SysBio2

404018

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Part A

Considering the equation system

$$\begin{aligned} x_1 &\xrightarrow{\lambda_1} x_1 + b & x_2 &\xrightarrow{\lambda_2 x_1} x_2 + 1 \\ x_1 &\xrightarrow{\beta_1 x_1} x_1 - 1 & x_2 &\xrightarrow{\beta_2 x_2} x_2 - 1 \end{aligned} \tag{1}$$

The CME would be as follows:

$$\begin{aligned} \frac{dP(x_1,x_2)}{dt} =& \underbrace{\lambda_1 P(x_1 - b, x_2) - \lambda_1 P(x_1, x_2)}_{\text{Synthesis of } x_1} + \underbrace{\beta_1 (x_1+1) P(x_1+1, x_2) - \beta_1 x_1 P(x_1, x_2)}_{\text{Degradation of } x_1} + \\ & \underbrace{\lambda_2 x_1 P(x_1, x_2 - 1) - \lambda_2 x_1 P(x_1, x_2)}_{\text{Synthesis of } x_2} + \underbrace{\beta_2 (x_2+1) P(x_1, x_2+1) - \beta_2 x_2 P(x_1, x_2)}_{\text{Degradation of } x_2} \end{aligned} \tag{2}$$

Part B

Using the method of exponents we can find H:

$$H = \begin{bmatrix} 1 & 0 \\ -1 & 1 \end{bmatrix} \tag{3}$$

As $M_{ij} = \frac{H_{ij}}{\tau_i}$ then we can find M:

$$M = \begin{bmatrix} \frac{1}{\tau_1} & 0 \\ -\frac{1}{\tau_2} & \frac{1}{\tau_2} \end{bmatrix} \tag{4}$$

Next we need to calculate the average step size for x_1 in order to calculate D. Using the definition of step size:

$$\begin{aligned} \langle s_x \rangle &= \sum_k |\delta_k| \frac{|\delta_k| \langle r_k(x) \rangle}{\sum_l |\delta_l| \langle r_l(x) \rangle} \\ &= \frac{b^2 \lambda_1 + 1^2 \beta_1 \langle x_1 \rangle}{b\lambda_1 + 1\beta_1 \langle x_1 \rangle} \\ &= \frac{b^2 \lambda_1 + \langle x_1 \rangle \frac{1}{\tau_1}}{b\lambda_1 + \langle x_1 \rangle \frac{1}{\tau_1}} \\ &= \frac{b^2 \lambda_1 \tau_1 + \langle x_1 \rangle}{b\lambda_1 \tau_1 + \langle x_1 \rangle} \end{aligned} \tag{5}$$

We can calculate the relationship between λ_1 and lifetimes using the equation for the change in abundance of x_1 and assuming stationarity:

$$\begin{aligned} \frac{d\langle x_1 \rangle}{dt} &= \langle R_1^+ \rangle - \langle R_1^- \rangle \\ &= b\lambda_1 - \beta_1 \langle x_1 \rangle \end{aligned} \tag{6}$$

Setting $\frac{d\langle x_1\rangle}{dt} = 0$ and using the equivalence $\beta_1 = \frac{1}{\tau_1}$

$$\begin{aligned} 0 &= b\lambda_1 - \frac{1}{\tau_1}\langle x_1\rangle \\ b\lambda_1 &= \frac{1}{\tau_1}\langle x_1\rangle \\ \lambda_1 &= \frac{1}{b}\frac{1}{\tau_1}\langle x_1\rangle \end{aligned} \tag{7}$$

Substituting this into the equation for $\langle x_1\rangle$ we get:

$$\begin{aligned} \langle s_1\rangle &= \frac{b^2\lambda_1\tau_1 + \langle x_1\rangle}{b\lambda_1\tau_1 + \langle x_1\rangle} \\ &= \frac{b^2\tau_1\frac{1}{b}\frac{1}{\tau_1}\langle x_1\rangle + \langle x_1\rangle}{b\tau_1\frac{1}{b}\frac{1}{\tau_1}\langle x_1\rangle + \langle x_1\rangle} \\ &= \frac{b\langle x_1\rangle + \langle x_1\rangle}{\langle x_1\rangle + \langle x_1\rangle} \\ &= \frac{\langle x_1\rangle(1+b)}{2\langle x_1\rangle} \\ &= \frac{(1+b)}{2} \end{aligned} \tag{8}$$

