PART VI

CHAPTER 18

Problem 18-1: Tumor Imaging

1. Overexpression or mutation of an integral membrane protein, epidermal growth factor receptor, plays a role in the progression of some cancers. To access tumor treatment, it is important to non-invasively image the tumors before, during, and after targeted therapy. Sometimes this can be done by real-time noninvasive quantitative fluorescent imaging of semiconductor nanocrystals (*i.e.* quantum dots, QD) that are conjugated to epithelial growth factor. Quantum dots are advantageous because they have unique size- and composition-dependent tunable emission from visible to near-infrared wavelengths, high fluorescence quantum yield, and photo-stability.

A two-compartment pool model has been developed to describe the fluorescent signal response of a tumor after injection of an ideal impulse of m_o moles of EGF-QD into the bloodstream. The concentration of QD-EGF in a central (blood) compartment changes as:

$$V_b \frac{dC_b}{dt} = k_{eff} C_t - (k_{elim} + k_{inf}) C_b + m_o \delta(t), \quad C_b(0^-) = 0$$

The concentration of QD-EGF in the tumor compartment changes according to:

$$V_t \frac{dC_t}{dt} = k_{inf} C_b - (k_{eff} + k_{ev}) C_t, \quad C_t(0) = 0$$

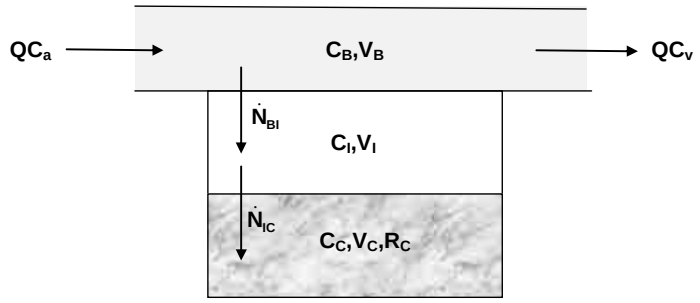
In these equations, the coefficients represent:

$k_{inf} \rightarrow$ influx from blood to tumor
$k_{eff} \rightarrow$ efflux from tumor to blood
$k_{elim} \rightarrow$ elimination from blood by transport to external tissues
$k_{ev} \rightarrow$ loss from tumor to external tissues because of evasion by cancer cells

(a) Draw the system diagram that represents the model equations.
(b) Obtain the Laplace transforms of this model in which $\tilde{C}_b(s) = \boldsymbol{L}\{C_b(t)\}$ and $\tilde{C}_t(s) = \boldsymbol{L}\{C_t(t)\}$. For convenience, define $K_1 = (k_{elim} + k_{inf})/V_b$ and $K_2 = (k_{eff} + k_{ev})/V_t$.
(c) Solve for $\tilde{C}_b(s)$ and $\tilde{C}_t(s)$.
(d) Obtain the time domain solution for the tissue concentration $C_t(t)$.
(e) What must be true of K_1 and K_2 if this is a well-behaved solution?

Problem 18-2: Blood-Tissue Model

Mass transport of a chemical species in a blood-tissue system consists of blood (B), interstitital (I) and intracellular (C) compartments.



Compartments I and C are well mixed with internal solute concentrations C_I and C_C, respectively. Compartment B is imperfectly mixed with an internal solute concentration C_B given by a linear combination of a constant arterial input concentration C_a and a venous output concentration C_v.

$$C_B(t) = (1-\alpha)C_a + \alpha C_v(t) \qquad (1 \geq \alpha \geq 0)$$

The volume V_i of each compartment i is constant and the volumetric rate of flow Q through the B compartment is constant. Transport of a solute between adjacent compartments i and j is by passive, ordinary diffusion at a molar rate:

$$\dot{N}_{ij} = K_{ij}S_{ij}\left(C_i - \lambda^{i,j}C_j\right)$$

where K_{ij} is an overall mass transfer coefficient, S_{ij} is the interfacial surface area, and $\lambda^{i,j}$ is the equilibrium partition coefficient between compartments i and j. The solute species reacts within the cells by Michaelis-Menten kintetics at an intensive molar rate

