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 EN.585.615.81.SP21 Mathematical Methods
 Take Home Project 1
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Question 1

The rates of change of C_e (free), $F^{18}DG$, and C_m (trapped), $F^{18}DG-6-P$ in brain tissue are given by the system of differential equations:

$$\begin{cases} \frac{d}{dt} C_e = k_1 C_p - (k_2 + k_3) C_e + k_4 C_m \\ \frac{d}{dt} C_m = k_3 C_e - k_4 C_m \end{cases}$$

Rearranging the terms of the differential equations gives:

$$\begin{cases} \frac{d}{dt} C_e + (k_2 + k_3) C_e - k_4 C_m = k_1 C_p \\ -k_3 C_e + \frac{d}{dt} C_m + k_4 C_m = 0 \end{cases}$$

First, since initial concentrations are assumed to be zero: $C_e(0) = C_m(0) = 0$ and thus:

$$\begin{aligned} \mathcal{L}\left\{\frac{d}{dt} C_e\right\} &= s\tilde{C}_e(s) - \tilde{C}_e(0) = s\tilde{C}_e(s) - 0 = s\tilde{C}_e(s) \\ \mathcal{L}\left\{\frac{d}{dt} C_m\right\} &= s\tilde{C}_m(s) - \tilde{C}_m(0) = s\tilde{C}_m(s) - 0 = s\tilde{C}_m(s) \end{aligned}$$

Next, we take the Laplace transform on both sides of the ODEs which gives:

$$\begin{cases} (s + k_2 + k_3)\tilde{C}_e(s) - k_4\tilde{C}_m(s) = k_1\tilde{C}_p(s) \\ -k_3\tilde{C}_e(s) + (s + k_4)\tilde{C}_m(s) = 0 \end{cases}$$

In matrix form, we have:

$$\begin{bmatrix} s + k_2 + k_3 & -k_4 \\ -k_3 & s + k_4 \end{bmatrix} \begin{bmatrix} \tilde{C}_e(s) \\ \tilde{C}_m(s) \end{bmatrix} = \begin{bmatrix} k_1\tilde{C}_p(s) \\ 0 \end{bmatrix}$$

Solving for $\tilde{C}_e(s)$ and $\tilde{C}_m(s)$, Cramer's rule gives us:

$$\tilde{C}_e(s) = \frac{\begin{vmatrix} k_1\tilde{C}_p(s) & -k_4 \\ 0 & s + k_4 \end{vmatrix}}{D} \quad \tilde{C}_m(s) = \frac{\begin{vmatrix} s + k_2 + k_3 & k_1\tilde{C}_p(s) \\ -k_3 & 0 \end{vmatrix}}{D}$$

where D is the determinant:

$$\begin{aligned}
\begin{vmatrix} s + k_2 + k_3 & -k_4 \\ -k_3 & s + k_4 \end{vmatrix} &= (s + k_2 + k_3)(s + k_4) - k_3k_4 \\
&= s^2 + (k_2 + k_3 + k_4)s + (k_2 + k_3)k_4 - k_3k_4 \\
&= s^2 + (k_2 + k_3 + k_4)s + k_2k_4
\end{aligned}$$

The roots of this quadratic expression are:

$$\begin{aligned}
r_1 &= \frac{1}{2} \left[- (k_2 + k_3 + k_4) - \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4} \right] \\
r_2 &= \frac{1}{2} \left[- (k_2 + k_3 + k_4) + \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4} \right]
\end{aligned}$$

And thus $D = (s - r_1)(s - r_2)$. We have an expression for C_i as $\tilde{C}_i(s) = \tilde{C}_e(s) + \tilde{C}_m(s)$ in s-space, but we want an expression of C_i in t-space. Therefore we take the inverse Laplace transform of $\tilde{C}_i(s)$. But first, we need a nice form for $\tilde{C}_e(s)$ and $\tilde{C}_m(s)$ so we can find their inverse Laplace transforms in a table.

