Lecture 31: Objectives/Overview

- Multi-compartment models
  - Permeability surface area product in cancer vascular supply
- Metabolically active agents
  - Compartmental models of trapped PET tracers
    - [18-F]fluorodeoxyglucose (FDG)
    - [18-F]fluorothymidine (FLT)
  - Linearizations
    - Patlak analysis
- Targeted Agents
  - Receptor mediated -> most common
  - In vitro labeled cells -> Cell trafficking
    - SPIO – labeling for MRI
      - Stem cell experiments
    - In-111 labeling for SPECT
      - Reporter genes/molecules
Freely Diffusible Tracer

\[
\frac{dT(t)}{dt} = K_1 C_p(t) - k_2 T(t)
\]

\[K_1 = F\]

\[k_2 = \frac{1}{t} \quad \text{where} \quad t \equiv \text{Mean Transit Time (MTT)}\]

\[V = F\tilde{t} = \frac{K_1}{k_2}\]

Assumption: Freely diffusible tracer with instantaneous mixing

Axel, 1983

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Assumption: Freely diffusible tracer with instantaneous mixing

\[
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K_1 = F
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k_2 = \frac{1}{\bar{t}} \text{ where } \bar{t} \equiv \text{Mean Transit Time (MTT)}
\]

\[
V = F\bar{t} = \frac{K_1}{k_2}
\]
Generalized Models

- 2 compartment closed system

\[ C_b(t) = C(\infty)(1 - e^{-kt}), \]
where \( k = k_1 + k_2 \)

- 2 compartment parallel

\[ C_{out}(t) = C_a(0)e^{-k_1t} + C_b(0)e^{-k_2t} \]
bi-exponential model
\[ k_1 = F_1/V_1; \ k_2 = F_2/V_2 \]
Multi-compartment modeling

Gd-DTPA tracer distribution (partially diffusible)

Bolus Injection of Gd-DTPA

Plasma: Two compartment ⇒ bi-exponential

\[ C_p(t) = D(a_1 e^{-\kappa_1 t} + a_2 e^{-\kappa_2 t}) \]

Leakage Space:

\[ \frac{dC_l(t)}{dt} = \frac{k}{v_lV_t} (C_p(t) - C_l(t)) \]

Extra-cellular space (whole body)

Plasma \( C_p(t) \)

kidneys

Lesion leakage Space \( C_l(t) \)

volume per unit volume of tissue

\( k \): permeability surface area product/unit volume of tissue

\( v_l \): fraction of lesion tissue which is occupied by the leakage space

[Tofts et al, 1991]
PS product and Perfusion

\[ \nu_i V_i \frac{dC_i(t)}{dt} = PS(C_p - C_i) \]

\[ \nu_l V_t \equiv \text{The leakage volume} \]

\[ P \equiv \text{permeability in units cm/min} \]

\[ S \equiv \text{surface area in units cm}^2 \text{ or cm}^2/g \]

Extraction

![Graph showing extraction vs perfusion with various PS values and legends for E (PS = 0.01), E (PS = 0.02), E (PS = 0.03), E (PS = 0.05), E (PS = 1.0), E (PS = 3.0), and E (PS = 5.0).]

Examples of lesion contrast kinetics

Type I and Type II Enhancement Curves for DCE-MRI
Tubular cancer & benign tumor

Subtracted image

Segmentation

Pharmacokinetic Analysis

Benign tumor, Mean K21 = 0.75 (low), Arrival time : 90 secs (late)
Trapped Radioactive Tracers

• Metabolically active agents
  – Compartmental models of trapped PET tracers
    • [18-F]fluorodeoxyglucose (FDG)
    • [18-F]fluorothymidine (FLT)
Radioactive tracers

• Measure
  – Radioactivity/volume
  – Units
    • Becquerel/mL (Bq/mL)
      – Transitions or “counts” per sec per milliliter
    • Curie/mL (Ci/mL)
      – $3.7 \times 10^{10}$ Bq
Standardized Uptake Value (SUV)

