Basic Principles of Tracer Kinetic Modelling

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The Spectrum of Medical Imaging

Structure	**X-ray/CT/MRI**
Physiology	**US, SPECT, PET, MRI/S**
Metabolism	**PET, MRS**
Drug distribution	**PET**
Molecular pathways	**PET**
Molecular targets	**PET, SPECT**

PET: Quantitative
Picomolar Sensitivity

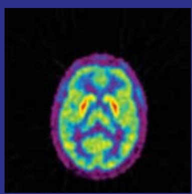
Jones, 1996

PET Diagnosis

Inject

Wait

Scan

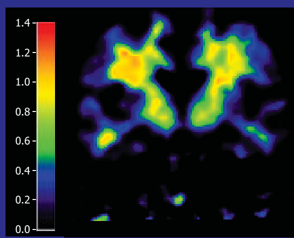


Increased uptake:

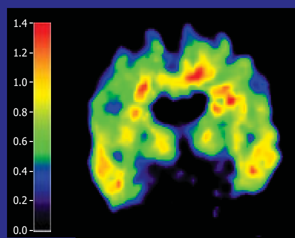
- Increased binding
- Increased flow and/or extraction
- Increased delivery

[11C]PIB Uptake

Control



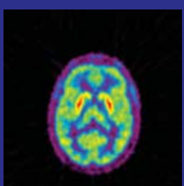
AD



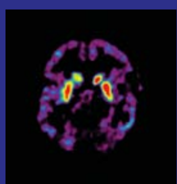
- Qualitative PET sufficient for diagnosis (sensitivity/specificity)
- Quantitative PET needed for monitoring disease progression and response to therapy

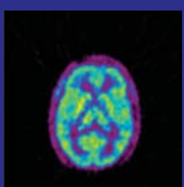
Data Tolboom, Ossenkoppele, et al.

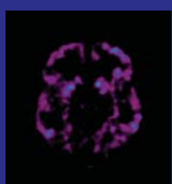
[11C]R116301: NK1 Receptor Ligand



base-line







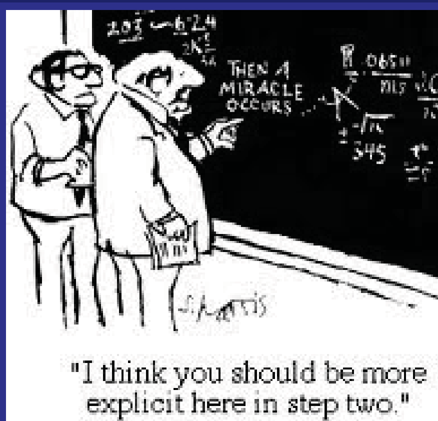
post-aprepitant

Summed image

$BP_{ND} = k_3 / k_4$

Data Wolfensberger et al.

Principles of Modelling



Tracer Model

PET scanner

Measurement Radioactivity

Tracer Model

Quantitative Evaluation Physiological Parameter

Principles of Modelling

Tracer Kinetic Modelling

Tracer Model: Mathematical description of the fate of the tracer in the human body, in particular in the organ under study

Purpose: To quantify functional entities given the distribution of radioactivity

Method: Divide possible distribution of tracer in a limited number of discrete compartments

Compartment Models

Blood

Blood volume tracer

Blood ⇄ Tissue

Blood flow tracer

Tissue

Blood ⇄ Free ⇄ Bound

Glucose metabolism

Receptor ligand

Multiple parameters → Dynamic scanning

Delivery through arterial blood → Input function

Nomenclature

Consensus nomenclature for in vivo imaging of reversibly binding radioligands

Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE

J Cereb Blood Flow Metab (2007) **27**: 1533–1539

Blood Flow

$H_2{}^{15}O$ as Perfusion Tracer

Advantages
- Freely diffusible
- Metabolically inert
- Simple kinetics
- Short half life (2 min) → Repeat measurements

Disadvantages
- Short half life → On-site cyclotron

Single Tissue Compartment Model

Blood | Tissue

C_A $\underset{k_2}{\overset{K_1}{\rightleftarrows}}$ C_T

$$dC_T/dt = K_1 \cdot C_A - k_2 \cdot C_T$$
$$K_1 = E \cdot F;\ \ H_2{}^{15}O: E = 1 \rightarrow K_1 = F$$
$$V_T = K_1/k_2 \rightarrow k_2 = K_1/V_T;\ \ H_2{}^{15}O: k_2 = F/V_T$$

