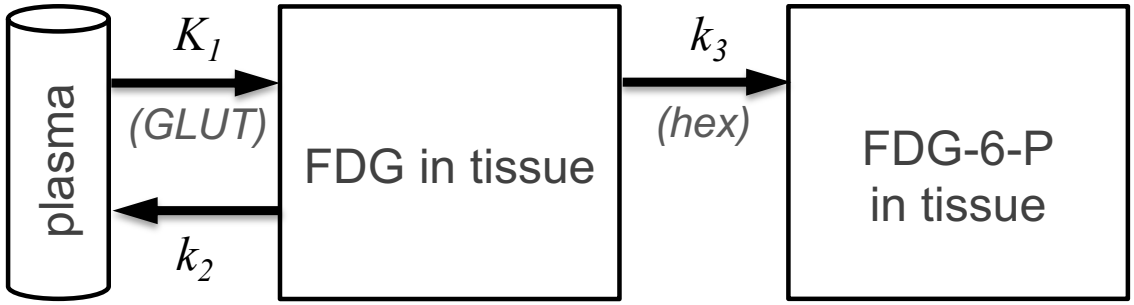


$$K_i = K_1\left(\frac{k_3}{k_2+k_3}\right) = \text{net influx rate (min}^{-1}\text{)}$$

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

C_{glu} = plasma glucose concentration
LC = lumped constant (glucose vs FDG)

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

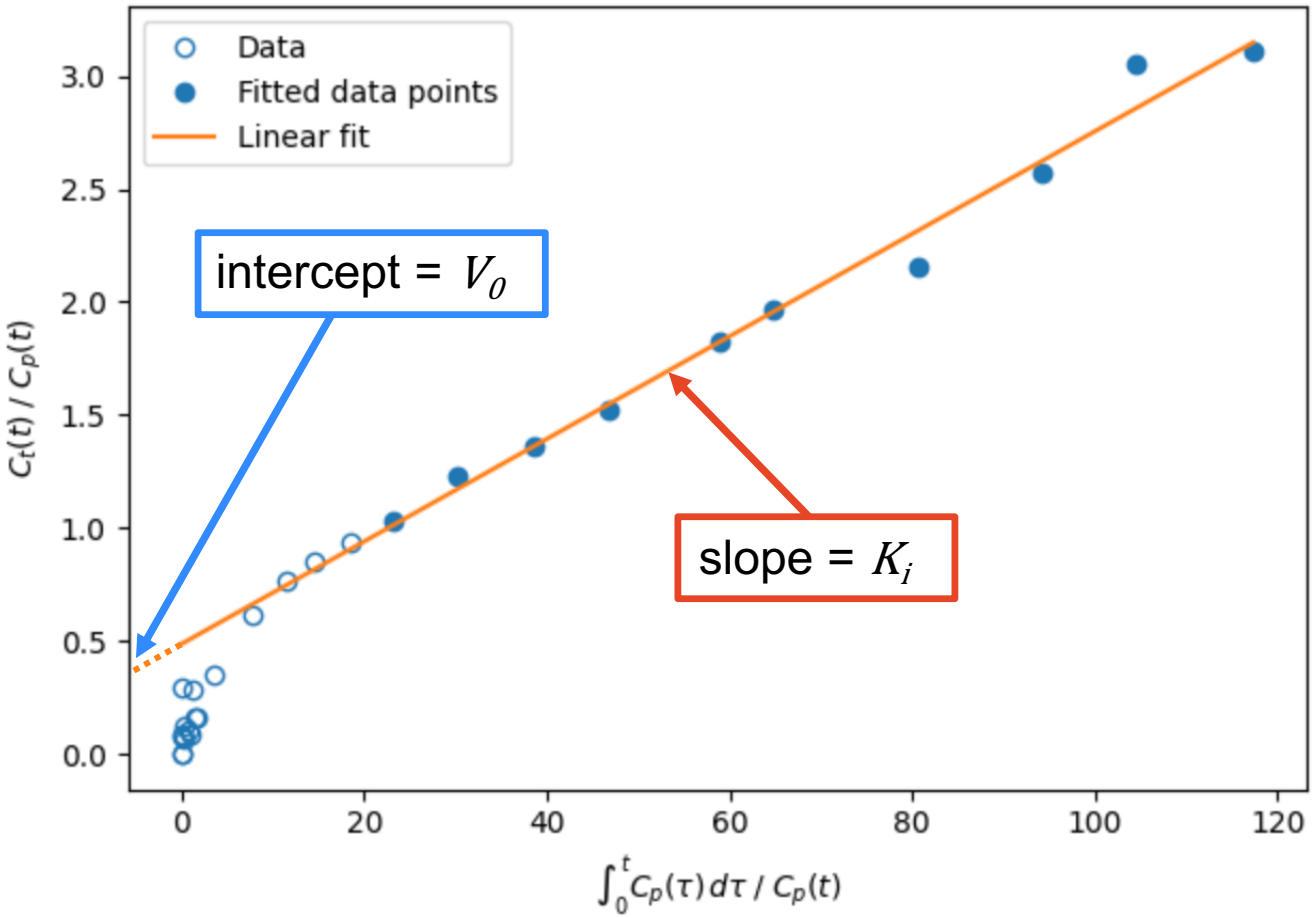
- Now, divide throughout by C_p and we get:

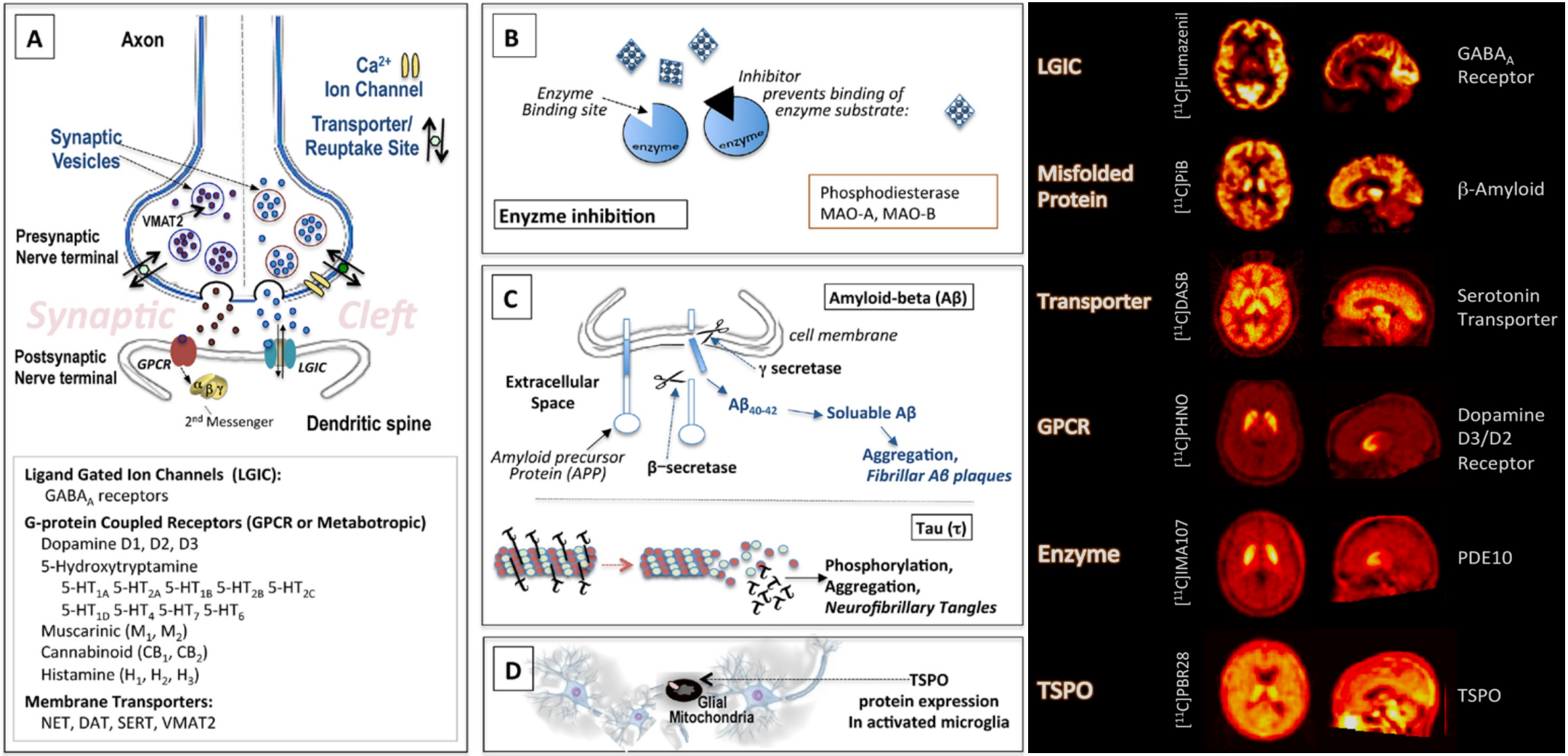
$$\frac{C_t(t)}{C_p(t)} = K_i \frac{\int_0^t C_p(\tau)d\tau}{C_p(t)} + V_0$$

