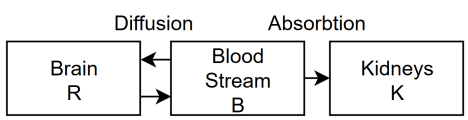
Math 5231 - Fall 2019
Problem Set 7

Modeling Construct systems of differential equations for the following pharmacokinetic models. You may assume that all transport is given by absorption, diffusion or flow. In each box, the amount of a chemical is indicated by a variable. You may write the equations in terms of amounts or concentrations (for example C_A). If constant's aren't specified you should provide them.
Recall that if X_i indicates a drug amount, C_{X_i} indicates a drug concentration, V_{X_i} indicates a systems volume and S_{ij} indicates the surface area, the absorption, diffusion and mass transport equations are

$$\begin{aligned}
&\text{Absorption from } X_1 \text{ to } X_2\text{:} && \frac{dC_{X_1}}{dt} = -\frac{rdS_{12}}{V_{X_1}}C_{X_1}\,, && \frac{dC_{X_2}}{dt} = \frac{rdS_{12}}{V_{X_2}}C_{X_1}\,.\\
&\text{Diffusion between } X_1 \text{ and } X_2\text{:} && \frac{dC_{X_1}}{dt} = \frac{rdS_{12}}{V_{X_1}}(C_{X_2} - C_{X_1})\,, && \frac{dC_{X_2}}{dt} = \frac{rdS_{12}}{V_{X_2}}(C_{X_1} - C_{X_2})\,.\\
&\text{Flow From } X_1 \text{ to } X_2\text{:} && \frac{dC_{X_1}}{dt} = -\frac{F}{V_1}C_{X_1}\,, && \frac{dC_{X_2}}{dt} = \frac{F}{V_2}C_{X_1}\,.\\
&\text{Flow From } X_1 \text{ to } X_2\text{:} && \frac{dX_1}{dt} = -F\frac{X_1}{V_1}\,, && \frac{dX_2}{dt} = F\frac{X_1}{V_1}\,.
\end{aligned}$$



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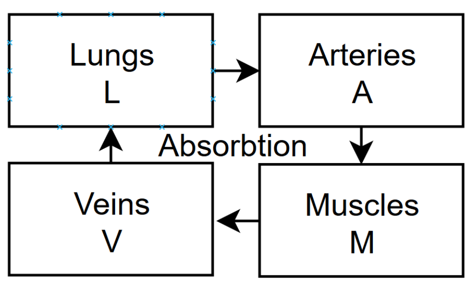

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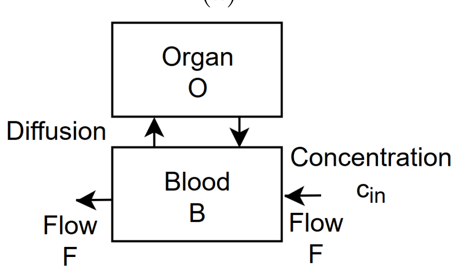

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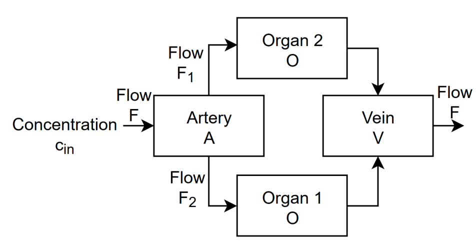

(4)

In class, we discussed a simple pharmacokinetic model where a drug was ingested in the stomach, was absorbed into the blood stream, and finally was removed by the kidneys. If the amount of drug in the stomach is S, the amount in the blood stream is B and the amount in the kidneys is K, we pharmacokinetic's uses the following simple model

$$S' = -r_1 A \tag{1}$$
$$B' = r_1 A - r_2 B \tag{2}$$
$$K' = r_2 B \tag{3}$$

Answer the following questions:
Question 5: When $A(0) = A_0$, $B(0) = 0$ and $C(0) = 0$, what are the equations for the amounts of drug at time t? What is the equation for t_max the maximum amount of drug in the blood stream?

Question 6: What are the equations for the amount of drug in the system when $A(0) = A_0$, $B(0) = B_0$ and $C(0) = 0.$?

Question 7: We want to find t_*, the time we should administer a new dose if we don't want the blood concentration to fall below B_{min}/V_{blood}. In the case that $r_1 >> r_2$, find a formula for the time at which blood concentration hits B_{min}.

Question 8: Pills don't immediately dissolve in the stomach.The rate at which a pill dissolves is proportional to it's surface area

$$\frac{dP}{dt} = -r_P \times \text{Surface Area}\,.$$

The amount of drug P is proportional by the density to the volume V: $P(t) = d_P \times V(t)$. Assuming a spherical pill,

$$\text{Volume} = \frac{4}{3}\pi r^3\,, \qquad\qquad \text{Surface Area} = 4\pi r^2\,.$$

Equate r to write the surface area in terms of the volume, and then in terms of P. Write a differential equation for dissolving of the pill.