$$\dot{R}_C = -V_C \frac{\beta C_C}{\gamma + C_C}$$

(a) From solute mass balances, obtain the specific equations for

$$\frac{d\left(V_k C_k\right)}{dt} = f_k(C_v, C_I, C_C) \qquad (k = B, I, C)$$

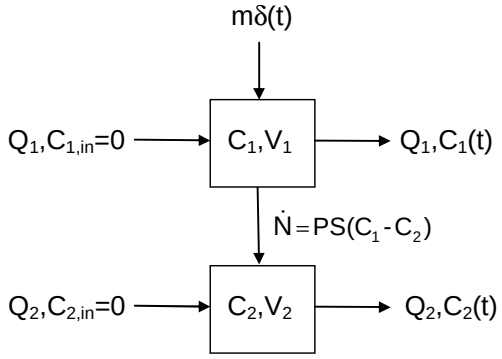
(b) Substitute the rate equations into these balance equations.
(c) Substitute the mixing equation for compartment B into the equations of part (b).
(d) Rewrite the equations of part (c) if the blood compartment is perfectly mixed.
(e) If transport is flow-limited (*i.e.*, $K_{B,I}S_{B,I} \to \infty$ and $K_{I,C}S_{I,C} \to \infty$ with $\dot{N}_{BI}$ and $\dot{N}_{IC}$ finite), what is the relationship between the solute concentrations in the three compartments. If this is the case, show that the model equations with the assumptions of perfect mixing of compartment B can be treated as a single well- mixed compartment.

$$V_{eff}\frac{dC_v}{dt} = ?$$

What is the effective volume V_{eff} of this compartment? Hint: Add the balance equations of part (a).

Problem 18-3: Two Compartment Multiple-Input-Multiple Output Model

In the model shown below, the compartments are perfectly mixed and have constant volumes. Fluid density is uniform throughout the system. Suppose that an ideal impulse of m moles of tracer is initially injected into compartment 1.



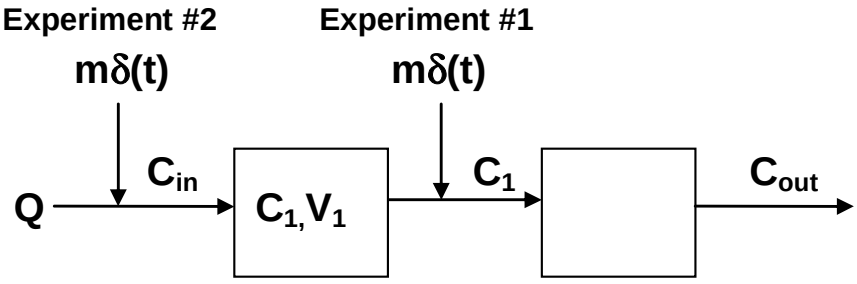
(a) Write the dynamic balances for the tracer concentrations $C_1(t)$ and $C_2(t)$ leaving the compartments if no tracer is present in the input flow streams.

(b) Assuming that Q_1 and Q_2 are constants and that there is no tracer within the compartments to start with, solve these balances for the output concentrations in the Laplace domain, $\tilde{C}_1(s)$ and $\tilde{C}_2(s)$.

(c) Using the derivative relationship in Eq. 18.3-12, determine the zeroth moments $\mu_{0,i}$, first moments $\mu_{2,i}$, and corresponding mean times $\tau_i \equiv \mu_{1,i}/\mu_{0,i}$ of the dynamic output concentrations $C_i(t)$ (i=1,2).

(d) Show that that the equations for $\mu_{0,1}$ and $\mu_{0,2}$ are consistent with overall conservation of tracer (*i.e.*, all m moles of injected tracer must eventually flow out of the system in the Q_1 and Q_2 streams).

Problem 18.4: Two Compartment Imperfectly Mixed Model



A system model consists of a perfectly mixed compartment 1 in series with compartment 2 that is not perfectly mixed. Compartment 1 has a constant volume V_1 and is fed by a constant volumetric flow rate Q of liquid. To characterize transport and mixing in this model, two experiments are performed with a tracer that neither reacts nor permeates across the walls of either chamber.

(a) In experiment #1, compartment 2 is characterized using an impulse input rate $m\,\delta(t)$ with m moles of tracer that yields an output $C_{out}(t)=k(e^{-at}+ce^{-bt})$ where a,b,c and k are constants. If the number of input and output moles of tracer are equal *(i.e.* the tracer is conserved), obtain the relation of k to a,b,c.