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

Patlak et al., J Cereb Blood Flow Metab 3: 1–7, doi:10.1038/jcbfm.1983.1

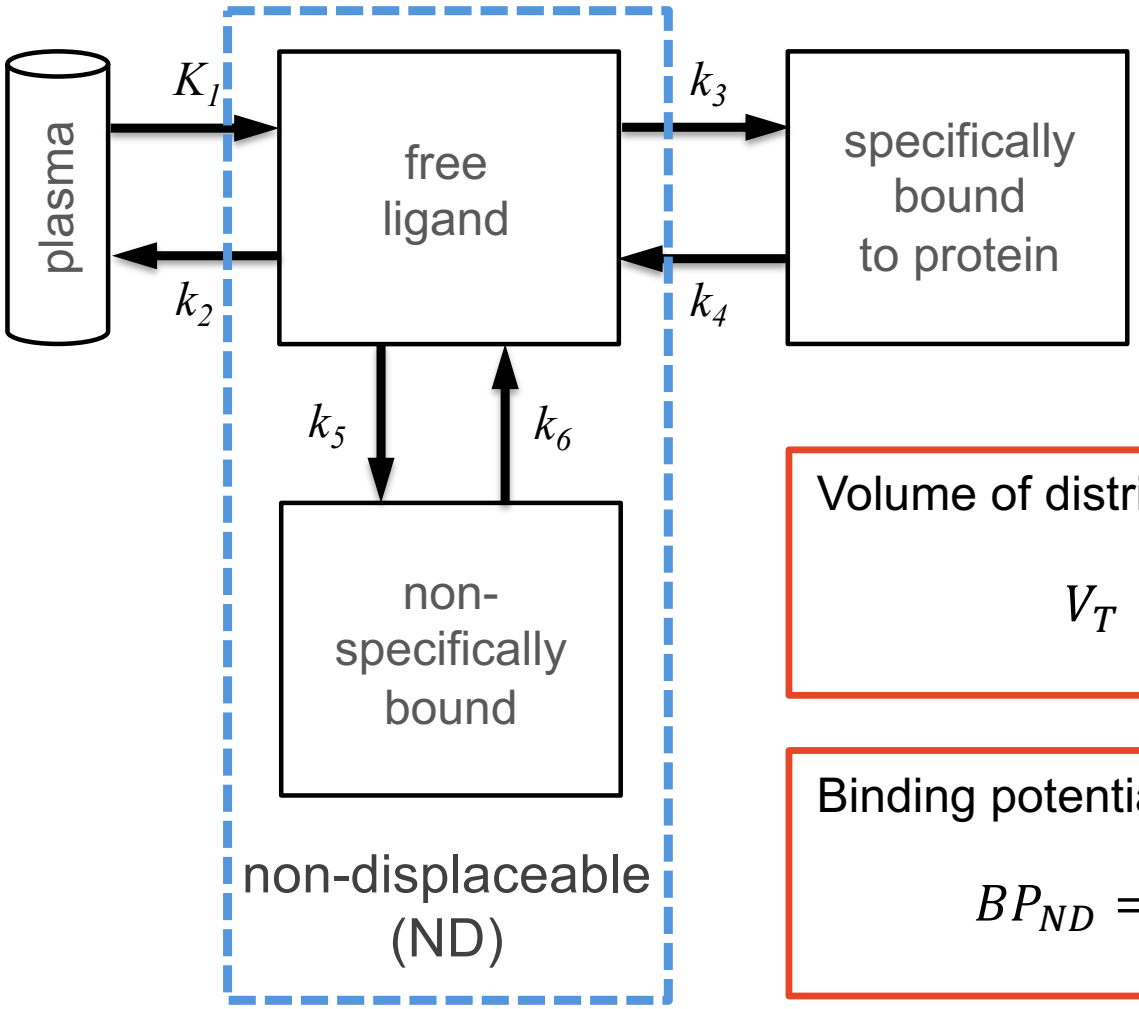
Patlak Plot for [^{18}F]FDG





Gunn et al., Phys Med Biol 60, 2015, DOI: doi:10.1088/0031-9155/60/22/R363