We can plug this into the equation for $D_{ii} = \frac{2}{\tau_i}\frac{\langle s_i\rangle}{\langle x_i\rangle}$, considering that the average step size for x_2 is 1. We can also consider the off diagonal elements of D to be zero as there are no equations requiring or producing both x_1 and x_2. This gives D:

$$D = \begin{bmatrix} \frac{1}{\tau_1}\frac{1+b}{\langle x_1\rangle} & 0 \\ 0 & \frac{2}{\tau_2}\frac{1}{\langle x_2\rangle} \end{bmatrix} \tag{9}$$

Next we can calculate η using the relationship $M\eta + (M\eta)^T = D$:

$$\begin{aligned} M\eta &= \begin{bmatrix} \frac{1}{\tau_1} & 0 \\ -\frac{1}{\tau_2} & \frac{1}{\tau_2} \end{bmatrix}\begin{bmatrix} \eta_{11} & \eta_{12} \\ \eta_{21} & \eta_{22} \end{bmatrix} \\ &= \begin{bmatrix} \frac{\eta_{11}}{\tau_1} & \frac{\eta_{12}}{\tau_1} \\ \frac{1}{\tau_2}(-\eta_{11}+\eta_{21}) & \frac{1}{\tau_2}(-\eta_{12}+\eta_{22}) \end{bmatrix} \\ M\eta + (M\eta)^T &= \begin{bmatrix} \frac{\eta_{11}}{\tau_1} & \frac{\eta_{12}}{\tau_1} \\ \frac{1}{\tau_2}(-\eta_{11}+\eta_{21}) & \frac{1}{\tau_2}(-\eta_{12}+\eta_{22}) \end{bmatrix} + \begin{bmatrix} \frac{\eta_{11}}{\tau_1} & \frac{1}{\tau_2}(-\eta_{11}+\eta_{21}) \\ \frac{\eta_{12}}{\tau_1} & \frac{1}{\tau_2}(-\eta_{12}+\eta_{22}) \end{bmatrix} = D \\ &= \begin{bmatrix} \frac{2\eta_{11}}{\tau_1} & \frac{\eta_{12}}{\tau_1} + \frac{1}{\tau_2}(-\eta_{11}+\eta_{21}) \\ \frac{\eta_{12}}{\tau_1} + \frac{1}{\tau_2}(-\eta_{11}+\eta_{21}) & \frac{2}{\tau_2}(-\eta_{12}+\eta_{22}) \end{bmatrix} = \begin{bmatrix} \frac{1}{\tau_1}\frac{1+b}{\langle x_1\rangle} & 0 \\ 0 & \frac{2}{\tau_2}\frac{1}{\langle x_2\rangle} \end{bmatrix} \end{aligned} \tag{10}$$

We know that $\eta_{21} = \eta_{12}$ so we can now write 3 simultaneous equations:

$$\begin{aligned} \frac{2\eta_{11}}{\tau_1} = \frac{1}{\tau_1}\frac{1+b}{\langle x_1\rangle} &\implies \eta_{11} = \frac{1+b}{2}\frac{1}{\langle x_1\rangle} \\ 0 = \frac{\eta_{12}}{\tau_1} + \frac{1}{\tau_2}(-\eta_{11}+\eta_{12}) &\implies \eta_{12} = \frac{\eta_{11}\tau_1}{\tau_1+\tau_2} \\ \frac{2}{\tau_2}(-\eta_{12}+\eta_{22}) = \frac{2}{\tau_2}\frac{1}{\langle x_2\rangle} &\implies \eta_{22} = \frac{1}{\langle x_2\rangle} + \eta_{12} \end{aligned} \tag{11}$$

Having solved η_{11} in terms of abundance and lifetimes we can now substitute into the other equations:

$$\eta_{12} = \frac{1+b}{2}\frac{1}{\langle x_1\rangle}\frac{\tau_1}{\tau_1+\tau_2}$$
$$\eta_{22} = \frac{1}{\langle x_2\rangle} + \frac{1+b}{2}\frac{1}{\langle x_1\rangle}\frac{\tau_1}{\tau_1+\tau_2} \tag{12}$$

Is your statement exact or approx - should be exact as these are linear equations?

Part C

We can first consider the case where $b = 1$:

$$\eta_{11} = \underbrace{\frac{1+b}{2}}_{=1}\frac{1}{\langle x_1\rangle}$$
$$\eta_{12} = \underbrace{\frac{1+b}{2}}_{=1}\frac{1}{\langle x_1\rangle}\frac{\tau_1}{\tau_1+\tau_2} \tag{13}$$
$$\eta_{22} = \frac{1}{\langle x_2\rangle} + \underbrace{\frac{1+b}{2}}_{=1}\frac{1}{\langle x_1\rangle}\frac{\tau_1}{\tau_1+\tau_2}$$

In this case $\eta_{11} = \frac{1}{\langle x_1\rangle}$ and therefore will be at the level of the poisson noise for this system. When $\tau_1 >> \tau_2$, $\eta_{22} \approx \frac{1}{\langle x_2\rangle} + \frac{1}{\langle x_1\rangle}$ but when $\tau_1 << \tau_2$, $\eta_{22} \approx \frac{1}{\langle x_2\rangle}$. Therefore we can see here that in the case of a non-bursting mRNA a long-lived protein and shortlived mRNA minimises variability in the protein level. This is unsurprising as a longlived protein will have slower fluctuations and therefore is likely to have a lower variability.