(b) As a continuation of part (a), find the transfer function of compartment 2 $\tilde{g}_2(s)=\tilde{C}_{out}(s)/\tilde{C}_1(s)$. Here $\tilde{C}_{out}(s)$ is the Laplace transform of $C_{out}(t)$ given in part (a), and $\tilde{C}_1(s)$ is the Laplace transform of the tracer input concentration $C_1(t)$. In specifying $C_1(t)$, assume that the input flow stream Q contains no tracer and the volumetric rate of the tracer impulse input is small compared to Q.

(c) In experiment #2, an impulse of m moles of tracer is injected into compartment 1. Write the molar balance on compartment 1 for this case. Assuming no tracer is present in the system before the impulse input, solve for the Laplace domain output: $\tilde{C}_1(s)$.

(d) Based on the result of part (c), find the transfer function $\tilde{g}_1(s)$ of compartment 1. What is the transfer function of the entire system $\tilde{g}_{sys}(s)\equiv\tilde{C}_{out}/\tilde{C}_{in}$?

(e) Using $\tilde{g}_{sys}(s)$, determine $C_{out}(t)$ that would be observed during the second experiment.

Problem 18-5: Compartmental Dispersion Model

Convective-dispersion of an inert tracer species 's' flowing through a cylindrical tube can be described by a one-dimensional species concentration equation, Eq. 15.5-53. Consider an experiment carried out in a very long tube with a tracer pulse inputted at z=0. To model the solute concentration measured at a finite distance z=L downstream of this input, we consider the tube to be infinitely long such that the concentration disturbance at z=0 has no effect on concentration in the limit as $z\to\infty$. The dynamics of the tracer concentration at z=L can then be characterized with mathematical moments obtained from a solution to Eq. 15.5-53 in the Laplace transform domain.

(a) State the boundary and initial conditions for the concentration $C_s(z,t)$ with the assumptions:
(1) no tracer in the tube at t=0;
(2) time varying input of tracer concentration $C_{s0}(t)$ at z=0;
(3) In the limit of $z\to\infty$, the input does not disturb the initial tracer concentration.

(b) Find the solution to this spatially distributed model in the Laplace domain. Express this solution in terms of the transfer function between the flow inlet at z=0 and a downstream position z=L:

$$\tilde{g}(s) \equiv \tilde{C}_s(z = L, s) / \tilde{C}_s(z = 0, s)$$

(c) To characterize this model by moments, the transfer function or its inverse $g(t)$ is needed. Explain why. Find the zeroth, first moments and second moments of $g(t)$.

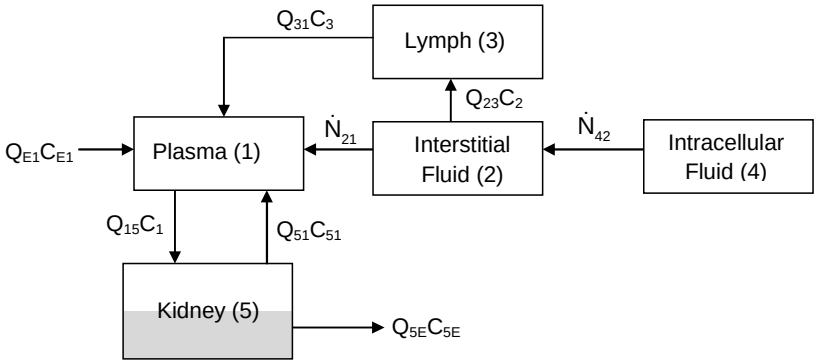
(d) Using these moments, determine the mean $\bar{t}_g$ and the variance σ_g^2 of g(t).

(e) Compare the result of part (d) to entry 4 in table 18.3-1 for the compartments-in-series model. When are $\bar{t}_g$ and the variance σ_g^2 for the two models equivalent?

CHAPTER 19

Problem 19-1: Renal Excretion

A physiologically based model to describe the dynamics of fluid balance and renal excretion consists of five compartments representing: (1) plasma, (2) interstitial fluid, (3) lymph, (4) intracellular fluid, and (5) kidney. Compartments 1, 2, 3, 4 are perfectly mixed at concentrations C_i and have a variable volumes $V_i(t)$. Compartment 5 is not well-mixed but has a constant volume. Solute enters compartment 5 in arterial blood at concentration C_1 and exits in venous blood at concentration C_{51}. A solute enters the model into plasma at concentration C_{E1} and exits the model in urine at concentration C_{5E}. Convective transport occurs between compartments at volumetric flows Q_{ij}. Membrane transport at molar rate $\dot{N}_{ij} = Q_{ij}C_{ij} + \dot{J}_{ij}$ combines convective and diffusive $\dot{J}_{ij}$ components between compartments 4 and 2 and compartments 2 and 1. The clearance of a solute from the kidneys is Q^C.