Receptor-Ligand Model



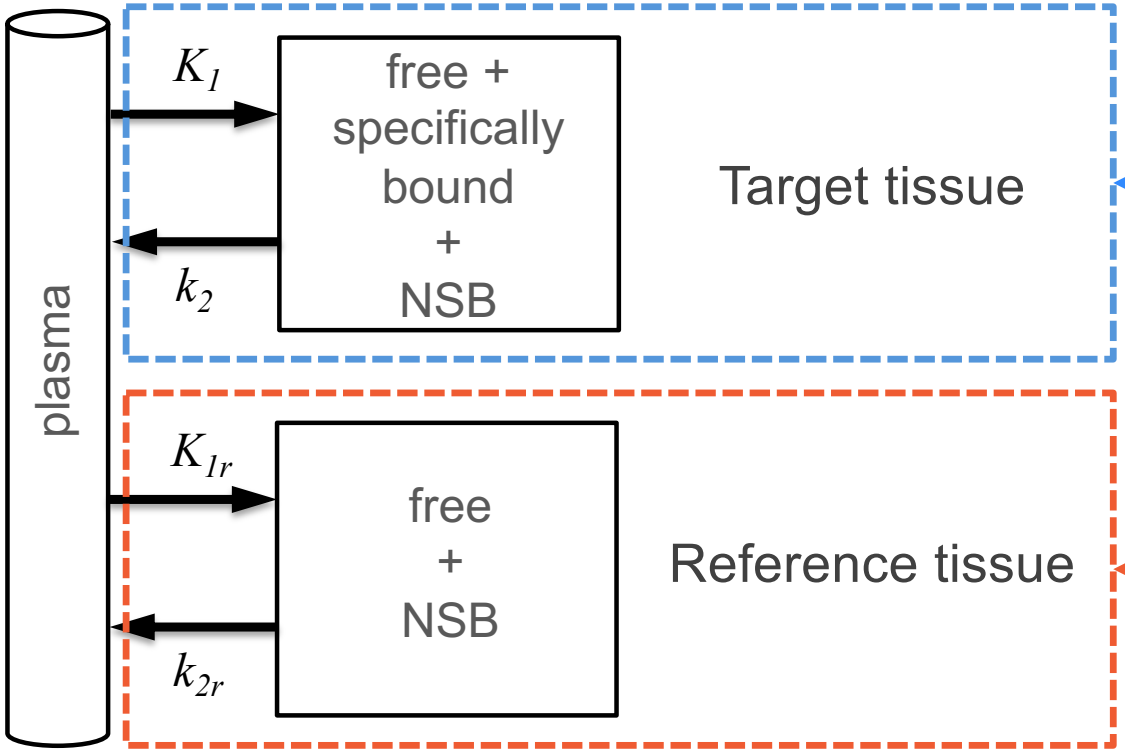
Volume of distribution:

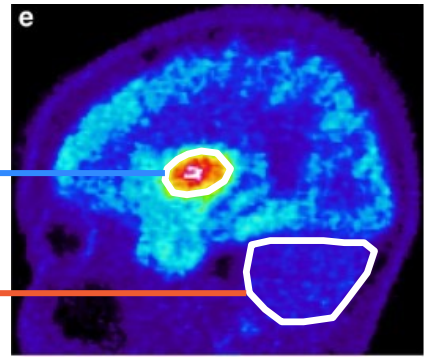
$$V_T = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right)$$

Binding potential:

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

Simplified Reference Tissue Model



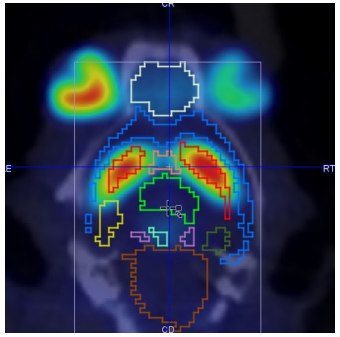


From: Cervenka et al. Transl Psychiatry, DOI: 10.1038/tp.2012.40, 2012

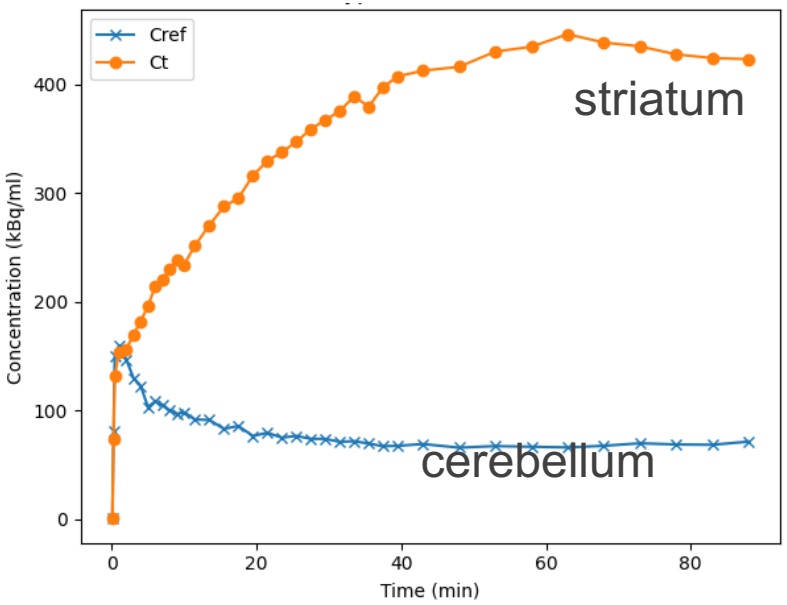
$$C_T(t) = R_1 C_R(t) + \left\{k_2 - \frac{R_1 k_2}{(1 + BP_{ND})}\right\} C_r(t) \otimes \exp\{-k_2 t/(1 + BP_{ND})\}, \quad R_1 = \frac{K_1}{K_{1r}}$$

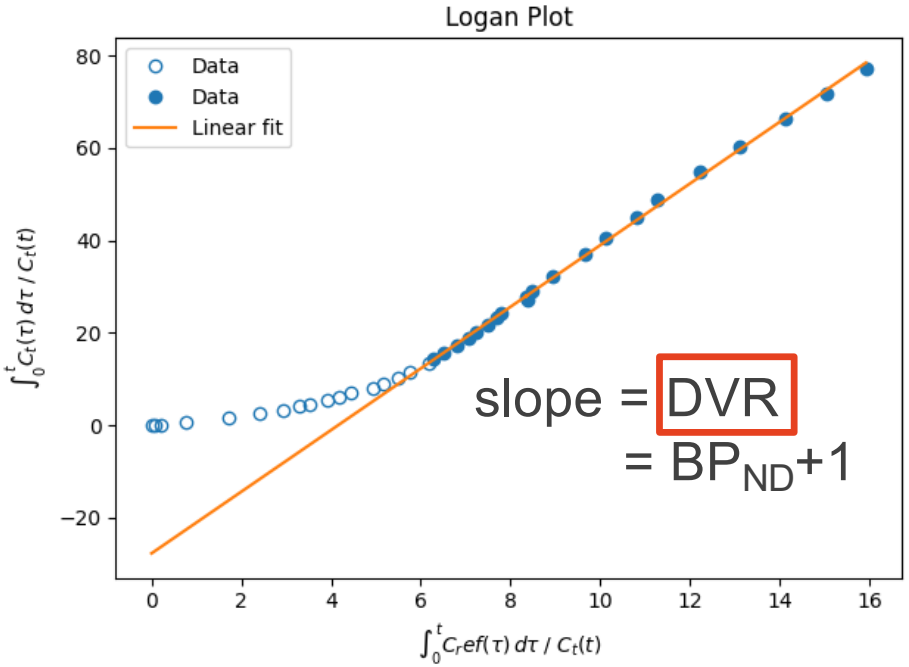
Lammertsma and Hume, Neuroimage 4, 153-158 1996, DOI: doi: 10.1006/nimg.1996.0066

Logan Plot



[^{18}F]Fallypride





$$Y = mX + b$$

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

Logan et al., J Cereb Blood Flow Metab 10:740-7, doi: 10.1038/jcbfm.1990.127

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, Hoye & 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