Assignment 9
Biophys 4322/5322

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1 Problem 1) Phillips 15.3

Consider $A \rightleftarrows B$ with he rate equations

$$\frac{dc_A}{dt} = -k_+ c_A + k_- c_B \tag{1}$$
$$\frac{dc_B}{dt} = -\frac{dc_A}{dt} \tag{2}$$
$$c_0 = c_A(t) + c_B(t) = \text{constant.} \tag{3}$$

1.1 Part a)

Solve the equations with the initial condition that only species A is present at $t = 0$. Make plots and show that the long time behavior is dictated by the ratio k_+/k_-.

We'll use Eq. (1), apply mass conservation Eq. (3) and then solve by separation of variables. Go:

$$\begin{aligned}
\frac{dc_A}{dt} &= -k_+ c_A + k_- c_B \\
&= -k_+ c_A + k_- \left(c_0 - c_A\right) = -\left(k_+ + k_-\right) c_A + k_- c_0 \\
&= -\left(k_+ + k_-\right)\left(c_A - c_0 \frac{k_-}{k_+ + k_-}\right) \\
\frac{dc_A}{c_A - c_0 \frac{k_-}{k_+ + k_-}} &= -\left(k_+ + k_-\right) dt \\
\int \frac{dc_A}{c_A - c_0 \frac{k_-}{k_+ + k_-}} &= \int -\left(k_+ + k_-\right) dt \\
\ln\left(c_A - c_0 \frac{k_-}{k_+ + k_-}\right) &= -\left(k_+ + k_-\right) t + A' \\
\exp\left[\ln\left(c_A + c_0 \frac{k_-}{k_+ + k_-}\right)\right] &= \exp\left[-\left(k_+ + k_-\right) t + A'\right] \\
c_A - c_0 \frac{k_-}{k_+ + k_-} &= A e^{-\left(k_+ + k_-\right)t} \\
c_A(t) &= c_0 \frac{k_-}{k_+ + k_-} + A e^{-\left(k_+ + k_-\right)t}.
\end{aligned} \tag{4}$$

To find the integration constant A, we apply the initial condition that at $t = 0$ $c_B(0) = 0$ so $C_A(0) = c_0$

i.e.

$$\begin{aligned}
c_A(0) = c_0 &= c_0 \frac{k_-}{k_+ + k_-} + A e^{-(k_+ + k_-)0} \\
&= c_0 \frac{k_-}{k_+ + k_-} + A \\
A &= c_0 - c_0 \frac{k_-}{k_+ + k_-} \\
&= c_0 \left(1 - \frac{k_-}{k_+ + k_-}\right),
\end{aligned} \tag{5}$$

which means that the solution for the concentration of A is

$$\begin{aligned}
c_A(t) &= c_0 \frac{k_-}{k_+ + k_-} + A e^{-(k_+ + k_-)t} \\
&= c_0 \frac{k_-}{k_+ + k_-} + c_0 \left(1 - \frac{k_-}{k_+ + k_-}\right) e^{-(k_+ + k_-)t} \\
&= \frac{c_0 k_+}{k_+ + k_-} \left[\frac{k_-}{k_+} + \left(\frac{k_+ + k_-}{k_+} - \frac{k_-}{k_+}\right) e^{-(k_+ + k_-)t}\right] \\
&= \frac{c_0}{1 + \frac{k_-}{k_+}} \left[\frac{k_-}{k_+} + e^{-(k_+ + k_-)t}\right].
\end{aligned} \tag{6}$$

Therefore by conservation of mass the concentration of B must be

$$\begin{aligned}
c_B(t) = c_0 - c_A(t) &= c_0 - \frac{c_0}{1 + \frac{k_-}{k_+}} \left[\frac{k_-}{k_+} + e^{-(k_+ + k_-)t}\right] \\
&= \frac{c_0}{1 + \frac{k_-}{k_+}} \left[1 - e^{-(k_+ + k_-)t}\right].
\end{aligned} \tag{7}$$

Plot these two against time.