Question 9: In the pill model above, a 1 gram pill dissolves completely in 20 minutes. How long until 50% of the pill is dissolved?

Answers:
Question 1: Since diffusion/absorption, let C_R, C_B and C_K be concentrations of chemical in each system.

$$
\begin{aligned}
C_R' &= -\frac{r_{RB} dS_{RB}}{V_R}(C_R - C_B) \\
C_B' &= \frac{r_{RB} dS_{RB}}{V_B}(C_R - C_B) - \frac{r_{BK} dS_{BK}}{V_R} C_R \\
C_K' &= \frac{r_{BK} dS_{BK}}{V_K} C_R
\end{aligned}
$$

Question 2: Since absorption, let C_L, C_A, C_M and C_V be concentrations of chemical in each system. Note, in the following we've assume d is the same for all transfers but this may not necessarily be true.

$$
\begin{aligned}
C_A' &= -\frac{r_1 dS_{AM}}{V_A} C_A + \frac{r_4 dS_{LA}}{V_M} C_L \\
C_M' &= -\frac{r_2 dS_{MV}}{V_M} C_M + \frac{r_1 dS_{AM}}{V_M} C_A \\
C_V' &= -\frac{r_3 dS_{VL}}{V_V} C_V + -\frac{r_2 dS_{MV}}{V_V} C_M \\
C_L' &= -\frac{r_4 dS_{LA}}{V_L} C_L + \frac{r_3 dS_{VL}}{V_L} C_V
\end{aligned}
$$

Question 3: Both diffusion and mass flow are involved, but we will use concentration. Let C_B, C_O, be concentrations of chemical in each system. Let V_B be the volume in the blood.

$$
\begin{aligned}
C_B' &= \frac{F}{V_B} c_{in} + \frac{r dS_{OB}}{V_B}(C_O - C_B) - \frac{F}{V_B} C_b \\
C_M' &= -\frac{r dS_{OB}}{V_O}(C_O - C_B)
\end{aligned}
$$

Question 4: Mass flow are involved, so we will just use amount. Let V_A, V_{O_1}, V_{O_2} and V_V be the volume of transport fluid in each system.

$$
\begin{aligned}
A' &= \frac{F}{c\ in} - \frac{F_1 + F_2}{V_A} A \\
O_1' &= \frac{F_1}{V_A} A - \frac{F_1}{V_{O_1}} O_1 \\
O_2' &= \frac{F_1}{V_A} A - \frac{F_1}{V_{O_2}} O_2 \\
V' &= \frac{F_1}{V_{O_1}} O_1 + \frac{F_1}{V_{O_2}} O_2 - \frac{F}{V_V} V
\end{aligned}
$$

Question 5:

$$\begin{aligned}
\frac{dA}{dt} &= A_0 e^{-r_1 t} \\
\frac{dB}{dt} &= -\frac{A_0 r_1}{r_1 - r_2}(e^{-r_1 t} - e^{-r_2 t}) \\
\frac{dAK}{dt} &= \frac{A_0}{r_1 - r_2}\left(r_2 e^{-r_1 t} - r_1 e^{-r_2 t}\right) + A_0
\end{aligned}$$

$t_{max} = \frac{\log(r_2/r_1)}{r_2 - r_1}$.

Question 6:

$$\begin{aligned}
\frac{dA}{dt} &= A_0 e^{-r_1 t} \\
\frac{dB}{dt} &= -\frac{A_0 r_1}{r_1 - r_2}(e^{-r_1 t} - e^{-r_2 t}) + B_0 e^{-r_2 t} \\
\frac{dAK}{dt} &= \frac{A_0}{r_1 - r_2}\left(r_2 e^{-r_1 t} - r_1 e^{-r_2 t}\right) - B_0 e^{-r_2 t} + A_0 + B_0
\end{aligned}$$

Question 7: $B(t) \approx (A_0 + B_0)e^{-r_2 t} - A_0 e^{-r_1 t} \approx (A_0 + B_0)e^{-r_2 t}$, since $r_1 \gg r_2$. Therefore

$$t_{min} \approx -r_2 \log \frac{B_{min}}{A_0 + B_0} .$$

$r_1 \gg r_2$ means absorption from stomach much faster than removal from blood stream to kidneys.

Question 8:

$$\frac{dP}{dt} = CP^{2/3}$$

where $C = 4\pi(3/4\pi d)^{2/3}$.

Question 9: Solution: Since $P(0) = 1$, $P = \frac{1}{27}(Ct + 3)^3$. Therefore $C = -1/20$. Solving for

$$.5 = (-t_{.5}/20 + 1)^3$$

we have $t_{.5} = 4.125$.