Introduction to PET Pharmacokinetics:

One and Two Tissue Compartment Models
Review

MASS ACTION LAW:

\[
\frac{dB}{dt} = k_{\text{ON}} (B_{\text{MAX}} - B)F - k_{\text{OFF}} B
\]

\[
\frac{dB}{dt} = k_{\text{ON}} B_{\text{MAX}} F - k_{\text{OFF}} B
\]

EQUILIBRIUM:

\[
B = B_{\text{MAX}} \times \frac{F}{K_D + F}
\]

\[
B = \frac{B_{\text{MAX}}}{F/K_D}
\]

NONSPECIFIC BINDING:

\[
\frac{dNS}{dt} = k_{\text{ON}} (M_{\text{MAX}} - \text{NS})F - k_{\text{OFF}} \text{NS}
\]

\[
\text{NS} \propto F
\]

TRANSPORT:

\[
\frac{dC_2}{dt} = f_1 C_1 - f_2 C_2
\]
Compartment Model Concept

- Simplified way to trace a quantity through different states
- The states of the quantity may or may not occupy the same physical space (in our case they will)
- Will only be concerned with *LINEAR* compartment models
RULES:  1. EACH COMPARTMENT IS DEPICTED BY A BOX
2. THE QUANTITY (RADIOACTIVITY, TRACER CONCENTRATION) MOVES BETWEEN STATES (COMPARTMENTS) IN DIRECTIONS DESIGNATED BY ARROWS

Goes from C1 to C2 and from C2 to C1 and effluxes from C2
Compartment Model Concept

RULES:  
1. EACH COMPARTMENT IS DEPICTED BY A BOX  
2. THE QUANTITY (RADIOACTIVITY, TRACER CONCENTRATION) MOVES BETWEEN STATES (COMPARTMENTS) IN DIRECTIONS DESIGNATED BY ARROWS  
3. RATE IS PROPORTIONAL TO CONCENTRATION IN COMPARTMENT OF ORIGIN; CONSTANTS OF PROPORTIONALITY ARE RATE CONSTANTS K.

![Diagram of Compartment Model](image)

- Forward Rate = $K_1 C_1$
- Backward Rate = $k_2 C_2$
RULES: 1. EACH COMPARTMENT IS DEPICTED BY A BOX 
2. THE QUANTITY (RADIOACTIVITY, TRACER CONCENTRATION) MOVES BETWEEN STATES (COMPARTMENTS) IN DIRECTIONS DESIGNATED BY ARROWS 
3. RATE IS PROPORTIONAL TO CONCENTRATION IN COMPARTMENT OF ORIGIN; CONSTANTS OF PROPORTIONALITY ARE RATE CONSTANTS K.

COMPARTMENT 1

COMPARTMENT 2

SOURCE

K_1

K_2

K_3

K_4
Compartment Model Concept

One Tissue Compartment Model (1TC, reversible)

\[
\frac{dC(t)}{dt} = K_1 C_p(t) - k_2 C(t)
\]

\(C(t)\) increases at the rate \(K_1 C_p(t)\)

\(C(t)\) decreases at the rate \(k_2 C(t)\)
Two Tissue Compartment Model (2TC, reversible)

\[
\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3)C_1(t) + k_4 C_2(t)
\]

\[
\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t)
\]
Two Tissue Compartment Model (2TC, irreversible)

\[
\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3)C_1(t)
\]

\[
\frac{dC_2(t)}{dt} = k_3 C_1(t)
\]
Compartment Model Application

\[ C_p(t) \xrightarrow{K_1} C_F(t) \xleftarrow{k_2} C_{NS}(t) \xrightarrow{k_5} C_s(t) \xleftarrow{k_6} \]

(RAPID EQUILIBRATION)
Compartment Model Application

\[ C_{ND}(t) = C_F + C_{NS} \]  (RAPID EQUILIBRATION)
Compartment Model Application

TRANSPORT LAW (FICK’S PRINCIPLE)  SPECIFIC BINDING (MASS ACTION)
Compartment Model Application