(a) From solution mass balances for each compartment, develop dynamic equations relating compartment volumes to volume transport rates. Assume that all solutions have constant and equal mass densities ($\rho_i = \rho$).

$$\frac{dV_i}{dt} = ? \quad (i=1,2,3,4,5)$$

What is sum of the rates of volume change of the entire system?

$$\sum_{i=1}^{5} \frac{dV_i}{dt} = ?$$

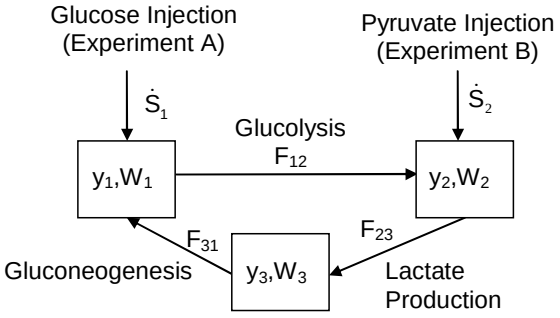
(b) Develop the dynamic equations for solute concentration C_i in each of the four compartments.

$$\frac{dC_i}{dt} = ? \quad (i=1,2,3,4,5)$$

(c) Write the solute balance for compartment 5. Using the clearance Q^C, relate C_1 and C_{51}.
(d) What additional information is necessary to completely solve for the concentrations of this model?

Problem 19 -2: Lactic Acid Cycle

The lactic acid (a.k.a. Cori) cycle is the metabolic pathway by which lactate (3) produced by anaerobic glycolysis (Eq. 1.1-4) via pyruvate (2) in muscles is transported to the liver. There it is converted by gluconeogenesis via pyruvate to glucose (1) and the glucose is transported back to the muscles to be converted to lactate. To study this process, Waterhouse and Keilson (J. Clinical Investigation, 48: 2359-2366, 1969) monitored blood levels of C^{14} glucose on seven healthy human subjects following bolus injection of C^{14} labeled glucose . Using the resulting data, we would like to estimate parameters in the pool model shown in the figure. Evaluation of these rate parameters provides a basis for characterizing abnormal conditions.



In this model, the mass of each pool i is W_i , the mass fraction of radiolabeled species in a pool is y_i, and the mass rate of transfer untagged plus tagged species from pool i to pool j is F_{ij}. In analyzing the tracer dynamics, we assume that 1) the radio decay of C^{14} can be neglected because its half-life is much longer than the 3-4 hour period of an experiment; 2) the bolus injection of tracer can be idealized as an exponential function, $\dot{m}e^{-t/\tau}$, with $t/\tau \to \infty$ at the end of an experiment; 3) the amount of tagged glucose in any pool is much less than untagged glucose; 4) W_1, W_2 and W_3 are constants; 5) gluconeogenesis is so fast that pool 3 behaves in a pseudo-steady manner.

(a) Formulate the mass balances on untagged glucose in the three pools.
(b) Formulate the mass balances on tagged glucose for the three pools.
(c) State the initial conditions necessary to the governing equations.
(d) Solve for $y_1(t)$ with the Laplace transform method. You will have to use the following inverse Laplace transform:

$$\mathcal{L}^{-1}\left\{\frac{(s+a)}{s(s+\alpha)(s+\beta)}\right\} = \frac{a}{\alpha\beta} + \frac{a-\alpha}{\alpha(\alpha-\beta)}e^{-\alpha t} + \frac{a-\beta}{\beta(\beta-\alpha)}e^{-\beta t}$$

(e) Formulate the fractional glucose dose F(t) as the amount of tagged glucose in the cycle, y_1W_1, relative to the total amount of tagged glucose injected during the entire experiment, $\int \dot{m}dt$.

(f) Use a non-linear regression of the model to the data shown in the table in order to estimate the three parameters, F_{13}/W_1, F_{13}/W_2 and τ.

Data From Waterhouse and Keilson

t(min)	5	15	30	60	90	150	210
F(t)	0.600	0.425	0.318	0.232	0.171	0.113	0.070

(g) How well does the model fit the data? How might the model be improved in order to better fit the data?

