Introduction to PET Pharmacokinetics:
Equilibrium Methods and Related Topics
Equilibrium Conditions:

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

What if Concentrations are all constant?

\[ \frac{C_{ND}(t)}{C_P(t)} = V_{ND} = \frac{K_1}{k_2} \]
\[ \frac{C_S(t)}{C_P(t)} = V_S = \frac{K_1 k_3}{k_2 k_4} \]
\[ \frac{C_T(t)}{C_P(t)} = V_T = \frac{K_1}{k_2} \left( 1 + \frac{k_3}{k_4} \right) \]
Pure Constant Infusion Input

$C_S \approx $ Constant

$C_{ND} \approx $ Constant
Bolus Input

Infusion Input

Bolus Response

Infusion response
Parameterizing the B/I ratio: KBol

KBol(minutes) = Total time required to infuse the bolus volume at the infusion rate

Example:

Syringe Volume = 60 cc
Rate of Infusion = 1 mL/min
Bolus Volume = 20 cc
KBol = 20 min
(max infusion duration = 40 min)
What happens if $\frac{dC_T}{dt} \neq 0$?

- $\frac{dC_T}{dt} < 0$
- $\frac{dC_{REF}}{dt} < 0$
- $\frac{dC_T}{dt} < \frac{dC_{REF}}{dt} < 0$
What happens if $dC_T/dt \neq 0$?

- Late phase following bolus: $C_T$ and $C_{REF}$ exceed their equilibrium point for $C_P$
- $C_T$ lags further behind than $C_{REF}$
- The ratio $C_T/C_{REF}$ will exceed DVR

\[ \frac{dC_T}{dt} < \frac{dC_{REF}}{dt} < 0 \]
What happens if \( \frac{dC_T}{dt} \neq 0 \) ?

Example: Assume 1TC in both regions, \( R_1 = 1 \)

\[
\begin{align*}
\frac{dC_{REF}(t)}{dt} &= K_1' C_p(t) - k_2' C_{REF}(t) \\
\frac{dC_T(t)}{dt} &= K_1 C_p(t) - k_{2a} C_T(t)
\end{align*}
\]

\[
\begin{align*}
C_{REF} &= V_{ND} \left( C_p + \frac{1}{K_1} \left| \frac{dC_{REF}}{dt} \right| \right) \\
C_T &= V_T \left( C_p + \frac{1}{K_1} \left| \frac{dC_T}{dt} \right| \right)
\end{align*}
\]

Slifstein, JNM, 2008
What happens if $dC_T/dt \neq 0$?

Example: Assume 1TC in both regions, $R_1 = 1$

\[
\frac{C_T}{C_{REF}} = \frac{V_T}{V_{ND}} \left( \frac{C_p + \frac{1}{K_1} \left| \frac{dC_T}{dt} \right|}{C_p + \frac{1}{K_1} \left| \frac{dC_{REF}}{dt} \right|} \right)
\]

$dC_T/dt < dC_{REF}/dt < 0$

(implies numerator factor > denominator factor)

Slifstein, JNM, 2008
What happens if \( \text{d}C_T/\text{d}t \neq 0 \) ?

More generally, bolus \( C_p \) is sum of exponentials, \( C_T \) is \( C_p \) convolved with exponentials (assume \( \beta \)'s, \( \alpha \)'s are in decreasing order \( 0 < \beta_K < ... < \beta_1; 0 < \alpha_J < ... < \alpha_1 \) and \( \beta_K < \text{all } \alpha \))

\[
C_p(t) = \sum_{k=1}^{K} B_k e^{-\beta_k t} \quad C_T(t) = C_p(t) \otimes \sum_{j=1}^{J} A_j e^{-\alpha_j t}
\]

\[
C_T(t) = \sum_{k} \sum_{j} B_k A_j \int_{0}^{t} e^{-\beta \tau} e^{-\alpha_j(t-\tau)} \text{d}\tau
\]

\[
= \sum_{k} \sum_{j} B_k A_j e^{-\alpha_j t} \int_{0}^{t} e^{(\alpha_j - \beta_k) \tau} \text{d}\tau
\]

\[
= \sum_{k} \sum_{j} B_k A_j \frac{e^{-\alpha_j t}}{\alpha_j - \beta_k} e^{(\alpha_j - \beta_k) t} \bigg|_{\tau=0}^{t}
\]

\[
= \sum_{k} \sum_{j} B_k A_j \frac{e^{-\alpha_j t}}{\alpha_j - \beta_k} \left( e^{(\alpha_j - \beta_k) t} - 1 \right)
\]

\[
= \sum_{k} \sum_{j} B_k A_j \frac{e^{-\beta_k t} - e^{-\alpha_j t}}{\alpha_j - \beta_k}
\]

Carson et al, JCBFM, 1993
What happens if $dC_T/dt \neq 0$?