WHAT WE SEE: \( C_T + \%BV \times C_B \)
WHAT WE SEE:  $C_T$

CANNOT DISAMBIGUATE $C_{ND}$ FROM $C_S$; ONLY THEIR SUM $C_T$
\[
\frac{dC_{ND}(t)}{dt} = K_1 C_P(t) - (k_2 + k_3)C_{ND}(t) + k_4 C_S(t)
\]
\[
\frac{dC_S(t)}{dt} = k_3 C_{ND}(t) - k_4 C_S(t)
\]
\[ 0 = K_1 C_p(t) - (k_2 + k_3)C_{ND}(t) + k_4 C_S(t) \]

\[ 0 = k_3 C_{ND}(t) - k_4 C_S(t) \]
Equilibria and Distribution Volumes

\[
\begin{align*}
\frac{C_{ND}}{C_P} &= V_{ND} = \frac{K_1}{k_2} \\
\frac{C_S}{C_P} &= V_S = \frac{K_1 k_3}{k_2 k_4} \\
\frac{C_T}{C_P} &= V_T = \frac{K_1}{k_2} \left(1 + \frac{k_3}{k_4}\right)
\end{align*}
\]

0 = \( K_1 C_P(t) - (k_2 + k_3)C_{ND}(t) + k_4 C_S(t) \)

0 = \( k_3 C_{ND}(t) - k_4 C_S(t) \)
Equilibria and Distribution Volumes

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

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

\[
\int_0^\infty \frac{dC(t)}{dt} \, dt = \lim_{T \to \infty} \left( C(T) - C(0) \right) = 0
\]
Equilibria and Distribution Volumes

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

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

\[
C_{\text{ND}}(T) = \lim_{T \to \infty} K_1 \int_0^T C_P \, dt - (k_2 + k_3) \int_0^T C_{\text{ND}} \, dt + k_4 \int_0^T C_S \, dt
\]

\[
C_S(T) = \lim_{T \to \infty} k_3 \int_0^T C_{\text{ND}} \, dt - k_4 \int_0^T C_S \, dt
\]
Equilibria and Distribution Volumes

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

\[
0 = k_3 \int_0^\infty C_{\text{ND}} \, dt - k_4 \int_0^\infty C_S \, dt
\]
Equilibria and Distribution Volumes

\[ V_{ND} = \frac{\int_{0}^{\infty} C_{ND} \, dt}{\int_{0}^{\infty} C_{P} \, dt} \quad V_{S} = \frac{\int_{0}^{\infty} C_{S} \, dt}{\int_{0}^{\infty} C_{P} \, dt} \quad V_{T} = \frac{\int_{0}^{\infty} C_{T} \, dt}{\int_{0}^{\infty} C_{P} \, dt} \]

\[ 0 = K_{1} \int_{0}^{\infty} C_{P} \, dt - (k_{2} + k_{3}) \int_{0}^{\infty} C_{ND} \, dt + k_{4} \int_{0}^{\infty} C_{S} \, dt \]

\[ 0 = k_{3} \int_{0}^{\infty} C_{ND} \, dt - k_{4} \int_{0}^{\infty} C_{S} \, dt \]
Equilibria and Distribution Volumes

\[
C_T = C_{ND} + C_S
\]

\[
\frac{C_T}{C_P} = \frac{C_{ND}}{C_P} + \frac{C_S}{C_P}
\]

\[
V_T = V_{ND} + V_S
\]
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

$F_L$ (perfusion; we call it flow)  
Units = \frac{\text{mL(blood)}}{\text{g(tissue)} \times \text{minute}}$

$E$ (First pass extraction fraction, unitless)  
\[ \frac{c_a - c_v}{c_a} \]

Kety: Rate of Delivery = $F_LEC_P(t)$

Units = \frac{\text{mL(blood)}}{\text{g(tissue)} \times \text{minute}} \times \frac{\text{mass}}{\text{mL(blood)}} = \frac{\text{mass}}{\text{gram} \times \text{minute}}$
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

Extraction Fraction $\sim$ exponential

Fick’s Principle: $\frac{dC_a(y)}{dt} \propto C_T(y) - C_a(y) \sim -kC_a(x)$
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