$$\begin{aligned}
\tilde{C}_e(s) &= \frac{\begin{vmatrix} k_1\tilde{C}_p(s) & -k_4 \\ 0 & s + k_4 \end{vmatrix}}{D} \\
\tilde{C}_e(s) &= k_1\tilde{C}_p(s) \frac{s + k_4}{(s - r_1)(s - r_2)}
\end{aligned}$$

We will now determine the partial fraction expansion of $\tilde{C}_e(s)$:

$$\begin{aligned}
\frac{s + k_4}{(s - r_1)(s - r_2)} &= \frac{A}{s - r_1} + \frac{B}{s - r_2} \\
&= \frac{A(s - r_2) + B(s - r_1)}{(s - r_1)(s - r_2)} \\
&= \frac{(A + B)s - Ar_2 - Br_1}{(s - r_1)(s - r_2)}
\end{aligned}$$

Equating on each side, coefficients for the same powers of s in the numerator:

$$s^1 : A + B = 1 \tag{1}$$

$$s^0 : -Ar_2 - Br_1 = k_4 \tag{2}$$

from (1) we have $B = 1 - A$ and substituting back into (2):

$$\begin{aligned}
A(r_1 - r_2) - r_1 &= k_4 \\
A &= \frac{k_4 + r_1}{r_1 - r_2} \\
B = 1 - A &= 1 - \frac{k_4 + r_1}{r_1 - r_2} = -\frac{k_4 + r_2}{r_1 - r_2}
\end{aligned}$$

Plugging back these values for A and B in $\tilde{C}_e(s)$:

$$\begin{aligned}
\tilde{C}_e(s) &= k_1 \frac{\tilde{C}_p(s)}{r_1 - r_2} \left[\frac{k_4 + r_1}{s - r_1} - \frac{k_4 + r_2}{s - r_2} \right] \\
&= k_1 \frac{k_4 + r_1}{r_1 - r_2} \frac{\tilde{C}_p(s)}{s - r_1} - k_1 \frac{k_4 + r_2}{r_1 - r_2} \frac{\tilde{C}_p(s)}{s - r_2}
\end{aligned}$$

The Laplace transform of the convolution between two functions is the product of the Laplace transform of these functions (p 227, equation 5.58 Riley book):

$$\mathcal{L}\{(f * g)(t)\} = \mathcal{L}\left\{\int_0^t f(t')g(t - t')dt'\right\} = \tilde{f}(s)\tilde{g}(s)$$

Let $\tilde{f}(s) = \tilde{C}_p(s)$ and $\tilde{g}(s) = \frac{1}{s - r_1}$, we have:

$$\begin{aligned}
\mathcal{L}^{-1}\{\tilde{f}(s)\} &= \mathcal{L}^{-1}\{\tilde{C}_p(s)\} = C_p(t) \\
\mathcal{L}^{-1}\{\tilde{g}(s)\} &= \mathcal{L}^{-1}\left\{\frac{1}{s - r_1}\right\} = e^{r_1 t}
\end{aligned}$$

Therefore:

$$\mathcal{L}\left\{\int_0^t C_p(t')e^{r_1(t-t')}dt'\right\} = \frac{\tilde{C}_p(s)}{s - r_1}$$

Taking the inverse Laplace transform on both side of the previous equation yields:

$$\int_0^t C_p(t')e^{r_1(t-t')}dt' = \mathcal{L}^{-1}\left\{\frac{\tilde{C}_p(s)}{s - r_1}\right\}$$

Similarly, we have:

$$\int_0^t C_p(t')e^{r_2(t-t')}dt' = \mathcal{L}^{-1}\left\{\frac{\tilde{C}_p(s)}{s - r_2}\right\}$$

We now take the inverse Laplace transform of $\tilde{C}_e(s)$ using the two previous expressions:

$$\begin{aligned}
& \mathcal{L}^{-1}\{\tilde{C}_e(s)\} \\
&= C_e(t) \\
&= k_1 \frac{k_4 + r_1}{r_1 - r_2} \mathcal{L}^{-1}\left\{\frac{\tilde{C}_p(s)}{s - r_1}\right\} - k_1 \frac{k_4 + r_2}{r_1 - r_2} \mathcal{L}^{-1}\left\{\frac{\tilde{C}_p(s)}{s - r_2}\right\} \\
&= k_1 \frac{k_4 + r_1}{r_1 - r_2} \int_0^t C_p(t') e^{r_1(t-t')} dt' - k_1 \frac{k_4 + r_2}{r_1 - r_2} \int_0^t C_p(t') e^{r_2(t-t')} dt'
\end{aligned}$$