We can now consider the case where $b > 1$:

$$\eta_{11} = \underbrace{\frac{1+b}{2}}_{\text{large}}\frac{1}{\langle x_1\rangle}$$
$$\eta_{12} = \underbrace{\frac{1+b}{2}}_{\text{large}}\frac{1}{\langle x_1\rangle}\frac{\tau_1}{\tau_1+\tau_2} \tag{14}$$
$$\eta_{22} = \frac{1}{\langle x_2\rangle} + \underbrace{\frac{1+b}{2}}_{\text{large}}\frac{1}{\langle x_1\rangle}\frac{\tau_1}{\tau_1+\tau_2}$$

We can see that for η_{11} increasing b i.e. mRNA being produced in bursts will increase η_{11}, and the only way for the cell to reduce normalised variance for x_1 is by increasing $\langle x_1\rangle$ - in this way variation will be proportionally smaller making the normalised variance smaller.

We can now consider η_{22}. In the case where $\tau_1 << \tau_2$ (a shortlived mRNA but longlived protein) $\frac{\tau_1}{\tau_1+\tau_2}$ will be small, which will minimise the impact of $\langle x_1\rangle$ on η_{22}:

$$\eta_{22} = \frac{1}{\langle x_2\rangle} + \underbrace{\frac{1+b}{2}}_{\text{large}}\frac{1}{\langle x_1\rangle}\underbrace{\frac{\tau_1}{\tau_1+\tau_2}}_{\approx 0} \tag{15}$$

However if $\tau_1 >> \tau_2 \longrightarrow \frac{\tau_1}{\tau_1+\tau_2} \approx 1$ we would expect that $\langle x_1\rangle > \langle x_2\rangle$ as the lifetime is much longer, so for the same or a similar rate of production x_2 will be degraded more quickly.

$$\eta_{22} = \underbrace{\frac{1}{\langle x_2\rangle}}_{> \frac{1}{\langle x_1\rangle}} + \underbrace{\frac{1+b}{2}}_{\text{large}}\underbrace{\frac{1}{\langle x_1\rangle}}_{< \frac{1}{\langle x_2\rangle}}\underbrace{\frac{\tau_1}{\tau_1+\tau_2}}_{\approx 1} \tag{16}$$

We can see again that a with $b > 1$ η_{22} can be minimised by having a longlived protein and shortlived mRNA. This makes sense as thhis will minimise noise propagation...

Part D

We can use the definition for step size to calculate the average step size:

$$\langle s_1 \rangle = \sum_k |\delta_k| \frac{|\delta_k| \langle r_k(x) \rangle}{\sum_l |\delta_l| \langle r_l(x) \rangle} \tag{17}$$

Average step size for production

We can first calculate the denominator of this equation:

$$\begin{aligned} \sum_l |\delta_l| \langle r_l(x) \rangle &= 1 \times 0.6\lambda_1 + 2 \times 0.3\lambda_1 + 3 \times 0.1\lambda_1 \\ &= 1.5\lambda_1 \end{aligned} \tag{18}$$

We can now consider the whole equation:

$$\begin{aligned} \langle s_1^+ \rangle &= \sum_k |\delta_k| \frac{|\delta_k| \langle r_k(x) \rangle}{\sum_l |\delta_l| \langle r_l(x) \rangle} \\ &= \sum_k |\delta_k| \frac{|\delta_k| \langle r_k(x) \rangle}{1.5\lambda_1 + \beta_1 \langle x_1 \rangle} \\ &= \frac{1^2 \times 0.6\lambda_1 + 2^2 \times 0.3\lambda_1 + 3^2 \times 0.1\lambda_1}{1.5\lambda_1} \\ &= \frac{0.6\lambda_1 + 1.2\lambda_1 + 0.9\lambda_1}{1.5\lambda_1} \\ &= \frac{2.7\lambda_1}{1.5\lambda_1} \\ &= 1.8 \end{aligned} \tag{19}$$