Extraction Fraction $\sim$ exponential
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

Extraction Fraction $\sim$ exponential

Time $\Delta t$
Distance $\Delta x$
Concentration $C_a(1-k\Delta t)$
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

Extraction Fraction $\sim$ exponential

<table>
<thead>
<tr>
<th>Time</th>
<th>$2\Delta t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance</td>
<td>$2\Delta x$</td>
</tr>
<tr>
<td>Concentration</td>
<td>$C_a(1-k\Delta t)^2$</td>
</tr>
</tbody>
</table>
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

Extraction Fraction $\sim$ exponential

\[
\begin{align*}
3\Delta t & \quad \text{Time} \\
3\Delta x & \quad \text{Distance} \\
C_a(1-k\Delta t)^3 & \quad \text{Concentration}
\end{align*}
\]
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

Extraction Fraction $\sim$ exponential

Time $\quad \cdot \cdot \cdot \cdot \cdot \quad n\Delta t$
Distance $\quad \cdot \cdot \cdot \cdot \cdot \quad n\Delta x$
Concentration $\quad \cdot \cdot \cdot \cdot \cdot \quad C_a(1-k\Delta t)^n$
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

Extraction Fraction $\sim$ exponential

\begin{align*}
\Delta t & \approx \frac{\Delta x}{v} \\
C_a(1-k'\Delta x)^n & = n\Delta x \\
n\Delta t & = n\Delta t
\end{align*}
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

Extraction Fraction $\sim$ exponential

Have established: $C_{CAP}(n \Delta x) \approx C_a \times (1 - k \Delta x)^n$

Taylor’s Theorem (or mean value theorem):

$\text{for } 0 < k \Delta x << 1, \quad e^{-k\Delta x} \approx 1 - k \Delta x$

$$(1 - k \Delta x)^n \approx (e^{-k\Delta x})^n = e^{-k(n\Delta x)}$$
Mathematical Aside: Exponential Decay

- Powers of a fixed number
- Start with a “base” number, say \( \frac{1}{2} \)
- Compute successive values \( (\frac{1}{2})^0, (\frac{1}{2})^1, (\frac{1}{2})^2, (\frac{1}{2})^3, \text{ etc} \)
Mathematical Aside: Exponential Decay

- Powers of a fixed number
- Start with a “base” number, say \( \frac{1}{2} \)
- Compute successive values \((\frac{1}{2})^0, (\frac{1}{2})^1, (\frac{1}{2})^2, (\frac{1}{2})^3, \text{ etc}\)

\[
\left(\frac{1}{2}\right)^1 - \left(\frac{1}{2}\right)^0 = -\frac{1}{2}
\]
Mathematical Aside: Exponential Decay

- Powers of a fixed number
- Start with a “base” number, say $\frac{1}{2}$
- Compute successive values $(\frac{1}{2})^0$, $(\frac{1}{2})^1$, $(\frac{1}{2})^2$, $(\frac{1}{2})^3$, etc

\[
\frac{(\frac{1}{2})^2 - (\frac{1}{2})^1}{2 - 1} = -\frac{1}{4}
\]
Mathematical Aside: Exponential Decay

- Powers of a fixed number
- Start with a “base” number, say \( \frac{1}{2} \)
- Compute successive values \( (\frac{1}{2})^0, (\frac{1}{2})^1, (\frac{1}{2})^2, (\frac{1}{2})^3, \) etc

\[
\left( \frac{1}{2} \right)^3 - \left( \frac{1}{2} \right)^2 = -\frac{1}{8}
\]

\[
\frac{\left( \frac{1}{2} \right)^3 - \left( \frac{1}{2} \right)^2}{3 - 2} = -\frac{1}{8}
\]
Mathematical Aside: Exponential Decay

- Powers of a fixed number
- Start with a “base” number, say $\frac{1}{2}$
- Compute successive values $(\frac{1}{2})^0$, $(\frac{1}{2})^1$, $(\frac{1}{2})^2$, $(\frac{1}{2})^3$, etc

