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, SPECT

Molecular targets

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\(_{AD}\) = \(k_3 / k_4\)

[11C]R116301: NK1 Receptor Ligand

Principles of Modelling

"I think you should be more explicit here in step two."
Tracer Model

**Measurement**

**Radioactivity**

**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 volume tracer
- Blood flow tracer
- Glucose metabolism
- Receptor ligand

Nomenclature

**Consensus nomenclature for in vivo imaging of reversibly binding radioligands**


Blood Flow
**H₂¹⁵O 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**

\[
\frac{dc_T}{dt} = K_1 C_A - k_2 C_T
\]

\[
C_T(t) = C_A(t) \cdot e^{-(F/V_T)t}
\]

**History**

- Delay and dispersion

**H₂¹⁵O Time-Activity Curves**

- Non-linear regression

**Volume of Distribution**

**Equilibrium - partition coefficient**

\[
\frac{dC_f}{dt} = 0; \frac{dC_p}{dt} = 0
\]

\[
V_T = C_f/C_p
\]

**Non-equilibrium**

\[
V_T = [C_f]/C_p
\]

**Single tissue compartment model**

\[
\frac{dC_f}{dt} = K_1 C_p(t) - k_2 C_f(t)
\]

At equilibrium:

\[
k_1 C_p(t) - k_2 C_f(t) = 0 \rightarrow V_T = C_f/C_p = k_1/k_2
\]

**Parametric Images**

- CBF
- VT
Receptor Studies

Three Tissue Compartment Model

Two Tissue Compartment Model

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**

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

\[ C_T(t) = C_{\text{ND}}(t) + C_S(t) \]

**Differential equations**

\[ \frac{dC_{\text{ND}}(t)}{dt} = K_1 C_{P}(t) - k_2 C_{\text{ND}}(t) - k_3 C_{\text{ND}}(t) + k_4 C_S(t) \]

\[ \frac{dC_S(t)}{dt} = k_3 C_{\text{ND}}(t) - k_4 C_S(t) \]

**Relationship with pharmacological parameters**

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

\[ k_4 = k_{\text{off}} \]

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

**Tracer alone**

\[ k_3 = f_{\text{ND}} \cdot k_{\text{on}} \cdot B_{\text{ avail}} \]

\[ k_4 = k_{\text{off}} \]

\[ K_D = k_{\text{off}}/k_{\text{on}} \]

\[ B_{\text{ND}} = k_3/k_4 = f_{\text{ND}} \cdot B_{\text{avail}}/K_D \]

**Receptor Studies**

**Parameter of interest**

- Binding Potential: \( B_{\text{ND}} = k_3/k_4 \)

**Tracer alone**

- \( B_{\text{ND}} = f_{\text{ND}} \cdot B_{\text{ avail}} / K_D \)

**Multiple studies in same subject**

- Separate assessment \( B_{\text{ avail}} \) and \( K_D \)

**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: \( dC_{\text{ND}}(t)/dt = dC_S(t)/dt = 0 \)

\[ dC_S/dt = k_3 C_{\text{ND}}(t) - k_4 C_S(t) \]

\[ dC_{\text{ND}}/dt = (k_3 C_P - C_S)/C_P = (k_3/k_4) \cdot C_{\text{ND}} \]

\[ V_T = K_1/k_2 \cdot (1+k_3/k_4) \]

\[ \text{Plasma input model} \]

**Direct**

- \( B_{\text{ND}} = k_3/k_4 \)

**But: often unstable**

**Indirect**

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

- Reference tissue: \( V_{T'} = K_1'/k_2' = K_1/k_2 \)

- \( B_{\text{ND}} = (V_T-V_{T'})/V_{T'} \)

**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:

$$BP_P = f_PB_{avail}/K_D = V_T - V_{ND} = K_1k_3/k_2k_4$$

Relative to free plasma concentration:

$$BP_F = B_{avail}/K_D = (V_T - V_{ND})/f_P = K_1k_3/k_2k_4$$

**Overview Kinetic Analysis Process**

**Overview kinetic analysis**

Dynamic PET scan

Kinetic model

Input function

Fitting routine

Kinetic parameters

**Limitations**

**Limitations Tracer Procedures**

**Theoretical**
- Model simplifications
- Complexity physiological process

**Practical**
- Performance scanner
- Imperfect implementation
- Complexity procedure

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**Model Simplifications**

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

**Blood sample:**
- 100% blood, concentration $C_A$

**PET scanner:**
- "tissue" concentration $C_T$

**Blood concentration is constant:**
- $tissue\ BV = C_T / C_A$
Model Simplifications

C¹⁸O is a red cell marker
Capillary haematocrit < large vessel hematocrit
Whole blood concentration is not 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