1. The model discussed in this section is analysed in Kubota and Maibach (1992).

A drug delivery vehicle, such as a skin patch, is attached to a patient. The amount of drug per unit area \((X)\) in the skin is described by the following differential equation

\[
\frac{dX}{dt} = - (k_{l2} + k_{1B}) X + k_{21} A_0, \quad X(0) = 0. \tag{1}
\]

In this equation \(A_0\) is the concentration of drug per unit area in the delivery device, which is maintained at a constant level. The parameters \(k_{l2}\) and \(k_{21}\) are the rate at which drug enters the vehicle from the skin and the skin from the vehicle respectively. The parameter \(k_{1B}\) is the rate at which drug leaves the skin and enters the blood stream.

(a) Solve equation (1) to find the amount of drug per unit area in the skin as a function of time. What is the medical significance of your answer?

(b) The cumulative amount of drug per unit area excreted from the skin \((A_{es})\) is expressed by

\[A_{es} = \int k_{1B} X \, dt, \quad A_{es}(0) = 0.\]

Determine \(A_{es}\).


**Solution**

(a) The differential equation can be written in the form of a first-order linear differential equation and can therefore be solved by finding an integrating factor.

\[
\frac{dX}{dt} + (k_{l2} + k_{1B}) X = k_{21} A_0,
\]

\[
R = \exp \left[ \int (k_{l2} + k_{1B}) \, dt \right],
\]

\[
= \exp \left[ \int (k_{l2} + k_{1B}) \, t \right] \Rightarrow \frac{d}{dt} \{ \exp \left[ \int (k_{l2} + k_{1B}) \, t \right] X \} = k_{21} A_0 \exp \left[ \int (k_{l2} + k_{1B}) \, t \right],
\]

\[
\Rightarrow \exp \left[ \int (k_{l2} + k_{1B}) \, t \right] X = \frac{k_{21} A_0}{k_{l2} + k_{1B}} \exp \left[ \int (k_{l2} + k_{1B}) \, t \right] + C,
\]

where \(C\) is an arbitrary constant. Applying the initial condition \(X(0) = 0\) we obtain \(C = -k_{21} A_0\). Thus

\[
X(t) = \frac{k_{21} A_0}{k_{l2} + k_{1B}} \{ 1 - \exp [-(k_{l2} + k_{1B}) \, t] \}
\]

(b)

\[
A_{es} = k_{1B} \int X(t) \, dt,
\]

\[
= k_{1B} \int \frac{k_{21} A_0}{k_{l2} + k_{1B}} \{ 1 - \exp [-(k_{l2} + k_{1B}) \, t] \} \, dt,
\]

\[
= \frac{k_{1B} k_{21} A_0}{k_{l2} + k_{1B}} \left\{ t + \frac{1}{k_{l2} + k_{1B}} \exp [-(k_{l2} + k_{1B}) \, t] \right\},
\]
where \( c \) is an arbitrary. Applying the initial condition \( Ae_s (0) = 0 \) we obtain \( c = -\frac{1}{k_1 B k_2 A_0} \). Thus

\[
Ae_s (t) = \frac{1}{k_1 B k_2 A_0} \left( t + \frac{1}{k_1 B + k_1 B} \exp\left[-\left(\frac{k_1 B + k_1 B}{k_1 B + k_1 B}\right)t\right] - \frac{1}{k_1 B + k_1 B} \right).
\]

2. After irradiation, the number of unavailable binding sites in the spleen for injected CFU decreases according to the differential equation

\[
\frac{dU}{dt} = -\lambda_1 U, \quad U (0) = U_0.
\]

The number \( F \) of available binding sites in the spleen changes according to

\[
\frac{dF}{dt} = \lambda_1 U - \lambda_2 F, \quad F (0) = 0,
\]

where the term \( \lambda_2 F \) represents the decay of available sites due to radiation damage.

(a) Solve equation (2) to find the number of unavailable sites as a function of time, \( U (t) \).
(b) Substitute your expression for \( U (t) \) into equation (3). Solve the resulting differential equation to find the number of available sites as a function of time, \( F (t) \).
(c) Find the value of \( t, t_{\text{max}} \), where the number of available sites \( (F) \) is maximised \( (F_{\text{max}}) \).
(d) Determine the maximum number of available sites available. Simplify your expression as far as possible.

This question is based upon Matioli (1976).


