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

$$\begin{cases} \frac{d}{dt}C_e = k_1C_p - (k_2+k_3)C_e + k_4C_m \\ \frac{d}{dt}C_m = k_3C_e - k_4C_m \end{cases}$$

Rearranging the terms of the differential equations gives:

$$\begin{cases} \frac{d}{dt}C_e + (k_2+k_3)C_e - k_4C_m & = k_1C_p \\ k_3C_e + \frac{d}{dt}C_m + k_4C_m & = 0 \end{cases}$$

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

$$\mathscr{L}\{\frac{d}{dt}C_e\} = s\tilde{C}_e(s) - \tilde{C}_e(0) = s\tilde{C}_e(s) - 0 = s\tilde{C}_e(s)$$
$$\mathscr{L}\{\frac{d}{dt}C_m\} = s\tilde{C}_m(s) - \tilde{C}_m(0) = s\tilde{C}_m(s) - 0 = s\tilde{C}_m(s)$$

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:

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

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 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 226 equation 5.58 Riley book):

$$
\mathscr{L}\{\int_0^t f(t')g(t - t')dt'\} = \tilde{f}(s)\tilde{g}(s)
$$

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

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

Therefore:

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

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

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

Similarly, we have:

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

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

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

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

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

Putting all together:

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

In the associated paper by Brooks:

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

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 $k_4 << k_2+k_3$, A and B reduce to:

$$
\begin{aligned}
A &\approx k_1k_3/(k_2+k_3) \\
B &\approx k_1k_2/(k_2+k_3)
\end{aligned}
$$