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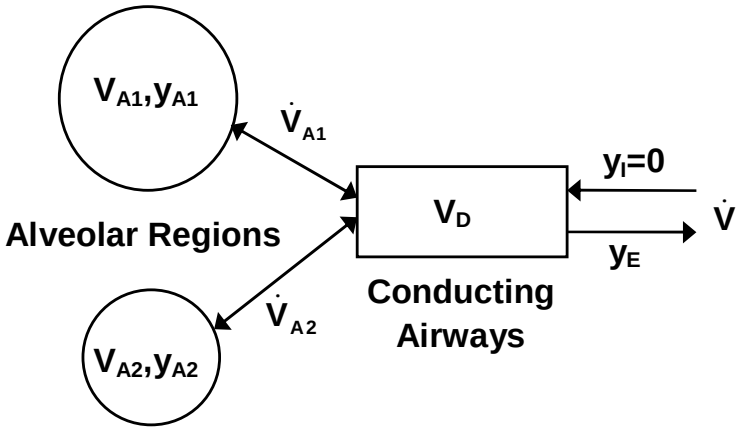
Problem 19-3 N_2 Washout With Inhomogeneous Ventilaion

In a multi-breath nitrogen washout test (section 19.1-2), the objective is to quantitatively characterize the mixing and distribution in the lungs that distinguishes homogenous from inhomogeneous ventilation. In this non-invasive measurement, a patient breathes through a mouthpiece with the nostrils clamped shut. On inhalation, the patient breathes pure oxygen (O_2) from a reservoir attached to the mouthpiece. On exhalation, the patient breathes out to the environment. The nitrogen (N_2) mole fraction and volume flow are continuously measured entering and leaving the mouth. Over successive breaths, the N_2 progressively falls until the N_2 fraction is much less than the initial N_2 fraction. Here, we model N_2 washout from diseased lungs represented by two alveolar regions that are inhomogeneously ventilated via conducting airways (i.e., a common dead space).



The assumptions of this model are as follows:

1. Mole density of this ideal gas mixture is uniform and constant everywhere: $c_{A1} = c_{A2} = c$. Therefore, moles of gas are proportional to volumes of gas, and mole fractions in the alveolar compartments, y_{A1} and y_{A2} are equivalent to volume fractions.
2. Average volumetric flows are constant through the conducting airways ($\dot{V}$) and between the conducting airways and alveolar regions ($\dot{V}_{A1}, \dot{V}_{A2}$). These flows have the same magnitude during inhalation and exhalation. Also, the flow ratio is constant: $\alpha \equiv \dot{V}_{A1} / \dot{V}$.
3. Tidal volume (V_T) does not change from breath to breath (*i.e.* $V_T = t_B \dot{V}$ where t_B is the constant and equal breathing half periods).

4. The well-mixed alveolar regions expand during inhalation and contract during exhalation. The alveolar volumes at the start of inspiration are $V_{A1}(0)$ and $V_{A2}(0)$. At the end of inspiration, they are $V_{A1}(t_B)$ and $V_{A2}(t_B)$.
5. There is no axial mixing in the conducting airways which have a constant dead space volume V_D which is less than V_T.
6. At the start of the first inhalation of O_2, the N_2 fractions in the alveolar regions and the dead space are all equal to the normal atmospheric value, $y_D(0)=y_{A1}(0)=y_{A2}(0)$.

Based on this information, answer the following:

(a) From a molar balance, relate $\dot{V}$ to $\dot{V}_{A1}$ and $\dot{V}_{A2}$. How is the flow ratio α related to $\dot{V}_{A2}$ and $\dot{V}$?

(b) How are the volume increases of each alveolar region during inhalation, $V_{A1}(t_B)-V_{A1}(0)$ and $V_{A2}(t_B)-V_{A2}(0)$, related to α and V_T?

(c) During the first inhalation of O_2 , what is the N_2 volume delivered from the dead space to each alveolar compartment, $\Delta V_{N,1}$ and $\Delta V_{N,2}$?