In general:
Slope between $(\frac{1}{2})^{p-1}$ and $(\frac{1}{2})^p$ is $- (\frac{1}{2})^p$
Mathematical Aside: Exponential Decay

• Exponentials: Need all real number powers, not just whole number powers

Reminder about powers:

\[
\left( \frac{1}{2} \right)^p = 2^{-p}
\]

This allows us to write:

\[
\left( \frac{1}{2} \right)^p \times 2^p = \left( \frac{1}{2^p} \right) \times 2^p = \frac{2^p}{2^p} = 2^{-p} \times 2^p
\]

\[
= 2^{(-p+p)}
\]

\[
= 2^0
\]

\[
= 1
\]
Mathematical Aside: Exponential Decay

- Powers of a fixed number
- Start with a “base” number, say \( \frac{1}{2} \)
- Compute successive values \( 2^0, 2^{-1}, 2^{-2}, 2^{-3}, \text{etc} \)

In general:
Slope between \( 2^{-(P-1)} \) and \( 2^{-P} \) is \( -2^{-P} \)
Mathematical Aside: Exponential Decay

- Exponentials: Need all real number powers, not just whole number powers

Monotonic:
For any $P_1 < P_2$,
$2^{-P_1} > 2^{-P_2}$
Mathematical Aside: Exponential Decay

- Exponentials: Need all real number powers, not just whole number powers.

Derivative is always proportional to the value of the function.
Mathematical Aside: Exponential Decay

There is a special base number called the “natural” base
\[ e \approx 2.72 \]
\[ \frac{1}{e} \approx \frac{1}{2.72} \]
Mathematical Aside: Exponential Decay

At each point, the derivative of $e^{-t}$ is $-e^{-t}$
Mathematical Aside: Exponential Decay

Make the powers go faster:
Let $\lambda > 1$

Consider $e^{-\lambda t}$

Slope = $-\lambda e^{-\lambda t}$
Mathematical Aside: Exponential Decay

DIFFERENTIAL EQUATION:

\[
\frac{dC(t)}{dt} = -\lambda C(t)
\]

\[
C(t) = C(0)e^{-\lambda t}
\]
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

$\Delta C_a(x) \sim \text{exponential}$

$P \ (\text{Permeability}) \quad \text{Units} = \frac{\text{mL(blood)} \times c_a}{\text{cm}^2 \ (\text{capillary \ surface}) (c_{\text{cap}} - c_T) \ \text{min}}$
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

\[ P \text{ (Permeability)} \quad \text{Units} = \frac{\text{mL (blood)} \times c_a}{\text{cm}^2 \text{ (capillary surface)} (c_{\text{cap}} - c_T) \text{min}} \]

\[ PS \text{ (perm* surface/g)} = \frac{\text{mL (blood)} \times c_a \times (\text{cm}^2 / \text{g})}{\text{cm}^2 \text{ (capillary surface)} (c_a - c_T) \text{min}} \]

\[ = \frac{\text{mL}}{\text{g} \times \text{min}} \]
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

- Approximate $c_{\text{CAP}}$ as its mean value
- Get the mean value from exponential model
- Obtain expression for $E$ in terms of PS and $F_L$
- Use Kety model to equate $K_1$ to $F_L E$

\[
E = 1 - \exp\left(- \frac{\text{PS}}{F_L}\right)
\]

\[
K_1 = F_L \left(1 - \exp\left(- \frac{\text{PS}}{F_L}\right)\right)
\]
Interpretation of Rate Constants

$K_1$ and the Renkin-Crone Model

$$K_1 = F_L \left( 1 - \exp\left( -\frac{PS}{F_L} \right) \right)$$

Two Extremes:

CASE 1: $F_L << PS$

$$\exp\left( -\frac{PS}{F_L} \right) \approx 0; \quad K_1 \approx F_L$$

“FLOW LIMITED DELIVERY”

CASE 2: $F_L >> PS$

$$1 - \exp\left( -\frac{PS}{F_L} \right) \approx \frac{PS}{F_L}; \quad K_1 \approx PS$$