Next, we follow the same steps for $C_m(t)$:

$$\begin{aligned}
\tilde{C}_m(s) &= k_1 k_3 \frac{\tilde{C}_p(s)}{(s - r_1)(s - r_2)} \\
&= k_1 k_3 \frac{\tilde{C}_p(s)}{(r_1 - r_2)} \left[\frac{1}{s - r_1} - \frac{1}{s - r_2} \right] \\
\mathcal{L}^{-1}\{\tilde{C}_m(s)\} &= C_m(t) \\
&= \frac{k_1 k_3}{r_1 - r_2} \left[\mathcal{L}^{-1}\left\{\frac{\tilde{C}_p(s)}{s - r_1}\right\} - \mathcal{L}^{-1}\left\{\frac{\tilde{C}_p(s)}{s - r_2}\right\} \right] \\
&= \frac{k_1 k_3}{r_1 - r_2} \int_0^t C_p(t') e^{r_1(t-t')} dt' - \frac{k_1 k_3}{r_1 - r_2} \int_0^t C_p(t') e^{r_2(t-t')} dt'
\end{aligned}$$

Putting all together:

$$\begin{aligned}
C_i(t) &= C_e(t) + C_m(t) \\
&= -\left(\frac{k_1(k_4 + r_2) + k_1 k_3}{r_1 - r_2}\right) \int_0^t C_p(t') e^{r_2(t-t')} dt' + \frac{k_1(k_4 + r_1) + k_1 k_3}{r_1 - r_2} \int_0^t C_p(t') e^{r_1(t-t')} dt' \\
&= -\left(\frac{k_1}{r_1 - r_2}\right)(k_3 + k_4 + r_2) \int_0^t C_p(t') e^{r_2(t-t')} dt' + \left(\frac{k_1}{r_1 - r_2}\right)(k_3 + k_4 + r_1) \int_0^t C_p(t') e^{r_1(t-t')} dt'
\end{aligned}$$

In the associated paper by Brooks:

$$\alpha_{1,2} = \frac{1}{2} \left[k_2 + k_3 + k_4 \pm \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4} \right]$$

Thus:

$$\begin{aligned}
r_1 &= -\alpha_2 \\
r_2 &= -\alpha_1
\end{aligned}$$

Substituting α_1 and α_2 into the expression we just obtained for $C_i(t)$ yields:

$$\begin{aligned} C_i(t) &= \frac{k_1(k_3 + k_4 - \alpha_1)}{\alpha_1 - \alpha_2} \int_0^t e^{-\alpha_1(t-t')} C_p(t') dt' + \frac{k_1(\alpha_2 - k_3 - k_4)}{\alpha_1 - \alpha_2} \int_0^t e^{-\alpha_2(t-t')} C_p(t') dt' \\ &= A \int_0^t e^{-\alpha_1(t-t')} C_p(t') dt' + B \int_0^t e^{-\alpha_2(t-t')} C_p(t') dt' \end{aligned}$$

with:

$$\begin{aligned} A &= k_1(k_3 + k_4 - \alpha_1)/(\alpha_1 - \alpha_2) \\ B &= k_1(\alpha_2 - k_3 - k_4)/(\alpha_1 - \alpha_2) \end{aligned}$$

We just have reproduced formula (4) in the associated paper by Brooks. Note that when $k_4 \ll k_2 + k_3$, A and B reduces to:

$$\begin{aligned} A &\approx k_1 k_3 / (k_2 + k_3) \\ B &\approx k_1 k_2 / (k_2 + k_3) \end{aligned}$$

We can express the same expression of $C_i(t)$ in terms of convolutions (with definition of the convolution defined in p.227 equation 5.58 in Riley book):

$$C_i(t) = A(C_p(t) * e^{-\alpha_1 t}) + B(C_p(t) * e^{-\alpha_2 t})$$