(d) At the end of inspiration, what is the N_2 volume fraction in each alveolar compartment, $y_{A1}(t_B)$ and $y_{A2}(t_B)$? Express these results in terms of the following dilution fractions:

$$\beta_1=[V_{A1}(0)+\alpha V_D]/[V_{A1}(0)+\alpha V_T], \qquad \beta_2=[V_{A2}(0)+(1-\alpha)V_D]/[V_{A2}(0)+ (1-\alpha)V_T]$$

(e) Generalize the result found in part (d) to relate the N_2 volume fractions in alveolar compartments i=1,2 at the end of two successive identical breaths, $y_{Ai}(k)$ and $y_{Ai}(k-1)$. Use these single-breath equations to relate the N_2 volume fractions in the two alveolar compartments i=1,2 between the beginning and the end of k successive identical breaths, $y_{Ai}(k)$ and $y_{Ai}(0)$.

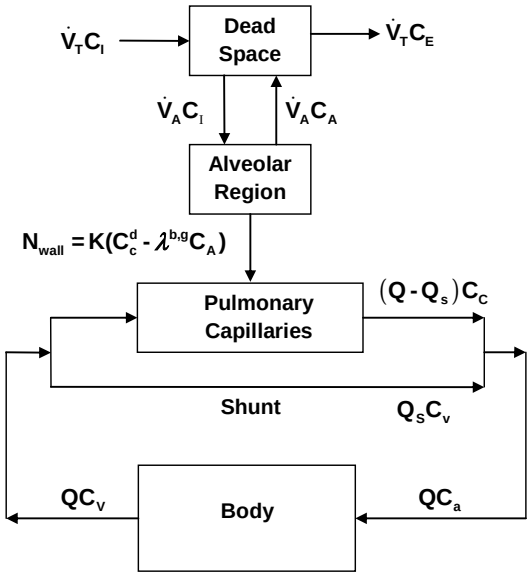
(f) Formulate the end-expired N_2 at the mouth for breath k, $y_E(k)$, in terms of α, β_1, β_2 and $y_D(0)$.

(g) Reduce the relation from (f) to an ideal lung in which the flows to the alveolar compartments are equal and their alveolar volumes are always equal. How does this result compare to Eq. 19.1-32a?

Problem 19-4: Blood Oxygenation With a Pulmonary Shunt

The effect of a pulmonary diffusion limitation and blood shunt on the excretion and retention of soluble inert gases was analyzed in section 19.1.3 of the book. In this problem, we will analyze the effect of blood shunting on steady-state O_2 transport. To account for O_2 metabolism, a body compartment with a volume rate $\dot{M}$ of O_2 loss has been added to the previous model. To simplify the analysis, you should:

- Assume that compartments including the pulmonary capillaries are perfectly mixed
- Consider O_2 binding to heme groups ($O_2 + Hb \rightleftarrows HbO_2$) to be in reaction equilibrium
- Express the model equations in terms of O_2 partial pressures and volumetric transfer rates specified at a standard temperature T and a pressure P



(a) Write the relationship between molar O_2 concentration C_i and partial pressure p_i in a gas stream i.

(b) Express the molar O_2 concentration in blood to (free) O_2 partial pressure p_i and (bound) O_2-Hb in blood stream i, $S_i = S(p_i)$. Start with Eq. 5.5-6.

(c) Assume that the mass transfer coefficient K is arbitrarily large, while the alveolar-to-capillary transfer flux N_{wall} remains finite. What is the relationship between the O_2 concentration C_A in the alveolar compartment and the dissolved O_2 concentration C_c^d in the capillary compartment? What is the corresponding relationship between the partial pressures p_A, and $p_{c\,in}$ these two compartments?

(d) The steady-state molar balance around the combined alveolar region and capillaries is expressed in terms of molar O_2 concentrations C_i by Eq. 19.1-38. Rewrite this balance equation in terms of O_2 partial pressures p_i and fractional O_2-Hb binding S_i .

(e) At the node where the shunt and end-capillary flows merge, the steady-state O_2 molar balance is specified in terms of molar O_2 concentrations C_i by Eq. 19.1-39. Express this equation in terms of O_2 partial pressures p_i and fractional O_2-Hb binding S_i.

(f) Develop a steady state O_2 mole balance around the perfectly mixed body compartment, first in terms of molar concentrations and then in terms of partial pressures p_i and O_2-Hb binding fractions S_i.