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$H_2{}^{15}O$ Compartment Model

Blood | Tissue

C_A $\underset{F/V_T}{\overset{F}{\rightleftarrows}}$ C_T

$$dC_T/dt = F \cdot C_A - (F/V_T) \cdot C_T$$

Solution: $C_T(t) = F \cdot C_A(t) \otimes e^{-(F/V_T)t}$ ⟶ History

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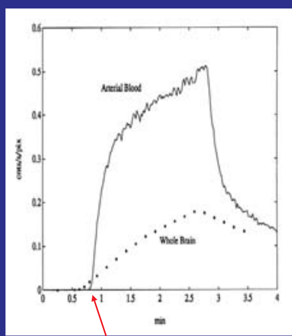
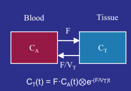
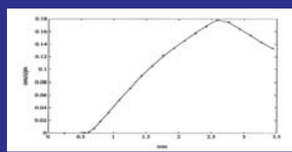
$H_2{}^{15}O$ Time-Activity Curves



Delay and dispersion



Non-linear regression



Lammertsma et al. (1990) *J Cereb Blood Flow Metab* **10**: 675-686.

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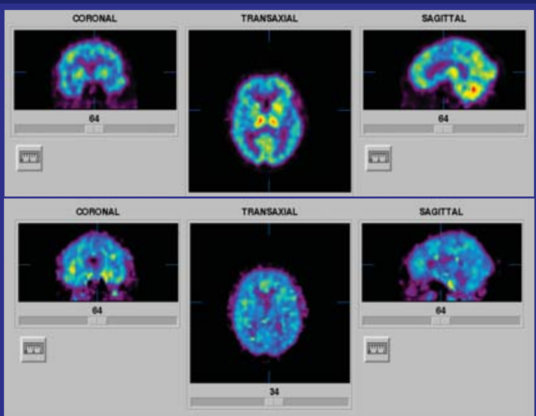
Parametric Images

CBF

V_T



Data Rijbroek, Boellaard, et al.

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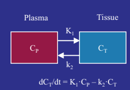
Volume of Distribution

Equilibrium - partition coefficient
- $dC_T(t)/dt = 0;\ dC_P(t)/dt = 0$
- $V_T = C_T/C_P$

Non-equilibrium
- $V_T = \int C_T / \int C_P$



Single tissue compartment model
- $dC_T(t)/dt = K_1 C_P(t) - k_2 C_T(t)$
- At equilibrium:
- $K_1 C_P(t) - k_2 C_T(t) = 0 \rightarrow V_T = C_T/C_P = K_1/k_2$

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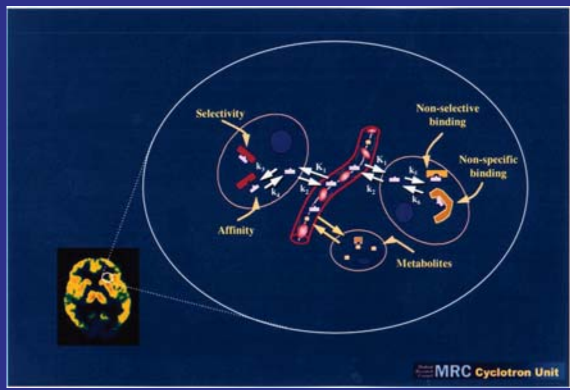
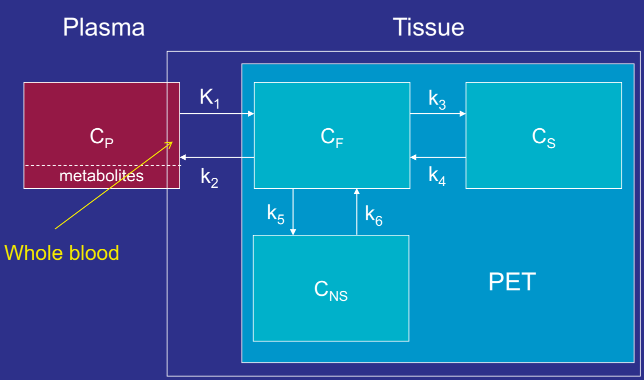
Receptor Studies