Since $0 < \beta_K < \alpha_j$, eventually all terms die out except the term $\beta_K$:

$$C_P(t) \approx B_K e^{-\beta_K t}, \quad t > T, \text{ for some large } T$$

$$C_T(t) \approx B_K \sum_j A_j \frac{e^{-\beta_K t}}{\alpha_j - \beta_K}$$

$$\frac{C_T(t)}{C_P(t)} \approx \frac{B_K \sum_j A_j e^{-\beta_K t}}{B_K e^{-\beta_K t}} = \sum_{j=1}^J \frac{A_j}{\alpha_j - \beta_K}$$

But:

$$V_T = \sum_{j=1}^J \frac{A_j}{\alpha_j} < \frac{C_T(t)}{C_P(t)} \quad \text{for} \quad t > T$$

Carson et al, JCBFM, 1993
What happens if $dC_T/dt \neq 0$?

Previous Example (Data generated by 2TCM):
VT(Anterior Cingulate) = 5.87
VT(Cerebellum) = 2.65
DVR = 2.22
Effects of Pharmacokinetics on Estimated Drug Occupany When Occupancy Changes Over Time
Setting:

• Drug occupancy by a drug at a target receptor is inferred by comparing scan data following an iv bolus of drug to baseline values.
• The radioligand is administered as a single bolus and data are analyzed by 2TC modeling.
• It is observed that the percent decrease of specific binding in one brain region is less than in another.

Question:

Can it be inferred that the drug will have different occupancy in the two regions under normal conditions of steady-state oral administration?

Answer:

Not necessarily, especially if the regions have very different B_{MAX}.
First Step: A model for $C_S$ when occupancy is time-varying

- Tracer is at, well …, TRACER DOSE
- At each time $t$, drug occupancy is approximately what it would be in the absence of the tracer
- Receptor availability will be $B_{MAX} \times (1 - \text{occ}(t))$
- This leads to ODEs with time-varying coefficients:
Differential Equation For Specific Binding:

\[
\frac{dC_s(t)}{dt} = f_{ND} k_{on} B_{MAX} (1 - \text{occ}(t)) C_{ND}(t) - k_4 C_s(t)
\]

\[
= k_3 (1 - \text{occ}(t)) C_{ND} - k_4 C_s(t)
\]

Formal Solution:

\[
C_s(t) = k_3 (1 - \text{occ}(t)) C_{ND}(t) \otimes \exp(-k_4 t)
\]

A convolution Integral!
Effect on Apparent % change across conditions ($\Delta BP$):

Ansatz: $\Delta BP = \text{function of change in AUC}$:

$$1 - \frac{BP_{P}(\text{drug condition})}{BP_{P}(\text{baseline})} = 1 - \frac{\int_{0}^{\infty} C_{S}^{\text{DRUG}}(t)dt \div \int_{0}^{\infty} C_{P}^{\text{DRUG}}(t)dt}{\int_{0}^{\infty} C_{S}^{\text{BASE}}(t)dt \div \int_{0}^{\infty} C_{P}^{\text{BASE}}(t)dt}$$

$IF$: $\int_{0}^{\infty} C_{P}dt$ is (nearly) equal across conditions, then

$$1 - \frac{BP_{P}(\text{drug condition})}{BP_{P}(\text{baseline})} \approx 1 - \frac{\int_{0}^{\infty} C_{S}^{\text{DRUG}}(t)dt}{\int_{0}^{\infty} C_{S}^{\text{BASE}}(t)dt}$$
What is $\int_0^\infty C_S(t)dt$?