Total average step size

We can first calculate the denominator of this equation:

$$\begin{aligned} \sum_l |\delta_l| \langle r_l(x) \rangle &= 1 \times 0.6\lambda_1 + 2 \times 0.3\lambda_1 + 3 \times 0.1\lambda_1 + \beta_1 \langle x_1 \rangle \\ &= 1.5\lambda_1 + \beta_1 \langle x_1 \rangle \end{aligned} \tag{20}$$

We can now consider the whole equation:

$$\begin{aligned} \langle s_1 \rangle &= \sum_k |\delta_k| \frac{|\delta_k| \langle r_k(x) \rangle}{\sum_l |\delta_l| \langle r_l(x) \rangle} \\ &= \sum_k |\delta_k| \frac{|\delta_k| \langle r_k(x) \rangle}{1.5\lambda_1 + \beta_1 \langle x_1 \rangle} \\ &= \frac{1^2 \times 0.6\lambda_1 + 2^2 \times 0.3\lambda_1 + 3^2 \times 0.1\lambda_1 + \beta_1 \langle x_1 \rangle}{1.5\lambda_1 + \beta_1 \langle x_1 \rangle} \\ &= \frac{0.6\lambda_1 + 1.2\lambda_1 + 0.9\lambda_1 + \beta_1 \langle x_1 \rangle}{1.5\lambda_1 + \beta_1 \langle x_1 \rangle} \\ &= \frac{2.7\lambda_1 + \beta_1 \langle x_1 \rangle}{1.5\lambda_1 + \beta_1 \langle x_1 \rangle} \end{aligned} \tag{21}$$

If we consider this system to be at stationarity we can solve using the equation for change in $\langle x_1 \rangle$ and setting this to be zero:

$$\begin{aligned}\frac{d\langle x_1\rangle}{dt} &= \langle \boldsymbol{R}_1^+\rangle - \langle \boldsymbol{R}_1^-\rangle \\ &= 1\times 0.6\lambda_1 + 2\times 0.3\lambda_1 + 3\times 0.1\lambda_1 - \beta_1\langle x_1\rangle \\ &= 1.5\lambda_1 - \beta_1\langle x_1\rangle\end{aligned} \tag{22}$$

At stationarity:

$$\begin{aligned}0 &= 1.5\lambda_1 - \beta_1\langle x_1\rangle \\ \beta_1\langle x_1\rangle &= 1.5\lambda_1\end{aligned} \tag{23}$$

Substituting in to the equation for step size:

$$\begin{aligned}\langle s_1\rangle &= \frac{2.7\lambda_1 + \beta_1\langle x_1\rangle}{1.5\lambda_1 + \beta_1\langle x_1\rangle} \\ &= \frac{2.7\lambda_1 + 1.5\lambda_1}{1.5\lambda_1 + 1.5\lambda_1} \\ &= \frac{4.2\lambda_1}{3\lambda_1} \\ &= 1.4\end{aligned} \tag{24}$$

Part E

I ran the Gillespie algorithm using the following code:

```
# Make a function to return bits and set amount of time in each state
simulate_gillespie2 <- function(lambda, beta, p, cycles = 10000) {

    # Set up some storage
    states <- data.frame(x = rep(0, times = 1e+05))

    x <- 0
    xs <- data.frame(x = rep(NA, times = cycles), time = rep(NA, times = cycles))

    for (i in 1:cycles) {

        # Choose wait time
        time <- wait_time(lambda + beta * x)

        # Choose reaction
        rxn <- choose_reaction(c(lambda, beta * x))

        # Update time in state prior to change
        if (i %in% 1000:cycles) {

            # Only save after stationarity
            states$x[x] <- states$x[x] + time
        }

        xs$x[i] <- x

        if (i == 1) {
            xs$time[i] <- time
        } else {
```

```
## Error in ggplot(gs3[[1]]):  object 'gs3' not found
## Error in ggplot(gs2[[1]]):  object 'gs2' not found
## Error in ggplot(gs3[[2]]):  object 'gs3' not found
## Error in ggplot(gs2[[2]]):  object 'gs2' not found
 ## Error in arrangeGrob(...):  object 'a' not found
```

Figure 1: Histograms of state and blah

```
            xs$time[i] <- xs$time[i - 1] + time
        }

        switch(rxn, `1` = {
            x <- x + rgeom(p) + 1
        }, `2` = {
            if (x != 0) {
                x <- x - 1
            }
        })

    }

    # Update time in state after change
    states$x[x] <- states$x[x] + time

    return(list(xs, states))

}
```

Running this with $p = 0.1$ and $p = 0.5$ I generated the following histograms and plots of states of x:

```
## Error in wait_time(lambda + beta * x):  could not find function "wait_time"
## Error in wait_time(lambda + beta * x):  could not find function "wait_time"
```