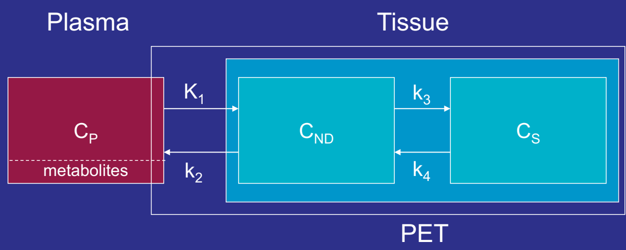
Receptor Ligand Uptake



Three Tissue Compartment Model

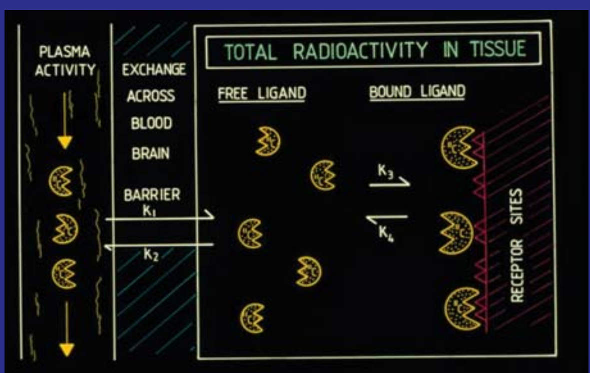


Two Tissue Compartment Model



Exchange between C_F and C_{NS} fast $\rightarrow$ $C_{ND} = C_F + C_{NS}$

Receptor Ligand Model



Quantitative PET Study

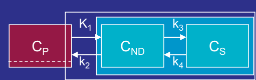
Injection of positron emitting tracer

Measurement of time-activity curves

Input: plasma (C_P) + whole blood (C_{WB})

Response:

- Ideal: tissue (C_T)
- Actual: PET (C_{PET})



Solution

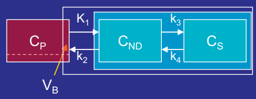
$C_{PET} = f\,(C_P, C_{WB}, \text{parameters})$

PET Receptor Studies

PET measurement

$C_{PET}(t) = (1\text{-}V_B)\cdot C_T(t) + V_B\cdot C_{WB}(t)$

$C_T(t) = C_{ND}(t) + C_S(t)$



Differential equations

$dC_{ND}(t)/dt = K_1C_P(t) - k_2C_{ND}(t) - k_3C_{ND}(t) + k_4C_S(t)$

$dC_S(t)/dt = k_3C_{ND}(t) - k_4C_S(t)$

PET Receptor Studies

Relationship with pharmacological parameters

$k_3 = f_{ND}\cdot k_{on}\cdot(B_{avail} - C_S(t)/SA)$

$k_4 = k_{off}$

Note: $B_{avail} = B_{max} - B_{occ}$ (e.g. endogenous ligand)

Tracer alone

$k_3 = f_{ND}\cdot k_{on}\cdot B_{avail}$

$k_4 = k_{off}$

$K_D = k_{off}/k_{on} \rightarrow BP_{ND} = k_3/k_4 = f_{ND}\cdot B_{avail}/K_D$

Receptor Studies

Parameter of interest

Binding Potential: $BP_{ND} = k_3 / k_4$

Tracer alone

$BP_{ND} = f_{ND} \bullet B_{avail} / K_D$

Multiple studies in same subject

Separate assessment B_{avail} and K_D

Receptor Studies

Parameters of interest

Binding Potential: $BP_{ND} = k_3/k_4$

Reflects specific binding

Tracer alone: $BP_{ND} = f_{ND}\cdot B_{avail}/K_D$

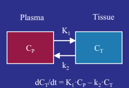
Volume of distribution: $V_T = K_1/k_2\cdot(1+k_3/k_4)$

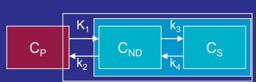
Contains non-displaceable component

Volume of Distribution

Single tissue compartment model

At equilibrium: $V_T = C_T/C_P = K_1/k_2$





Two tissue compartment model

At equilibrium: $dC_{ND}(t)/dt = dC_S(t)/dt = 0$

$dC_S/dt = k_3C_{ND}\text{-}k_4C_S = 0 \rightarrow C_S = (k_3/k_4)\cdot C_{ND}$

$\rightarrow V_T = C_T/C_P = (C_{ND}+C_S)/C_P = (1+k_3/k_4)\cdot C_{ND}/C_P$

$dC_{ND}/dt+dC_S/dt = K_1C_P\text{-}k_2C_{ND} = 0 \rightarrow C_{ND} = (K_1/k_2)\cdot C_P$