The long time limits are

$$\begin{aligned}
\lim_{t\to\infty} c_A(t) &= \lim_{t\to\infty} \frac{c_0}{1 + \frac{k_-}{k_+}} \left[\frac{k_-}{k_+} + e^{-(k_+ + k_-)t}\right] \\
&= \frac{c_0}{1 + \frac{k_-}{k_+}} \left[\frac{k_-}{k_+}\right]
\end{aligned} \tag{8}$$

$$\begin{aligned}
\lim_{t\to\infty} c_B(t) &= \lim_{t\to\infty} \frac{c_0}{1 + \frac{k_-}{k_+}} \left[1 - e^{-(k_+ + k_-)t}\right] \\
&= \frac{c_0}{1 + \frac{k_-}{k_+}}.
\end{aligned} \tag{9}$$

They are controlled by the ratio of the rate constants.

1.2 Part b)

Using the current recording for a single sodium ion channel shown in Figure 7.2(A) (p. 259), estimate the opening and the closing rate of the channel. Use the result from Part a) to plot the probability that the channel is open and the probability it is closed as a function of time. Assume the channel to be closed initially.

Say A is closed and B is open then what we are looking for is the steady state solution of Eq. (1) which is very simply

$$\begin{aligned}
\frac{dc_A}{dt} &= 0 = -k_+ c_A + k_- c_B \\
\frac{c_A}{c_B} &= \frac{k_-}{k_+}.
\end{aligned} \tag{10}$$

In Figure 7.2(A), the channel seems to spend equal time open and closed therefore

$$\begin{aligned}\frac{c_A}{c_B} &\approx 1\\ k_- &\approx k_+.\end{aligned} \tag{11}$$

Using this information the probability that they are open or closed become

$$\begin{aligned}c_A(t) &= \frac{c_0}{1+\frac{k_-}{k_+}}\left[\frac{k_-}{k_+} + e^{-(k_+ + k_-)t}\right]\\ &\approx \frac{c_0}{2}\left[1 + e^{-(k_+ + k_-)t}\right]\end{aligned} \tag{12}$$

$$\begin{aligned}c_B(t) &= \frac{c_0}{1+\frac{k_-}{k_+}}\left[1 - e^{-(k_+ + k_-)t}\right]\\ &\approx \frac{c_0}{2}\left[1 - e^{-(k_+ + k_-)t}\right].\end{aligned} \tag{13}$$

but to get values we also need to estimate $k_+ + k_-$ and recognize that starting all in the closed state means $c_A(0) = 1 \to c_0 = 1$. We can guess $k_+ + k_-$ because ≈ 20 transitions from open to closed happen in $\approx 80\mu s$ so

$$k_+ + k_- \approx \frac{20}{80\mu s} = \frac{1}{4\mu s} \tag{14}$$

which means the probabilities are

$$\begin{aligned}c_A(t) &\approx \frac{c_0}{2}\left[1 + e^{-(k_+ + k_-)t}\right]\\ &\approx \frac{1}{2}\left[1 + e^{-t/(4\mu s)}\right]\end{aligned} \tag{15}$$

$$\begin{aligned}c_B(t) &\approx \frac{c_0}{2}\left[1 - e^{-(k_+ + k_-)t}\right]\\ &\approx \frac{1}{2}\left[1 - e^{t/(4\mu s)}\right].\end{aligned} \tag{16}$$

2 Problem 2) Phillips 15.6

2.1 Part a)

Deduce the following equations for the probability distributions $p_+(n,t)$ and $p_-(n,t)$ which give the probability of finding a microtubule by writing a master equation for $p_+(n,t)$ and $p_-(n,t)$ by noting that there are four processes that can change the probability at each instant:

1. **the $n-1$ polymer can grow and become an n polymer, characterized by a rate v_+**
2. **the n polymer can grow and become an $n+1$ polymer, also characterized by a rate v_+**
3. **the $n+$ polymer can switch from growing to shrinking with a rate f_{+-}**
4. **the $n-$ polymer can switch from growing to shrinking with a rate f_{-+}.**

Use a Taylor expansion on factors like $p_+(n-1,t) - p_+(n,t)$ to obtain the equations.