(g) Using the Hill model (Eq. 5.5-1) of O_2-Hb saturation fraction $S(p_i)$, solve numerically the 3 equations of parts (d),(e) and (f) to evaluate the O_2 partial pressures in the venous stream, p_v, arterial stream p_a and capillary stream, p_c. Plot these partial pressures as a function of the shunt fraction $1 > Q_s/Q \geq 0$. Use the following values of parameters that are typical for a resting adult person:

$\dot{V}_A = 5$ L(STP)/min

$Q = 5$ L/min

$\dot{M} = 0.250$ L(STP)/min

α=0.000219 ml O_2(STP)/ml blood/kPa

$\hat{C}_{max} = 0.209$ L O_2(STP)/L blood

$\kappa_p = 0.283$ kPa^{-1}

$n = 2.8$

$P = 101$ kPa

$p_I = 19$ kPa

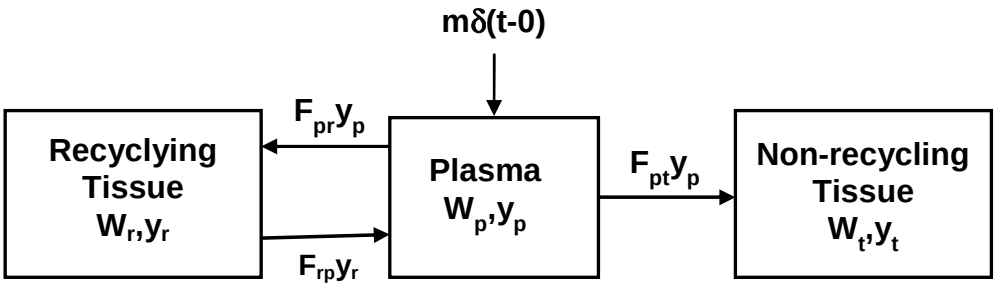
(h) Explain what these results mean.

Problem 19-5: A Three Pool Model for Systemic Iron Distribution

The distribution of iron is important to many aspects of human heath, particularly as it affects the formation of hemoglobin. Najean and colleagues (Am. J. Physiol. 213:533-546, 1967) measured the progressive reduction in plasma radioactivity following rapid bolus injection of an iron radioisotope into plasma. These data averaged over the several human subjects tested were expressed by a double exponential equation:

$$\frac{y_p(t)}{y_p(0)} = (0.994 \pm 0.005)\exp[(-11.2 \pm 2.8)t] + (0.005 \pm 0.003)\exp[(-0.35 \pm 14)t] + (0.001 \pm 0.0005)$$

Here, $y_p(t)/y_p(0)$ represents the gram-atoms of radioisotope in plasma at a time t(days) relative to the initial gram-atoms in plasma. A possible three-compartment model of this behavior consists of a plasma pool p that irreversibly loses a portion of its radioactive iron to a pool of red cells r while simultaneously exchanging radioactive iron with the remaining red cells and other body tissues t. In each pool i=p,r,t of the model: W_i is the total gram-atoms of iron in both radioactively tagged and untagged forms; y_i represents the gram-atoms of tagged iron relative to W_i. The parameter F_{ij} is the total gram-atoms of iron transferred from pool i to pool j.



(a) Assuming that each pool i is perfectly mixed and that W_i and F_{ij} are constants, write the mass

balance equations for the three compartments when an ideal impulse of m gram-atoms of radiolabeled iron is injected into the plasma pool.

(b) With no radioactive iron initially present, what are the initial conditions associated with the equations of part (a)?

(c) Take the Laplace transform of the model equations and solve for $\tilde{y}_p(s) = L\{y(t)\}$ in the form $f(s)/(s-r_1)(s-r_2)$.

(d) Noting that

$$L^{-1}\left\{\frac{1}{(s-r_1)(s-r_2)}\right\} = \frac{e^{r_1 t} - e^{r_2 t}}{r_1 - r_2}, \qquad L^{-1}\left\{\frac{s}{(s-r_1)(s-r_2)}\right\} = \frac{r_1 e^{r_1 t} - r_2 e^{r_2 t}}{r_1 - r_2}$$

obtain the time domain solution $y_p(t)$. What is $y_p(0)$? Express the final model equation as $y_p(t)/y_p(0)$.

(e) Because of the strong effect of measurement noise at low levels of radioactivity, the additive constant (0.001 ± 0.0005) in Najean's empirical equation is unreliable. Ignoring this constant, determine the values for the model parameters, F_{rp}/W_r, F_{pr}/W_p, and F_{pt}/W_p. Comparing the parameters values for the exchange and the irreversible loss processes, which of the two takes longer to occur.