• The amount of radioactivity in the tissue normalized to the injected dose:

\[ SUV = \frac{Tissue\ Activity\ (mCi/L)}{\rho^{(kg/L)} \cdot Injected\ Dose\ (mCi) / body\ weight\ (kg)} \]

where \( \rho \approx 1.07\ kg/L \)
FDG Pharmacokinetics

FDG in plasma $\xrightarrow{K_1} \text{FDG in cell} \xrightarrow{k_3} \text{Entrapment of FDG-6-P in cell}$

Transport:
Reversible component in equilibrium with blood pool

Phosphorylation by hexokinase

$$C_t(t) = c_f + c_b = \frac{K_1}{k_2 + k_3} (k_2 e^{-(k_1+k_2)t} + k_3) * C_p(t),$$


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Generalized Trapped Tracer Model

\[ C_t(t) = (\kappa_1 e^{-\kappa_2 t} + \kappa_3 e^{-0t}) * C_p(t) \]

\[ C_t(t) = c_f + c_b = \frac{K_1}{k_2 + k_3} (k_2 e^{-(k_1 + k_2)t} + k_3) * C_p(t), \]

\[ \kappa_1 = \frac{k_2 K_1}{k_2 + k_3}, \ \kappa_2 = k_2 + k_3, \ \kappa_3 = \frac{k_3 K_1}{k_2 + k_3} \]
• Recall single-tissue-compartment model of perfusion:

\[ C_t(t) = K_1 e^{-k_2 t} \ast C_p(t) \]

\[
\frac{dC_t(t)}{dt} = K_1 C_p(t) - k_2 C_t(t)
\]

\[
C_t(t) = K_1 \int_0^t C_p(\tau)d\tau - k_2 \int_0^t C_t(\tau)d\tau
\]

\[ y(t) = K_1 - k_2 x(t), \]

where \[ y(t) = \frac{C_t(t)}{\int_0^t C_p(\tau)d\tau} \]

and \[ x(t) = \frac{\int_0^t C_t(\tau)d\tau}{\int_0^t C_p(\tau)d\tau} \]
Linearization: Trapped Tracer Model

\[ C_t(t) = (\kappa_1 e^{-\kappa_2 t} + \kappa_3 e^{-0t}) \ast C_p(t) = (\kappa_1 e^{-\kappa_2 t} + \kappa_3) \ast C_p(t) \]

\[ C_t(t)/C_p(t) \text{ will rapidly reach equilibrium assuming free diffusion between these compartments:} \]

\[ C_t(t) = u_1 + u_2 \rightarrow \frac{\kappa_1}{\kappa_2} C_p(t) + \kappa_3 \int_0^t C_p(\tau)d\tau, \]

\[ \frac{C_t(t)}{C_p(t)} \rightarrow \kappa_1 \frac{\kappa_1}{\kappa_2} + \kappa_3 \frac{\int_0^t C_p(\tau)d\tau}{C_p(t)} \]

\[ \kappa_1 = \frac{k_2 K_1}{k_2 + k_3}, \kappa_2 = k_2 + k_3, \kappa_3 = \frac{k_3 K_1}{k_2 + k_3} \]

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Image Fusion: MRI and $^{18}\text{F}]\text{DG-PET}$

Small Animal Imaging
($\sim10$ cm FOV)

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Details of Patlak Analysis

Right Lung (Background)

Left Lung (Lesion)
Fluorothymididine

- Trapped after phosphorylation by thymidine kinase 1
- Incorporated in DNA
- Increased (order of magnitude) as cells enter DNA synthetic phase
- Cancers rapidly proliferating
Results: FLT

Shields et al., Nature Medicine, 1998
Summary

• Biologically active tracers can be trapped in proportion to cellular activity
• Simple compartmental models can allow quantification of trapped component
• Potential for specific evaluation of cellular processes
  – Inflammation
  – Cancer proliferation