So the terms (using what very well may be the worst notation in the world) for each of the four processes are

1. $+v_+ p_+(n-1,t)$
2. $-v_+ p_+(n,t)$
3. $-f_{+-} p_+(n,t)$

4. $+f_{-+}p_{-}(n,t)$;

therefore, the equation for the probability distribution is

$$\begin{aligned}\frac{\partial p_+}{\partial t} &= v_+p_+(n-1,t) - v_+p_+(n,t) - f_{+-}p_+(n,t) + f_{-+}p_-(n,t) \\ &= v_+\left[p_+(n-1,t) - p_+(n,t)\right] - f_{+-}p_+(n,t) + f_{-+}p_-(n,t).\end{aligned} \tag{17}$$

We see the Taylor expansion there: $\partial p_+(n,t)/\partial n \simeq p_+(n,t) - p_+(n-1,t)$ and so the equation becomes

$$\frac{\partial p_+(n,t)}{\partial t} \simeq -v_+\frac{\partial p_+(n,t)}{\partial n} - f_{+-}p_+(n,t) + f_{-+}p_-(n,t). \tag{18}$$

The equation for shrinking has equivalent terms and so is

$$\frac{\partial p_-(n,t)}{\partial t} \simeq v_-\frac{\partial p_-(n,t)}{\partial n} - f_{-+}p_-(n,t) + f_{+-}p_+(n,t). \tag{19}$$

2.2 Part b)

Solve these equations in the steady state and show that in the steady state the probabilities decay exponentially with the constant

$$\sigma = \frac{v_+f_{-+} - v_-f_{+-}}{v_+v_-}.$$

Assuming steady state

$$\frac{\partial p_\pm(n,t)}{\partial t} = 0$$

the equations become

$$v_+\frac{\partial p_+(n,t)}{\partial n} = f_{-+}p_-(n,t) - f_{+-}p_+(n,t) \tag{20}$$

$$v_-\frac{\partial p_-(n,t)}{\partial n} = f_{-+}p_-(n,t) - f_{+-}p_+(n,t), \tag{21}$$

which is a linear system of ODEs and can be written in matrix notation:

$$\frac{\partial}{\partial n}\begin{pmatrix}p_+(n,t)\\p_-(n,t)\end{pmatrix} = \begin{pmatrix}-\frac{f_{+-}}{v_+} & \frac{f_{-+}}{v_+}\\ -\frac{f_{+-}}{v_-} & \frac{f_{-+}}{v_-}\end{pmatrix}\begin{pmatrix}p_+(n,t)\\p_-(n,t)\end{pmatrix} \tag{22}$$

with eigenvalues that are the solution of

$$\begin{aligned}0 &= \begin{vmatrix}-\frac{f_{+-}}{v_+} - \lambda & \frac{f_{-+}}{v_+}\\ -\frac{f_{+-}}{v_-} & \frac{f_{-+}}{v_-} - \lambda\end{vmatrix}\\ 0 &= \left(-\frac{f_{+-}}{v_+} - \lambda\right)\left(\frac{f_{-+}}{v_-} - \lambda\right) - \frac{f_{-+}f_{+-}}{v_+v_-}\\ \lambda &= \left[0,\ \frac{v_+f_{-+} - v_-f_{+-}}{v_+v_-}\right].\end{aligned} \tag{23}$$

Eigenvalue $\lambda = 0$ gives the eigenvector

$$\begin{pmatrix}p_+(n,t)\\p_-(n,t)\end{pmatrix} = \begin{pmatrix}\frac{f_{-+}}{f_{+-}}\\1\end{pmatrix} \tag{24}$$

and the eigenvalue $\lambda = \sigma = \frac{v_+f_{-+} - v_-f_{+-}}{v_+v_-}$ gives

$$\begin{pmatrix}p_+(n,t)\\p_-(n,t)\end{pmatrix} = \begin{pmatrix}\frac{v_-}{v_+}\\1\end{pmatrix}. \tag{25}$$

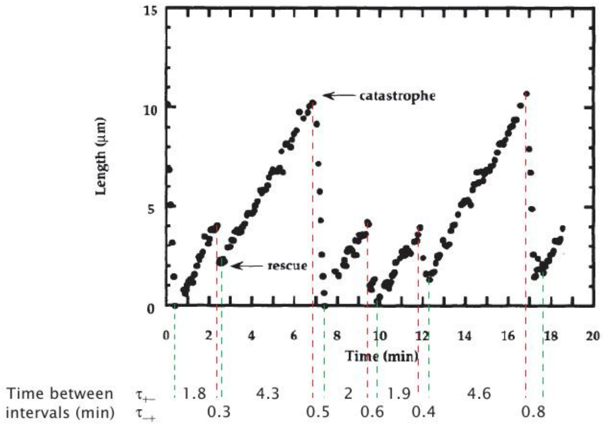

Figure 1: Copy of Phillips Fig. 15.35.