“PERMEABILITY LIMITED DELIVERY”
Interpretation of Rate Constants

\[ K_1 = F_L E = F_L (1 - \exp(PS/F_L)) \]
\[ k_2 = K_1/V_{ND} \]
\[ k_3 = k_{ON} B_{MAX} f_{ND} \]
\[ k_4 = k_{OFF} \]

\[
\frac{dC_S}{dt} = k_{ON} B_{MAX} f_{ND} C_{ND} - k_{OFF} C_S
\]

LINEARIZED MASS ACTION LAW
Binding Potentials

First, recall $V_{ND}$ derived from Fick’s Principle:

AT EQUILIBRIUM

Free in Arterial Plasma = Free in Brain

$$f_P C_P = f_{ND} C_{ND}$$

$$\frac{C_{ND}}{C_P} = \frac{f_P}{f_{ND}}$$
Recall $V_S = \frac{K_1k_3}{k_2k_4}$
Binding Potentials

\[ V_S = \frac{K_1 k_3}{k_2 k_4} = \frac{f_P}{f_{ND}} \frac{k_{ON}}{k_{OFF}} \]
Binding Potentials

\[ V_S = \frac{K_1 k_3}{k_2 k_4} = f_P \frac{B_{MAX}}{K_D} = BP_P \]
Binding Potentials

\[ V_S = \frac{K_1 k_3}{k_2 k_4} = f_P \frac{B_{MAX}}{K_D} = BP_P \]

\[ \frac{V_S}{f_P} = \frac{K_1 k_3}{f_P k_2 k_4} = \frac{B_{MAX}}{K_D} = BP_F \]

\[ \frac{V_S}{V_{ND}} = \frac{k_3}{k_4} = \frac{f_{ND}}{f_P} BP_P = f_{ND} \frac{B_{MAX}}{K_D} = BP_{ND} \]
Introduction to Data Fitting and Parameter Estimation

- We have shown that **DISTRIBUTION VOLUMES** and **BINDING POTENTIALS** are functions of the **RATE CONSTANTS**

- How do we extract the **RATE CONSTANTS** from the **DATA**?
Introduction to Data Fitting and Parameter Estimation

METHOD 1:
• LET THE COMPUTER DO ALL THE WORK!
• USE A NUMERICAL DIFF. EQ. SOLVER
• USE AN OPTIMIZER (LEAST SQUARES MINIMIZER)

\[
\frac{dC(t)}{dt} = K_1C_P(t) - k_2C(t)
\]

\[
\frac{C(t + \Delta t) - C(t)}{\Delta t} \approx K_1C_P(t) - k_2C(t)
\]

\[
C(t + \Delta t) \approx C(t) + \left(K_1C_P(t) - k_2C(t)\right)\Delta t
\]
Introduction to Data Fitting and Parameter Estimation

METHOD 1:
• LET THE COMPUTER DO ALL THE WORK!
• USE A NUMERICAL DIFF. EQ. SOLVER
• USE AN OPTIMIZER (LEAST SQUARES MINIMIZER)

\[\min_{K_1, K_2 > 0} \sum_{j=1}^{N} \left( \text{PET}(t_j) - \text{MODEL}(t_j) \right)^2\]
Are Rate Constants Estimated Robustly Enough to Estimate Binding Potentials from their formulae?
Are the parameters unique in a *deterministic* sense? Yes;

\[
\frac{L(C_T)}{L(C_p)} = K_1 \frac{s + k_3 + k_4}{(s + \alpha_1)(s + \alpha_2)}
\]

(transfer function)

s is the Laplace Transform variable
the \( \alpha \)'s are the eigenvalues of the system (functions of the k's)

It can be shown that for a given \( C_T \) and \( C_p \) pair,
These are all unique.

(Bellman, 1960)
Are the parameters unique in *practical* terms? NO!

K1      0.0887  k1      0.0576
k2      0.5195  k2      0.1526
k3      0.2487  k3      0.1379
k4      0.0117  k4      0.015
k3/k4   21.3228 k3/k4   9.2151
Previous Example  $V_T$ within 1%

$V_T = 3.8122$

$V_T = 3.8575$