$$\int_0^\infty C_S(\tau)d\tau = \int_0^\infty d\tau \times \left[ \langle k_3 (1 - \text{occ}(t))C_{ND}(t) \rangle \otimes \exp(-k_4 t) \right]$$

Property of convolution integrals:

$$\int_0^\infty A \otimes B \ d\tau = \int_0^\infty A \ d\tau \int_0^\infty B \ d\tau$$

$$\int_0^\infty C_S(\tau)d\tau = \int_0^\infty k_3 (1 - \text{occ}(\tau))C_{ND}(\tau)d\tau \times \int_0^\infty \exp(-k_4 \tau)d\tau$$

$$\int_0^\infty C_S(\tau) d\tau = \int_0^\infty \frac{k_3}{k_4} (1 - \text{occ}(\tau))C_{ND}(\tau)d\tau$$
What is $\Delta BP$?

Baseline:

$$\int_0^\infty \frac{k_3}{k_4} C_{ND}^{Baseline}(\tau) d\tau$$

Drug:

$$\int_0^\infty \frac{k_3}{k_4} (1 - occ(\tau)) C_{ND}(\tau) d\tau$$

$$\Delta BP = 1 - \frac{\int_0^\infty (1 - occ(\tau)) C_{ND}^{Drug}(\tau) d\tau}{\int_0^\infty C_{ND}^{Baseline}(\tau) d\tau}$$

If $\int_0^\infty C_{ND}$ is unchanged across conditions ...

"$\Delta BP$"

$$\int_0^\infty occ(\tau) C_{ND}^{Drug}(\tau) d\tau$$

$$\frac{\int_0^\infty C_{ND}^{Baseline}(\tau) d\tau}{\int_0^\infty C_{ND}(\tau) d\tau}$$
A Convex Sum of $\text{occ(t)}$:

\[
\int_0^\infty \text{occ}(\tau)C_{ND}^{\text{DRUG}}(\tau)d\tau \leq \int_0^\infty C_{ND}^{\text{Baseline}}(\tau)d\tau
\]

This is \textit{approximately}

\[
\sum_{n=1}^\infty \text{occ}(n\Delta t)\omega_n
\]

where:

\[
\omega_n = \frac{C_{ND}(n\Delta t)\Delta t}{\sum_{m=1}^\infty C_{ND}(m\Delta \tau)\Delta \tau}
\]

\[
\sum_{n=1}^\infty \omega_n = 1
\]
ΔBP is a function of the product integral

\[ \int_0^\infty \text{occ}(\tau)C_{ND}^{\text{DRUG}}(\tau)d\tau \]

\[ \int_0^\infty C_{ND}^{\text{Baseline}}(\tau)d\tau \]

How (if at all) does this vary across regions?
Regions with higher $B_{\text{MAX}}$ have more capacitance:
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Example: $[^{18}\text{F}]$ fallypride:

- High Binding in Striatum
- Moderate Binding in:
  - Hippocampus
  - Amygdala
  - Thalamus
  - Temporal Cortex
Example: $[^{18}\text{F}]$ fallypride:

- **STRIATUM**
  - $\text{CND} (\text{Baseline})$
  - $\text{CND} (50\% \text{ initial Occ.})$
  - $\text{BP}_{\text{ND}} = 22$

- **HIPPOCAMPUS**
  - $\text{CND} (\text{Baseline})$
  - $\text{CND} (50\% \text{ initial Occ.})$
  - $\text{BP}_{\text{ND}} = 1.4$
Simulation Design:

- Two simulated regions with typical fallypride parameters: striatum ($BP_{ND} = 22$) and hippocampus ($BP_{ND} = 1.4$) and 240 min of data generated.
- Exponentially decreasing drug occupancy with 3 different half-lives: 600, 900 and 1200 minutes (i.e. 10 - 20 hr).
- Three initial occupancies: 60, 75 and 90%.
- For each region - initial occupancy - half life combination, 1000 simulated curves in each region at baseline and during drug with 5% added gaussian noise.
- Data were fitted and estimated $\Delta BP$ recorded.
Simulation Results:

Half lives (decrease over 240 min):
- 600 min (24%)
- 900 min (17%)
- 1200 min (13%)

In each case: Initial ≥ Hippocampus > Striatum ~ True Average