$\rightarrow \mathbf{V_T = K_1/k_2\cdot(1+k_3/k_4)}$

Binding Potential

Plasma input model

Direct

$BP_{ND} = k_3/k_4$

But: often unstable

Indirect

Target tissue: $V_T = K_1/k_2\cdot(1+k_3/k_4)$

Reference tissue: $V_T' = K_1'/k_2' = K_1/k_2$

$BP_{ND} = (V_T\text{-}V_T')/V_T'$

But: reference tissue required

Reference tissue model

Binding Potential Definitions

Relative to non-displaceable concentration:

$BP_{ND} = f_{ND}B_{avail}/K_D = (V_T - V_{ND})/V_{ND} = k_3/k_4$

Relative to total plasma concentration:

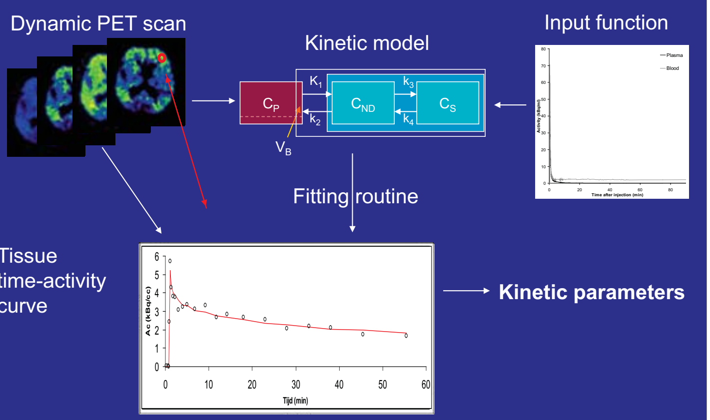
$BP_P = f_P B_{avail}/K_D = V_T - V_{ND} = K_1 k_3/k_2 k_4$

Relative to free plasma concentration:

$BP_F = B_{avail}/K_D = (V_T - V_{ND})/f_P = K_1 k_3/f_P k_2 k_4$

Overview Kinetic Analysis Process

Overview kinetic analysis



Limitations

Limitations Tracer Procedures

Theoretical
- Model simplifications
- Complexity physiological process

Practical
- Performance scanner
- Imperfect implementation
- Complexity procedure

Model Simplifications

Measurement of blood volume using $C^{15}O$

Blood sample:

100% blood, concentration C_A

Blood

PET scanner:

"tissue" concentration C_T

Tissue

Blood concentration is constant:

tissue BV = C_T / C_A

Model Simplifications

$C^{15}O$ is a red cell marker

Capillary haematocrit < large vessel hematocrit

- Whole blood concentration is <u>not</u> constant

Correction for haematocrit difference required

- Separate haematocrit measurement
- Alternative: fixed haematocrit ratio
  - Assumed haematocrit ratio to be checked in pathology

Pathophysiology

A tracer procedure should be reassessed for each new pathophysiological condition

↓

Possible breakdown of the model should be considered in interpreting clinical data

Limitations Tracer Procedures

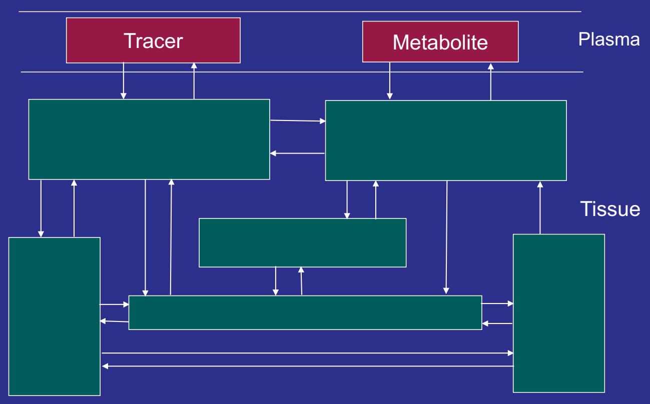
Theoretical

- Model simplifications
- Complexity physiological process

Practical

- Performance scanner
- Imperfect implementation
- Complexity procedure

Complexity Physiological Process



Questions