**Solution**

(a) This equation can be written as a first-order linear differential equation. Its solution can therefore be found by finding an integrating factor. Alternatively, it can be solved by treating it as a separable differential equation.

\[
\int_{U_0}^{U} \frac{dU}{U} = -\lambda_1 \int_0^t dt,
\]

\[
\Rightarrow \ln \left| \frac{U}{U_0} \right| = -\lambda_1 t,
\]

\[
\Rightarrow U = U_0 \exp\left[-\lambda_1 t \right].
\]

3. After substituting in the expression for \( U (t) \) that we have just calculated the differential equation can be written as a first-order linear differential equation. Its solution can therefore be found by finding an integrating factor.

\[
\frac{dF}{dt} + \lambda_2 F = U_0 \lambda_1 \exp\left[-\lambda_1 t\right],
\]

\[
R (x) = \exp \left[ \int \lambda_2 dt \right],
\]

\[
= \exp[\lambda_2 t],
\]

\[
\Rightarrow \frac{d}{dt} \left[ \exp[\lambda_2 t] F \right] = U_0 \lambda_1 \exp \left[ (\lambda_2 - \lambda_1) t \right],
\]

\[
\Rightarrow \exp[\lambda_2 t] F = \frac{U_0 \lambda_1}{\lambda_2 - \lambda_1} \exp \left[ (\lambda_2 - \lambda_1) t \right] + c,
\]

where \( c \) is an arbitrary constant. Note that in integrating we have assumed that \( \lambda_1 \neq \lambda_2 \). Applying the initial condition \( F (0) = 0 \) we obtain \( c = -\frac{U_0 \lambda_1}{\lambda_2 - \lambda_1} \). Thus

\[
F = \frac{U_0 \lambda_1}{\lambda_2 - \lambda_1} \{ \exp \left[ -\lambda_1 t \right] - \exp \left[ -\lambda_2 t \right] \}.
\]
4. The maximum value will occur when \( \frac{dF}{dt} = 0 \). Using the solution to our previous question we obtain

\[
\frac{dF}{dt} = \frac{U_0 \lambda_1}{\lambda_2 - \lambda_1} \left( -\lambda_1 \exp[-\lambda_1 t] + \lambda_2 \exp[\lambda_2 t] \right).
\]

After some algebra we find that

\[
\frac{dF}{dt} = 0, \\
\Rightarrow t_{\text{max}} = \frac{1}{\lambda_2 - \lambda_1} \ln \left( \frac{\lambda_2}{\lambda_1} \right).
\]

5. To find the maximum number of free sites we substitute the expression for \( t_{\text{max}} \) into the solution \( f(t) \).

\[
F_{\text{max}} = \frac{U_0 \lambda_1}{\lambda_2 - \lambda_1} \left\{ \exp \left[ -\lambda_1 \frac{\lambda_1}{\lambda_2 - \lambda_1} \ln \left( \frac{\lambda_2}{\lambda_1} \right) \right] - \exp \left[ -\lambda_2 \frac{\lambda_1}{\lambda_2 - \lambda_1} \ln \left( \frac{\lambda_2}{\lambda_1} \right) \right] \right\},
\]

\[
= \frac{U_0 \lambda_1}{\lambda_2 - \lambda_1} \left\{ \exp \left[ \frac{\lambda_1}{\lambda_1} \right] - \exp \left[ -\lambda_2 \frac{\lambda_1}{\lambda_2 - \lambda_1} \ln \left( \frac{\lambda_2}{\lambda_1} \right) \right] \right\},
\]

\[
= \frac{U_0 \lambda_1}{\lambda_2 - \lambda_1} \left\{ \frac{\lambda_1}{\lambda_2} - \frac{\lambda_1}{\lambda_2} \ln \left( \frac{\lambda_2}{\lambda_1} \right) \right\},
\]

\[
= \frac{U_0 \lambda_1}{\lambda_2 - \lambda_1} \left\{ \frac{\lambda_1}{\lambda_2} \frac{\lambda_2}{\lambda_2 - \lambda_1} \right\},
\]

\[
= \frac{U_0 \lambda_1}{\lambda_2 - \lambda_1} \left\{ \frac{\lambda_1}{\lambda_2} \right\},
\]

\[
= U_0 \left( \frac{\lambda_1}{\lambda_2} \right)^{1 + \frac{\lambda_1}{\lambda_2 - \lambda_1}}.
\]

In the mid-session test and/or the final exam you may be asked a question about Maple.

Your answer should include all maple code that you used to obtain the answer.

3. The Shannon function is defined as

\[
H(p) = -[p \log_{10} (p) + (1 - p) \log_{10} (1 - p)],
\]

where \( 0 < p < 1 \).

(a) Plot the Shannon function.

(b) What value of \( p \) maximises the value of the Shannon function?

(c) What is the maximum value of the Shannon function?
The importance of the Shannon function is described in Bruen & Forcinito (section 9.2, pages 162-164).

**Solution** This is a straightforward question. Make sure that you define the Shannon function using `log10` and *not* `log`

Maple code is at the end of the question.

(a) See figure 1.

(b) \( p = \frac{1}{2} \).

(c) \( \frac{\ln 2}{\ln 10} \).

```
# week8-2007.maple
# 21.09.07
#
#
# NOTE the use of log10 rather than log to define the Shannon function.
H := -(p*log10(p) + (1-p)*log10(1-p));

lprint("Part (a)");
plot(H,p=0..1,color=BLACK,labels=["p","Shannon function H(p)"], \
   labeldirections=[horizontal,vertical]);

lprint("Part (b)");
p := solve(diff(H,p),p);

lprint("Part (c)");
```
H;