Therefore the solutions are of the form

$$\begin{aligned} p_+(n,t) &= \frac{f_{-+}}{f_{+-}} A e^{0\times n} + \frac{v_-}{v_+} B e^{\sigma n} \\ &= \frac{f_{-+}}{f_{+-}} A + \frac{v_-}{v_+} B e^{\sigma n} \\ p_-(n,t) &= 1 \times A e^{0\times n} + 1 \times B e^{\sigma n} \\ &= A + B e^{\sigma n}. \end{aligned}$$

We won't bother to find the constant B but we can say something about A we want it to be impossible for the microtubule to be infinite, therefore when $n \to \infty$ we must have $p = 0$ which demands $A = 0$. So then

$$p_+(n,t) = \frac{v_-}{v_+} B e^{\sigma n} \tag{26}$$

$$p_-(n,t) = B e^{\sigma n}. \tag{27}$$

2.3 Part C)

Use Figure 15.35 from Phillips to estimate the parameters and find the average length of the polymers which is predicted by this simple model. To find the average length you will need to sum over all lengths with their appropriate probability. The slopes of the growth and decay regions tell you about the on and off rates, and the durations of the growth and decay periods tell you something about the parameters. Note that by fitting the dynamical data, you are deducing/predicting something about the distribution of lengths.

The figure is included and from it we can see that the time between catastrophes is $\tau_{+-} \approx 3$min and the time after that for a rescue is only about $\tau_{-+} \approx 0.5$min. The inversions five us the frequencies:

$$f_{+-} = \frac{1}{\tau_{+-}} \approx 0.\bar{3}\text{min}^{-1} \tag{28}$$

$$f_{-+} = \frac{1}{\tau_{-+}} \approx 2\text{min}^{-1}. \tag{29}$$

The microtubule seems to grow to about $\ell \approx 10\mu$m before catastrophe so the velocities are approximately

$$v_+ = \approx 2\mu\text{m/min} \tag{30}$$

$$v_- = \approx 20\mu\text{m/min}. \tag{31}$$

Substituting these all into σ gives

$$\sigma = \frac{v_+ f_{-+} - v_- f_{+-}}{v_+ v_-} = \frac{2 \times 2 - 20 \times 0.\overline{3}}{2 \times 20} \mu\text{m}^{-1}$$
$$= -0.07 \mu\text{m}^{-1} \tag{32}$$

It's good that it's negative. A positive result would have indicated bad estimates since it's unphysical. Since σ is in units of length let's let $n \to z$ where z is the length of the microtubule.

Now that we have physically relevant parameters, we are ready to estimate the average length to be (note: remember when applying the integration limits that σ is negative)

$$\langle z \rangle = \frac{\int_0^\infty z p(z) dz}{\int_0^\infty p(z) dz} = \frac{\int_0^\infty z \left[p_+ + p_-\right] dz}{\int_0^\infty \left[p_+ + p_-\right] dz}$$
$$= \frac{\int_0^\infty z \left[\frac{v_-}{v_+} B e^{\sigma z} + B e^{\sigma z}\right] dz}{\int_0^\infty \left[\frac{v_-}{v_+} B e^{\sigma z} + B e^{\sigma z}\right] dz} = \frac{B \left[\frac{v_-}{v_+} + 1\right]}{B \left[\frac{v_-}{v_+} + 1\right]} \frac{\int_0^\infty z e^{\sigma z} dz}{\int_0^\infty e^{\sigma z} dz}$$
$$= \frac{\int_0^\infty z e^{\sigma z} dz}{\int_0^\infty e^{\sigma z} dz} = \frac{\left[e^{\sigma z} \left(\sigma z - 1\right) / \sigma^2\right]_0^\infty}{\left[e^{\sigma z} / \sigma\right]_0^\infty} = \frac{0 - 1\left(0 - 1\right) / \sigma^2}{0 - 1/\sigma}$$
$$= -\frac{1}{\sigma} \tag{33}$$
$$\approx 14 \mu\text{m} \tag{34}$$

which seems a little long compared to the figure.